2020 INFECTIOUS DISEASE BOARD REVIEW

GW | Office of Continuing Education in the Health Professions

25th Annual

COMPREHENSIVE REVIEW *for* INFECTIOUS DISEASE BOARD PREPARATION

DAY 1

COURSE DIRECTORS:
John E. Bennett, MD
Henry Masur, MD

COURSE CO-DIRECTORS:
Paul Auwaerter, MD
David N. Gilbert, MD
Roy M. Gulick, MD, MPH
Andrew Pavia, MD
Richard J. Whitley, MD

www.IDBoardReview.com

AGENDA

SATURDAY, AUGUST 22, 2020

#	START		END	PRESENTATION	SPEAKER(S)
01	9:45 AM	-	10:00 AM	**Introduction**	*John Bennett, MD* *Henry Masur, MD*
02	10:00 AM	-	10:30 AM	**Daily Question Preview 1**	*Henry Masur, MD (Moderator)*
03	10:30 AM	-	11:30 AM	**Clinical Immunology and Host Defense**	*Steven Holland, MD*
04	11:30 AM	-	12:15 PM	**Respiratory Viral Infections including Influenza, Immunocompetent, and Immunocompromised Patients**	*Andrew Pavia, MD*
	12:15 PM	-	12:30 PM	***BREAK***	
05	12:30 PM	-	1:15 PM	**Board Review Session 1**	*Drs. Pavia (Moderator), Bennett, Bloch, Chambers, Gandhi, and Nelson*
06	1:15 PM	-	2:00 PM	**Bone and Joint Infections**	*Sandra Nelson, MD*
07	2:00 PM	-	2:45 PM	**Syndromes that Masquerade as Infections**	*Karen Bloch, MD*
08	2:45 PM	-	3:45 PM	**Endocarditis of Native and Prosthetic Devices, and Infections of Pacers and Ventricular Assist Devices**	*Henry Chambers, MD*
	3:45 PM	-	4:00 PM	***BREAK***	
09	4:00 PM	-	4:15 PM	**Penicillin Allergies**	*Sandra Nelson, MD*
10	4:15 PM	-	5:15 PM	**Staphylococcal Diseases**	*Henry Chambers, MD*
11	5:15 PM	-	5:30 PM	**Pharyngitis Syndromes including Group A Strep Pharyngitis**	*Karen Bloch, MD*
12	5:30 PM	-	6:15 PM	**Photo Opportunity I: Photos and Questions to Test Your Board Preparation**	*Rajesh Gandhi, MD*
13	6:15 PM	-	7:00 PM	**HIV-Associated Opportunistic Infections I**	*Henry Masur, MD*

COURSE OVERVIEW

ABOUT THE COURSE

This course is designed specifically for physicians planning to certify or recertify in the Infectious Disease Subspecialty of the American Board of Internal Medicine and is also suitable for physicians planning to take Infectious Disease sections of the internal medicine board examination. As the latest information is not on these examinations, the course does not intend to be an update, though speakers may choose to include some of that information in their talks.

The Infectious Disease Board Review Course is designed not only to expand your knowledge, but also to help you find areas in which you need to increase your knowledge. Neither the talks nor the questions cover all the topics that may be on the ABIM exam. The questions during the live course and online should give you a better idea of the format and depth of detail you can expect from the ABIM exam. You can compare your scores with other registrants. Now that the MOC exam allows access to "Up-to-date" during the entire exam, registrants who have access to "Up-to-date" through their institution could experiment ahead of the exam, accessing IDBR online questions and "Up-to-date" simultaneously, perhaps using different browsers. After answering an IDBR online question, the correct answer and rationale are provided, so users will know if their search produced the needed information. As the exam is time-limited, we anticipate that searching "Up-to-date" will need to be focused and limited. The certifying exam does not provide "Up-to-date" access.

The lectures, board review sessions, and web-based material will be available for one year following the course so that registrants can access the material as often as desired. The faculty are all experts in their content area, and are experienced educators. Most have extensive experience writing ABIM-style questions, although all adhere to the ABIM pledge not to divulge specific questions they may have read while taking their own examinations, or while previously working on ABIM committees.

EDUCATIONAL OBJECTIVES

1. Review the core infectious disease information that would prepare a physician to take the American Board of Internal Medicine Certification or Recertification Examination in infectious disease.
2. Answer questions written in the format used by the ABIM for the certification and recertification examinations.
3. Provide a comparison of knowledge and test-taking experience with colleagues likely to be taking the certification or recertification tests in infectious diseases.
4. Review state of the art clinical practice for the specialty of infectious diseases.

PROGRAM FACILITATORS

The George Washington University
Office of Continuing Education in the Health Professions
2600 Virginia Avenue, NW, Suite 300
Washington, DC 20037
Ph: 202.994.4285
Email: IDBR@gwu.edu

FACULTY LISTING

COURSE DIRECTORS

John E. Bennett, MD*
Henry Masur, MD*

CO-DIRECTORS

Paul G. Auwaerter, MD
Johns Hopkins University
Baltimore, Maryland

David N. Gilbert, MD
Oregon Health and Science University
Portland, Oregon

Roy M. Gulick, MD, MPH
Weill Cornell Medical College
New York, New York

Andrew T. Pavia, MD
University of Utah
Salt Lake City, Utah

Richard J. Whitley, MD
University of Alabama at Birmingham
Birmingham, Alabama

FACULTY

Barbara D. Alexander, MD, MHS
Duke University
Durham, North Carolina

David M. Aronoff, MD, FIDSA
Vanderbilt University Medical Center,
Nashville, Tennessee

Taison Bell, MD
University of Virginia
Charlottesville, Virginia

Karen Bloch, MD
Vanderbilt University Medical Center Nashville,
Tennessee

Helen Boucher, MD
Tufts University School of Medicine
Boston, Massachusetts

Henry F. Chambers, MD
University of California San Francisco
San Francisco, California

Shireesha Dhanireddy, MD
University of Washington
Seattle, Washington

Susan Dorman, MD
Medical University of South Carolina
Charleston, South Carolina

Herbert Dupont, MD
The University of Texas-Houston Medical School
Houston, Texas

Rajesh T. Gandhi, MD
Harvard Medical School
Boston, Massachusetts

Khalil G. Ghanem, MD, PhD
Johns Hopkins University
Baltimore, Maryland

John Gnann, MD
College of Medicine
Charleston, South Carolina

Steven M. Holland, MD*
Bethesda, Maryland

Frank Maldarelli, MD, PhD*
Bethesda, Maryland

Kieren A. Marr, MD
Johns Hopkins University
Baltimore, Maryland

Edward Mitre, MD
Uniformed Services
University of the Health Sciences
Bethesda, Maryland

Sandra Nelson, MD
Massachusetts General
Hospital
Boston, Massachusetts

Robin Patel, MD
Mayo Clinic
Rochester, Minnesota

Michael S. Saag, MD
University of Alabama at
Birmingham
Birmingham, Alabama

David L. Thomas, MD, MPH
Johns Hopkins University
Baltimore, Maryland

Allan R. Tunkel, MD, PhD
Brown University
Providence, Rhode Island

Robert A. Weinstein, MD
Rush Medical College
Chicago, Illinois

Kevin Winthrop, MD, MPH
Oregon Health & Science University
Portland, Oregon

*Individual employees of the National Institutes of Health (NIH) have participated in the planning and development of the course, although the NIH is not an official sponsor. The views expressed by the participants do not necessarily represent the opinions of the NIH, DHHS, or the Federal Government.

FACULTY DISCLOSURES AND RESOLUTIONS

In accordance with the Accreditation Council for Continuing Medical Education's Standards for Commercial Support, The George Washington University Office of CEHP requires that all individuals involved in the development of activity content disclose their relevant financial relationships and that all conflicts of interest be identified, resolved, and communicated to learners prior to delivery of the activity. The following faculty and CME staff members, upon submission of a disclosure form, made no disclosures of commercial relationships:

FACULTY (SPEAKERS)

- David Aronoff, MD
- Taison Bell, MD
- Karen C. Bloch, MD, MPH, FIDSA, FACP
- Henry F. Chambers, MD
- Shireesha Dhanireddy, MD
- Susan Dorman, MD
- Roy M. Gulick, MD,MPH
- Steven M. Holland, MD
- Frank Maldarelli, MD
- Edward Mitre, MD
- Sandra Nelson, MD
- Michael Saag, MD
- W. Michael Scheld, MD
- Allan R. Tunkel, MD, PhD, MACP
- Robert A. Weinstein, MD

PLANNERS

- John E. Bennett, MD
- Henry Masur, MD

Both planners also resolved financial disclosures

STAFF

- Leticia Hall
- Naomi Loughlin
- Sheena P. King

The following faculty members (speakers) disclosed commercial relationships:

FACULTY MEMBER (Speaker)	FINANCIAL DISCLOSURE(S)
Paul G. Auwaerter, MD	• Scientific Advisory Board: DiaSorin, Adaptive Bio Therapeutics • Grantee: MicroBplex, NIH/SBIR (Lyme disease diagnostics) • Equity-JNJ
Helen Boucher, MD	• Editor: ID Clinics of North America, Antimicrobial Agents and Chemotherapy • Treasurer: Infectious Diseases Society of America • Member: ID Board, American Board of Internal Medicine • Voting Member: Presidential Advisory Council on Combating Antibiotic Resistant Bacteria (PACCARB)
Khalil G. Ghanem, MD	• UpToDate royalties for topics related to STDs
Robin Patel, MD	• Grantee: CD Diagnostics, Merck, Hutchison Biofilm Medical Solutions, Accelerate Diagnostics, ContraFect, TenNor Therapeutics Limited, Shionogi • Consulting: Curetis, Specific Technologies, Next Gen Diagnostics, PathoQuest, Selux Diagnostics, 1928 Diagnostics, PhAST, Qvella, Mayo Clinic • Patent-holder: Bordetella pertussis/parapertussis PCR, A device/method for sonication with royalties paid by Samsung to Mayo Clinic, Anti-biofilm substance • Travel reimbursement: ASM, IDSA • Editor's stipend: IDSA • Honorarium: NBME, Up-to-Date, Infectious Diseases Board Review Course
Andrew T. Pavia, MD	• Consulting: Merck and Co (Zoster Vaccine)
David Thomas, MD, MPH	• Commercial Interests: Antimicrobial Therapy Inc, WebMD, Genentech, Merck

Richard J. Whitley, MD	• Member of the Board of Directors and the Health Policy Advisory Board: Gilead Sciences • Chairperson: GlaxoSmithKline Independent Data Management Committee for Zoster Protocol 047 • Chairperson: Merck Letermovir DSMB
Kevin L. Winthrop, MD	• Research: Insmed • Consulting: Insmed, Johnson & Johnson, Paratek, Red Hill Biopharma, Horizon

GUIDE TO COURSE MATERIALS APP

This course offers a mobile app and website for course attendees to access the syllabus and other course features.

With the App you can:

- Draw on presentation slides, highlight text, and take notes
- Access the full course schedule and create a personal schedule by starring the sessions you plan to attend
- Message other app users
- Receive alerts and updates for the meeting
- Access supplemental resources

To Access the App via Mobile Device:

1. Search for "eventScribe" in the Apple App Store or Google PlayStore.
2. Install and open the eventScribe app.
3. Search for your event app by entering "**IDBR 2020**."
4. To start using the app, please log in with the email and password emailed to you prior to your arrival.

To Access the App via PC:

1. Go to: https://tinyurl.com/IDBR2020.
2. To start using the app, please log in with the email and password emailed to you prior to your arrival.

Please Note:

- You will need internet access to download the app and any slides.
- After you have downloaded the slides to the app, you can access them anywhere on your tablet or smartphone, even without an internet connection.
- If you are experiencing difficulties with the App please go to the Registration Desk where we will be happy to assist you.

Using the "2020 IDBR" App

Make the Most of Your On-Site Experience!*

Notetaking & Bookmarking
Annotate directly on presentation slides and bookmark specific slides to view at a later time.

Personal Summary
Notes and bookmarked slides can be viewed, exported as PDFs, or printed at any time.

Create & Share Schedules
Attendees can schedule sessions and personal items, then sync with their own calendars!

Social Features
Attendees can view and communicate with other app users, speakers, and exhibitors.

***Download before you go!** On-Site WiFi service can affect the functionality of the app.

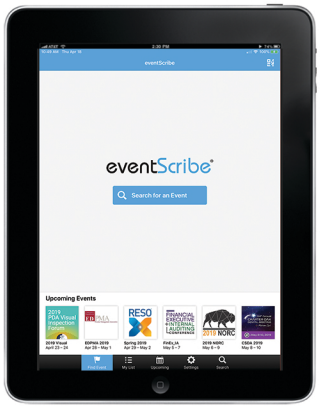
1. Download the "eventScribe" App

Search for **"eventScribe"** in the Apple App Store or Google Play Store.

INSTALL and **OPEN** the app then **SELECT** the event:

"2020 IDBR"

CLICK the icon to launch your app.



Event Name:
2020 IDBR

2. Login to your event App

To start using your event app, select **"Create Account"** and type your name and email address.

If you already have an account, select **"Login"** and enter your username (your email) and password.

3. Take notes on presentation slides

Find the presentation you need and interact with the presentation by drawing on slides or highlighting text. Use the note-taking mode to type your notes next to each slide. Access your notes and print them out by clicking the "My Notes" on the home screen or "Online Personal Summary" in the hamburger menu.

No mobile device? No Problem.

As long as you have an internet connection, you can take notes on presentations through your **laptop** via this link:

https://www.tinyurl.com/2020IDBR

support@eventscribe.com | 410.638.9239

ACCREDITATION, CME & MOC CLAIM INFORMATION - PHYSICIANS

TYPES OF CREDIT

There are two types of CME credit for Live Course participants:

1. Attending the Live Course - 43 credits
2. Completing the Online Materials - 58 credits

Please note that there are separate evaluation and credit claim processes for each type of CME credit, which is described in further detail in the subsequent pages.

LIVE COURSE

Accreditation

This activity has been planned and implemented in accordance with the Essential Areas and policies of the Accreditation Council for Continuing Medical Education through the joint providership of The George Washington University School of Medicine and Health Sciences and the Infectious Disease Board Review, LLC. The George Washington University School of Medicine and Health Sciences is accredited by the ACCME to provide continuing medical education for physicians.

CME Credit for Physicians

The George Washington University School of Medicine and Health Sciences designates this live activity for a maximum of *43 AMA PRA Category 1 Credit(s*) ™. Physicians should claim only the credit commensurate with the extent of their participation in the activity.

Claiming MOC Points

Successful completion of this CME activity enables the participant to earn up to 43 MOC points in the American Board of Internal Medicine's (ABIM) Maintenance of Certification (MOC) program.

Participants will earn MOC points equivalent to the amount of CME credits claimed for the activity. It is the CME activity provider's responsibility to submit participant completion information to ACCME for the purpose of granting ABIM MOC credit.

Deadline for Claiming MOC Points

ABIM Board Certified physicians need to claim MOC points for this course **by December 31, 2020** in order **for the MOC points to count toward any MOC requirements that are due by the end of 2020.**

OVERVIEW AND INSTRUCTIONS FOR CLAIMING CME CREDIT AND MOC POINTS

LIVE MATERIALS

<table>
<tr><th colspan="2">Live Lectures</th></tr>
<tr><td colspan="2">

- Participants can receive CME credits and MOC points by listening to the live lectures, participating in the daily ARS questions, and completing the course evaluation.
- In addition, the archived recordings of these lectures will be available on or before September 8th and will be organized chronologically by day. You have the option to view them online with the slides with streaming audio, or you can download the MP3 audio file onto your personal computer or mobile device.

</td></tr>
<tr><td>CME Hours:

43</td><td>To Claim CME Credit:
1. Complete the five (5) daily session/speaker evaluations (emailed at the end of each day).
2. Complete the final course evaluation (emailed on the final day of the course).
3. Upon completing the final course evaluation, you will be redirected to the link to claim CME credit where you will be asked to check the Attestation Statement box and enter the number of CME credits commensurate with the extent of your participation in the activity.</td></tr>
<tr><td>MOC Points:

43</td><td>To Claim MOC Points:
1. You must pass the Post-Test and claim CME credit prior to claiming MOC points.
2. After claiming your CME hours, you will be asked to attest whether you want your participation in the live course to be reported to the ABIM.
3. If you select yes, you will be asked to input your name, ABIM number, and date of birth.</td></tr>
<tr><th colspan="2">Post-Test</th></tr>
<tr><td colspan="2">

- Prior to claiming CME credit and MOC points, participants are asked to complete a set of thirty (30) content-related questions to assess their mastery of the information presented.

</td></tr>
<tr><td>CME</td><td rowspan="2">1. You must pass the test in the 30-minute allotted time frame.
2. You will be given three (3) attempts to pass the Post-Test (minimum performance level = 70% correct).
3. After each attempt, you may read the rationales prior to taking the test again.
4. If you do not pass the Post-Test within three (3) attempts, you cannot claim MOC points for this activity; however, you can still receive CME credit.</td></tr>
<tr><td>MOC</td></tr>
</table>

ONLINE MATERIALS

Credit

The George Washington University School of Medicine and Health Sciences designates this enduring material for a maximum of 58 *AMA PRA Category 1 Credit(s)™.* Physicians should claim only the credit commensurate with the extent of their participation in the activity.

MOC Points

Successful completion of this CME activity enables the participant to earn up to 58 MOC points in the American Board of Internal Medicine's (ABIM) Maintenance of Certification (MOC) program.

Participants will earn MOC points equivalent to the amount of CME credits claimed for the activity. It is the CME activity provider's responsibility to submit participant completion information to ACCME for the purpose of granting ABIM MOC credit.

Claiming Credit and MOC

Participants can earn up to 58 hours of CME credit and MOC points by completing the below online activities associated with the course.

After the completion of each set of activities, participants will be asked to attest to the number of CME hours and MOC points that they wish to claim. Please note that you do not have to complete the online activity in its entirety and you may claim partial CME/MOC credit.

Deadlines for Claiming MOC Points

ABIM Board Certified physicians need to claim MOC points for this course **by December 31, 2020** in order **for the MOC points to count toward any MOC requirements that are due by the end of 2020.**

CEHP will continue to submit participant completion data for the course until **August 16, 2021. No ABIM MOC credit will be awarded for this activity after August 16, 2021**.

OVERVIEW OF ONLINE MATERIALS AND INSTRUCTIONS FOR CLAIMING CREDIT AND MOC

Online Only Lectures	CME Hours: 2	MOC Points: 2
• These lectures feature topics that were not covered in the live course.		
Board Prep Questions	**CME Hours: 11 CME per question set**	**MOC Points: 11 MOC per question set**
• There are four (4) sets of 100 board prep questions. • You will see the correct answer and rationale after submitting each question. • You can only go in the forward direction when answering questions. • You cannot go backwards, but you can retake each set of questions as many times as you like.		
Online Primers and Study Guides	**CME Hours: 12**	**MOC Points: 12**
• There are eight (8) study guides and primers that present core material for you to review. • This PDF reviews information that summarizes important topics in photos, tables and short summaries.		

CEHP will continue to submit participant completion data for the course until **August 16, 2021**.
No ABIM MOC credit will be awarded for this activity after August 16, 2021.

GUIDE TO ONLINE MATERIALS ACCESS

Initial Notification

- If you registered on or before June 14, you will receive an email from IDBR@gwu.edu before or on June 15 with information on accessing the online materials.
- If you registered after June 14, you will receive the access information in 2-3 business days after your registration date.

Current Access

Accessing the Online Content:

1. Please create your account at https://cme.smhs.gwu.edu
    - Next page: Instructions to create an account
2. Once you have an account and are logged in, click the **My Courses** tab in the "My Account" drop-down menu.
3. Under the **Pending Activities** tab, you will see the Infectious Disease Board Review Course materials.

Instructions to Create an EthosCE User Account

EthosCE

School of Medicine & Health Sciences
THE GEORGE WASHINGTON UNIVERSITY

smhs.gwu.edu

EthosCE User Account

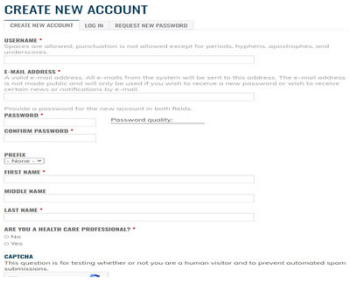
Create New Account

1. Go to: **cme.smhs.gwu.edu**
2. In the upper right, click **Register**
3. Enter required information
   - Username – can be your email address
   - E-mail Address
   - Password/Confirm Password
   - Name
   - Health Care Professional
   - CAPTCHA

School of Medicine & Health Sciences
THE GEORGE WASHINGTON UNIVERSITY

smhs.gwu.edu

EthosCE User Account



School of Medicine & Health Sciences
THE GEORGE WASHINGTON UNIVERSITY

smhs.gwu.edu

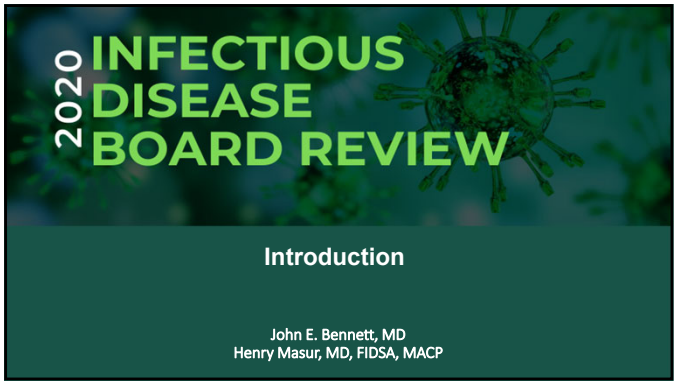
01

Introduction

Drs. Bennett and Masur

01 – Introduction

Speaker: John Bennett, MD and Henry Masur, MD



The Inaugural Virtual Edition of IDBR

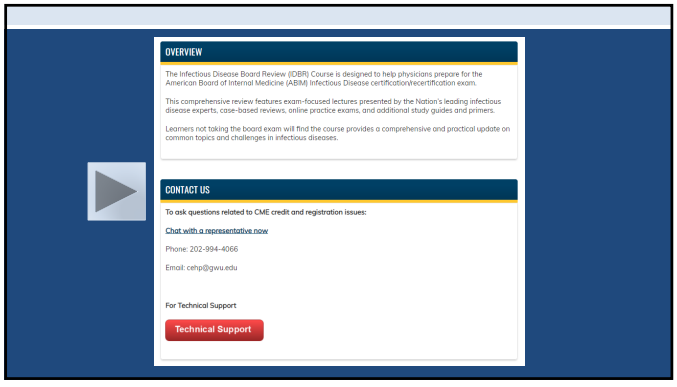
- **Goal**
  - To provide a course that is as close to the live experience as possible….with the convenience of virtual access
- **All Materials Are Available On Website**
  - Lectures, syllabus, preview questions, "lunch time" board review, answers to board review, and other questions
  - Updated materials will be posted on website
  - Syllabus: current lectures will be replaced on e-version with the slides "as presented" (in case there are minor changes or answers included that were absent from syllabus)

Components of the Virtual Course

- **Preview Questions**
  - Audience will answer "audience response questions" for 30 min to start Saturday-Tuesday mornings (there is no preview Wednesday), questions read by moderator and audience vote by SLIDO
- **Lectures**
  - Registrants are encouraged to answer each faculty question by SLIDO
  - If there is time for questions, faculty will answer as many as possible
- **Faculty interaction sessions**
  - Following each lecture the speaker will be available to answer registrant questions at "lobby session": see your daily email or contact IDBR
- **"Lunch" Board Review**
  - Faculty will read questions, registrants will vote in SLIDO, faculty will discuss

Make sure you have zoom account

https://zoom.us/signin



IDBR APP

- **Download the IDBR App from Apple store or Google Play store**
  - Download Event Scribe
  - Search for course by entering "2020 IDBR"
  - Log in with the email and password that was emailed to you
  - Problems: email idbr@gwu.edu or call 202-994-4066
- **You can use this app during the course, or until 12/2021, on your cell phone or tablet to look at the syllabus**

01 – Introduction

Speaker: John Bennett, MD and Henry Masur, MD

SLIDO

- **Log in to Slido.com**
  - Use a separate browser window from zoom
    - Have a large zoom window, and a much smaller slido window and keep both open
  - Alternatively, download the slido app from the apple store onto your cell phone
  - Create a temporary username in the upper right corner
- **Enter Slido Code we provide at the meeting**
- **On the blue bar at the top of the screen, click "polling"**
- **When the first polling question is presented, you should see the opportunity to vote, and after voting the audience cumulative results will appear on your slido window**

This Is Board Review

- **This is Board Review**
  - …not meant to be "What's New"
  - This may not mimic your practice but
    - Hopefully it will mimic exam
    - Faculty provides their *"best guess"* about the information and type of questions likely to be on the certification, recertification, and check-in exams
- **ABIM Rules**
  - We abide by confidentiality rules of ABIM
  - We will tell you what is plausible/appropriate for the exams
  - We will NOT tell you what has been on past exams…even if we know!!!

Infectious Disease Board Review Blue Print (Certification = MOC) Accessed 7/20

Medical Content Category	% of Exam (Cert and MOC)
Bacterial Diseases	27%
Human Immunodeficiency Virus (HIV) Infection	15%
Antimicrobial Therapy	9%
Viral Diseases	7%
Travel and Tropical Medicine	5%
Fungi	5%
Immunocompromised Host (Non-HIV Infection)	5%
Vaccinations	4%
Infection Prevention and Control	5%
General Internal Medicine, Critical Care and Surgery	18%

http://www.abim.org/~/media/ABIM%20Public/Files/pdf/exam-blueprints/certification/infectious-disease.pdf

http://www.abim.org/~/media/ABIM%20Public/Files/pdf/exam-blueprints/maintenance-of-certification/infectious-disease.pdf

How Questions Are Chosen by ABIM

4 sets of 60 questions for Cert, Recert
2 sets of 45 for Check-In

"At least 70% of exam questions will address high-importance content"

"No more than 30% of exam questions will address medium-importance"

"No exam questions will address low-importance content"

"Independent of the importance and task ratings
- No more than 15% of exam questions will address low-frequency content"

Multiple editions, or "forms," of the exam are used, and they may differ in question order and content

Certification exams are entirely closed book

Recertification and Knowledge Check-in permit Up to Date access

Which Will You Be?

How To Get The Most Out of Virtual Course

- **This is a Long Course and It's (obviously) Virtual**
  - Decide how you learn best over 10+ hours x 4.5 days
  - If you don't/can't watch the lectures consecutively…they are all archived
- **Use the ARS System (SLIDO)**
  - To stay awake, be engaged and competitive!
  - Answer the questions and see how you compare to your peers

01 – Introduction

Speaker: John Bennett, MD and Henry Masur, MD

Course Resources for You to Use Before, During, and After Course

- Virtual course for 4.5 days
  - Live Board Review Questions During Virtual Course
    - Rationales and daily scores published online by pin # at end of each day
- Online Board Review Type Questions
  - 400 Online questions with rationales
- Online Primers (Tables or Charts or Photos)
  - Clinical Microbiology
  - Resistance: Antibacterial, Antifungal, Antiviral, HIV
  - Skin Ulcers
  - Rickettsia
  - 115 "Images You Should Know" – rapid pre-exam review
- Online Recordings of 2020 Lectures (posted within a few days-2 weeks after course)
  - Listen to audio by MP3 (download and transfer to any device)
  - Watch slides while listening to synchronized audio
- Online Only Lectures
  - Talks we wished we had time for during these 4.5 days
  - Equally important as live lectures

Accessing The Course

- Problems access lectures or chat room
  - Telephone help line: 202-994-4285
  - Email help hotline: idbr@gwu.edu
- Faculty welcome your questions
  - Send email to idbr@gwu.edu
  - Join zoom "lobby chat" with faculty member immediately following his/her lecture: see daily email from IDBR for zoom access

CME and MOC
Total Possible: 101 CME and 101 MOC

- CME
  - You must fill out lecture evaluations (via IDBR website)
  - You must request CME (via IDBR website)
  - No pre-test or post-test
  - Total possible hours - 101
    - Lectures – 43
    - Enduring Material 58 (online IDBR website)
- MOC: one hour CME = 1 MOC credit
  - You must obtain CME per above
  - You must give IDBR your ABIM number
  - You must apply via ABIM website so we can link to ABIM
  - You must get 70% on post-test
    - (three tries of same test permitted with rationales available after each try)

IDBR Directors and Co-Directors



Richard Whitley
University of Alabama


Andy Pavia
University of Utah


Trip Gulick
Weill Cornell


Paul Auwaerter
Johns Hopkins


David Gilbert
University of Oregon

Behind Scenes Staff


Leticia Hall-Salam
IDBR Program Director


Sheena P. King
CE Coordinator


Naomi Loughlin
IDBR Program Coordinator


Mike D'Anthony
Recording

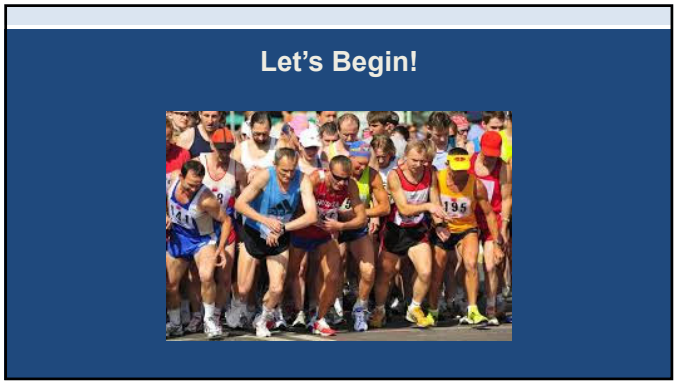

Mark LaBue
AV Director


Austin McLoughlin
ARS Director

Advice from Jack Bennett MD

01 – Introduction

Speaker: John Bennett, MD and Henry Masur, MD



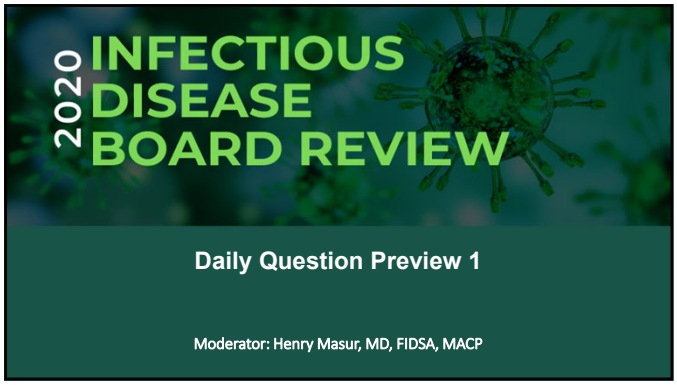
02

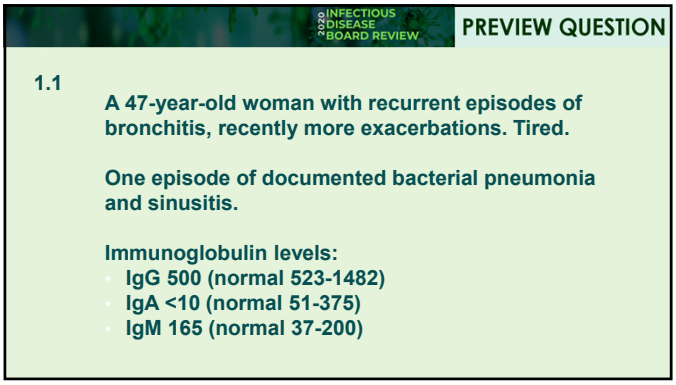
Daily Question Preview 1

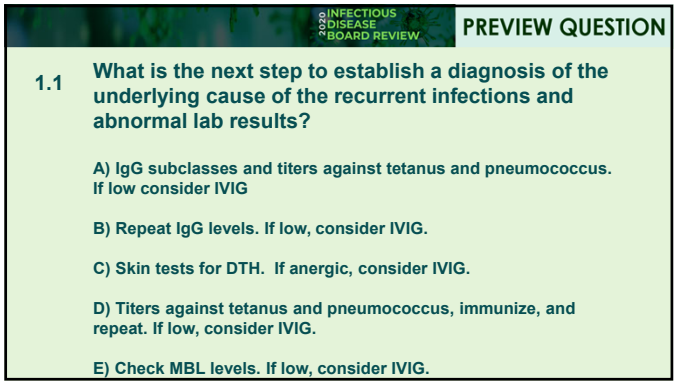
Dr. Henry Masur (Moderator)

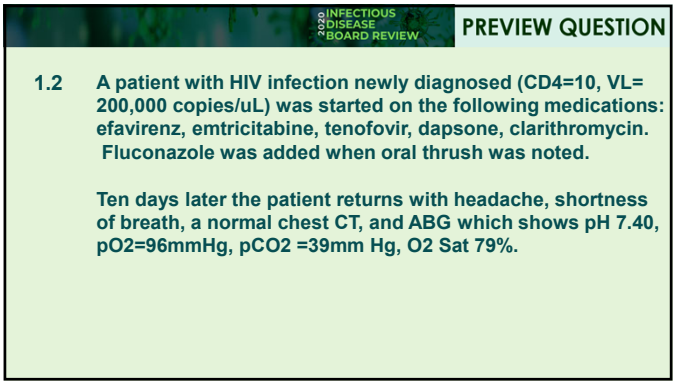
01 – Introduction

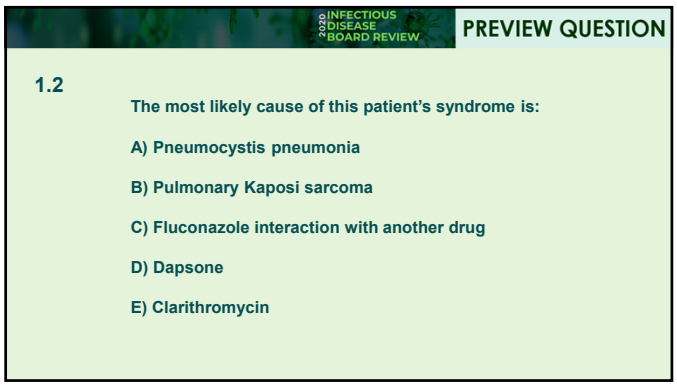
Speaker: John Bennett, MD and Henry Masur, MD

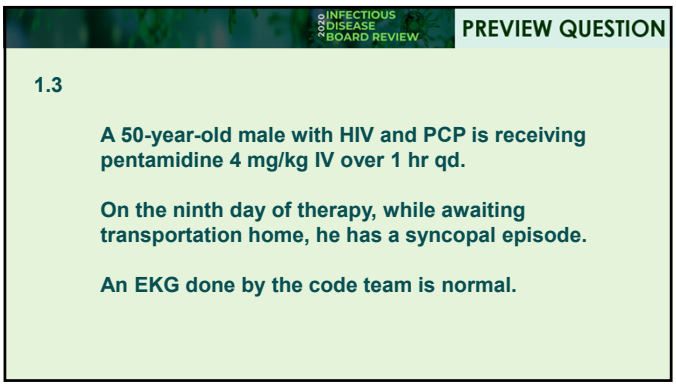












INFECTIOUS DISEASE BOARD REVIEW 2020 — PREVIEW QUESTION

1.3

What non cardiac toxicity of pentamidine would be most likely:

A) Hyponatremia

B) Seizure

C) Hypoglycemia

D) Hypertensive crisis and stroke

E) Pulmonary embolus

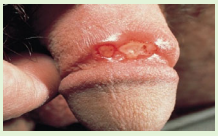
INFECTIOUS DISEASE BOARD REVIEW 2020 — PREVIEW QUESTION

1.4

An 18-year-old man presents with a history of malaise, low-grade fevers, and new-onset painful genital lesions seen in the picture below.

He had unprotected sexual intercourse with a female partner 2 weeks earlier.

Neither he nor his partner has traveled outside the United States.



INFECTIOUS DISEASE BOARD REVIEW 2020 — PREVIEW QUESTION

1.4

Which of the following diagnostic tests is most likely to yield the specific diagnosis?

A) Serum RPR

B) Serum FTA-Abs

C) Darkfield microscopy

D) Glycoprotein-G 1 serum antibodies

E) PCR on lesion swab

INFECTIOUS DISEASE BOARD REVIEW 2020 — PREVIEW QUESTION

1.5

What complication would you be most concerned about in this patient with zoster involving his ear?

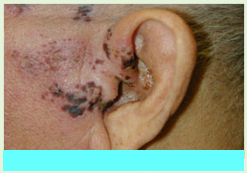
A) Facial paralysis

B) Keratitis

C) Encephalitis

D) Optic neuritis

E) Oculomotor palsies



INFECTIOUS DISEASE BOARD REVIEW 2020 — PREVIEW QUESTION

1.6

A 67-year-old woman is hospitalized with nosocomial meningitis due to MSSA.

She has a history of allergy to penicillin that is listed in the records as rash; the family recalls that she went to the ED when the rash occurred.

She is not able to corroborate history. She has not received penicillin or cephalosporin antibiotics since the rash occurred a few years ago. Two of her daughters have allergies to penicillin.

INFECTIOUS DISEASE BOARD REVIEW 2020 — PREVIEW QUESTION

1.6

You are asked about optimal antibiotic treatment. What do you advise?

A) Administer nafcillin without prior testing

B) Administer nafcillin after test dose

C) Skin test for penicillin reaction; if negative then administer nafcillin after test dose

D) Administer vancomycin

E) Desensitize to nafcillin

01 – Introduction

Speaker: John Bennett, MD and Henry Masur, MD

INFECTIOUS DISEASE BOARD REVIEW 2020

PREVIEW QUESTION

1.7

A 43-year-old man with diabetes is hospitalized with a closed tibial fracture.

Three years ago when he was being treated for a foot infection with piperacillin-tazobactam he developed a very itchy rash after several weeks of treatment.

The anesthesiologist calls to ask advice about surgical antibiotic prophylaxis prior to operative fixation.

INFECTIOUS DISEASE BOARD REVIEW 2020

PREVIEW QUESTION

1.7

What advice do you give?

A) Administer clindamycin

B) Administer cefazolin

C) Administer cefazolin after intraoperative test dose

D) Administer ceftriaxone

E) Administer vancomycin

INFECTIOUS DISEASE BOARD REVIEW 2020

PREVIEW QUESTION

1.8

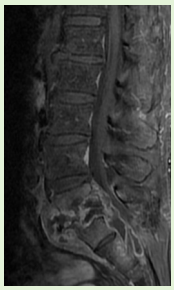
A 57-year-old male presented with a 3-month history of progressive lower back pain.

On ROS he denied fevers or chills but his wife noticed he had weight loss.
Originally the patient was from Cambodia, emigrated as a child.
He is mployed at a seafood processing plant

ESR 84 CRP 16

MRI with discitis and osteomyelitis at L5-S1

Blood cultures grew Staph epidermidis in 2 of 4 bottles



INFECTIOUS DISEASE BOARD REVIEW 2020

PREVIEW QUESTION

1.8

What is the best next step in management?

A) Repeat 2 sets of blood cultures

B) Initiate vancomycin; place PICC for six week treatment course

C) Obtain interferon gamma release assay

D) Percutaneous biopsy of disc space

E) Empiric treatment with rifampin, isoniazid, ethambutol, and pyrazinamide

INFECTIOUS DISEASE BOARD REVIEW 2020

PREVIEW QUESTION

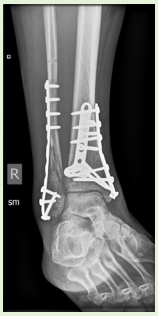
1.9

44-year-old woman, previously healthy, suffered a right ankle closed pilon fracture

- She underwent an open reduction and internal fixation

Impaired wound healing was noted
- Chronically discharging wound despite courses of cephalexin and trimethoprim-sulfamethoxazole

3 months after Open Reduction and Internal Fixation (ORIF), wound culture grows methicillin-susceptible Staph aureus



INFECTIOUS DISEASE BOARD REVIEW 2020

PREVIEW QUESTION

1.9

What are your next steps?

A) Nafcillin followed by long-term trimethoprim- sulfamethoxazole

B) Hardware removal; six weeks of oxacillin

C) Hardware removal; six weeks of oxacillin and rifampin

D) Debridement without hardware removal; six weeks of oxacillin and rifampin

E) Debridement and hardware replacement; six weeks of oxacillin and rifampin

INFECTIOUS DISEASE BOARD REVIEW 2020

PREVIEW QUESTION

1.10

A 39-year-old woman is seen on day 4 of hospitalization for high fever and leukocytosis.

The fever had been present for 3 ½ weeks and was accompanied by severe arthralgias of the knees, wrists and ankles as well as myalgias.

A severe sore throat was present during the first week of the illness.

INFECTIOUS DISEASE BOARD REVIEW 2020

PREVIEW QUESTION

1.10

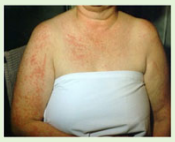
Exam: T=104.2° F.

Tonsilar swelling and erythema is present, with tender cervical LN.

Spleen tip is palpable.

The R wrist is swollen and painful.

A rash present on the trunk and extremities, most prominently under the breasts and in the area of her underwear waistband.



INFECTIOUS DISEASE BOARD REVIEW 2020

PREVIEW QUESTION

1.10 Labs:

Ferritin 3600 ng/ml (nl 40-200)
WBC 32,200 (89% neutrophils)
AST and ALT 3x normal
ESR and CRP 5x normal
ANA and RF negative
Throat and blood cultures negative

On afternoon rounds with the attending, the fever resolved with Tylenol and the rash is no longer present.

INFECTIOUS DISEASE BOARD REVIEW 2020

PREVIEW QUESTION

1.10

The most likely diagnosis is?

A) Lymphoma

B) Adult Still's Disease

C) Acute Rheumatic Fever

D) Cryoglobulinemia

E) Kikuchi's Disease

INFECTIOUS DISEASE BOARD REVIEW 2020

PREVIEW QUESTION

1.11

A 24-year-old man is referred from the ED for ulcers of the mouth and penis. Three months ago he came to the U.S. from Japan to attend graduate school.

He has a history of intermittent, painful oral ulcers for 3-4 years. Four days ago he developed a painful ulcer on the penile shaft. He recalls a similar lesion 2 months earlier. He takes no medicines and denies sexual contact for the past 5 years.

INFECTIOUS DISEASE BOARD REVIEW 2020

PREVIEW QUESTION

1.11

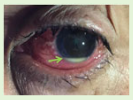
Exam: afebrile

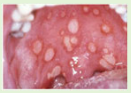
Left eye is inflamed and there is a hypopyon. Numerous ulcers on the oral mucosa.

There is a 0.5cm ulcer on the penis.

A 6mm papulo-pustular lesion is present in the right antecubital fossa; the patient says that is where they drew blood yesterday in the ED

Labs: Hb 12.1; WBC 13,750. HIV negative





01 – Introduction

Speaker: John Bennett, MD and Henry Masur, MD

INFECTIOUS DISEASE BOARD REVIEW 2020

PREVIEW QUESTION

1.11

The most likely diagnosis is?

A) Syphilis

B) Behçet's disease

C) Herpes simplex virus infection

D) Sarcoidosis

E) Cytomegalovirus infection

INFECTIOUS DISEASE BOARD REVIEW 2020

PREVIEW QUESTION

1.12

A 19-year-old recent immigrant from Iraq is hospitalized for 2 day history of fever and severe abdominal pain.

He says he has had similar episodes on at least 3 previous occasions over the past 7 years.

At the first episode he underwent appendectomy; the removed appendix was normal.
Other episodes resolved spontaneously after 2-3 days.

INFECTIOUS DISEASE BOARD REVIEW 2020

PREVIEW QUESTION

1.12

Exam:
T 102.2; pulse 114; no rash
Abdominal guarding, rebound tenderness, hypoactive bowel sounds.

Labs:

Hb 12.4; WBC 16,650; UA normal
Basic metabolic panel normal
No occult blood in stool
CT of abdomen and pelvis normal

INFECTIOUS DISEASE BOARD REVIEW 2020

PREVIEW QUESTION

1.12

The most likely diagnosis is:

A) Hereditary angioneurotic edema

B) Familial Mediterranean fever

C) Systemic lupus erythematosus

D) Crohn's disease

E) Acute intermittent porphyria

INFECTIOUS DISEASE BOARD REVIEW 2020

PREVIEW QUESTION

1.13

A 63-year-old man with no significant past medical history presents with a week of fever, rigors, and progressive dyspnea on exertion.

Exam : BP 160/40 P110 , 39.5
Rales ½ way up bilaterally
Loud diastolic decrescendo murmur, lower left sternal border
Labs and studies
WBC 23,000 90% PMNS, HCT 30. Platelets 110.
Creatinine 1.6 mg/dl

TTE 1.5 cm oscillating mass, on bicuspid AV with severe aortic regurgitation

3/3 blood cultures: Gram positive cocci in clusters.

INFECTIOUS DISEASE BOARD REVIEW 2020

PREVIEW QUESTION

1.13

What antibiotic regimen would you recommend pending further information about Gram-positive cocci?

A) Nafcillin

B) Vancomycin

C) Vancomycin + nafcillin

D) Vancomycin + gentamicin

E) Vancomycin + gentamicin + rifampin

INFECTIOUS DISEASE BOARD REVIEW 2020

PREVIEW QUESTION

1.14

A 72-year-old man type 2 diabetes mellitus, stage II chronic kidney disease (CKD), and a history of mild aortic stenosis is admitted to the hospital with fever, dysuria, and urinary frequency.

Exam: T38.9oC, Pulse 110 , BP 145/95 mm Hg.
Lungs are clear
3/6 systolic ejection murmur at the right upper sternal boarder.
Lab results
Serum glucose 340 mg/dl
Serum creatinine 1.7 mg/dl
BMP otherwise normal
UA: 3+ protein, 20-50 wbcs/high power field, 4+ glucose.

Two blood cultures and a urine culture are positive for ampicillin-susceptible Enterococcus faecalis.

INFECTIOUS DISEASE BOARD REVIEW 2020

PREVIEW QUESTION

1.14

What antibiotic regimen would you recommend for definitive therapy of this patient's infection?

A) Ampicillin for 2 weeks

B) Penicillin + gentamicin for 4 weeks

C) Ampicillin + gentamicin for 4 weeks

D) Ampicillin + ceftriaxone for 6 weeks

E) Daptomycin for 8 weeks

INFECTIOUS DISEASE BOARD REVIEW 2020

PREVIEW QUESTION

1.15

A 44-year-old man presents with a subjective fever for 3 months, diarrhea for over a year, has lost 30 pounds, and complains of intermittent arthralgias, mainly in his hands.

Exam: BP 172/52 P 92 R 24 T38C
Loud decrescendo blowing diastolic murmur at the lower left sternal border, and rales halfway up bilaterally.

Blood cultures (6 sets): negative after 21 days

Valvular tissue obtained at valve replacement reveals foamy macrophages by PAS stain.

INFECTIOUS DISEASE BOARD REVIEW 2020

PREVIEW QUESTION

1.15

Which of the following is the most likely etiologic agent?

A) A member of the HACEK group

B) Coxiella burnetii

C) Tropheryma whipplei

D) Bartonella quintana

E) Abiotrophia defectiva

INFECTIOUS DISEASE BOARD REVIEW 2020

PREVIEW QUESTION

1.16

On day 9 of nafcillin therapy for complicated methicillin-sensitive S. aureus bacteremia a patient has developed new neutropenia (1,000 neutrophils).

MICs (µg/ml) of the blood isolate are:
penicillin 0.12 (S),
cefazolin 0.5 (S)
vancomycin 1 (S)
daptomycin 0.5 (S)
ceftaroline 0.5 (S)

INFECTIOUS DISEASE BOARD REVIEW 2020

PREVIEW QUESTION

1.16

Which one of the alternative agents would you recommend?

A) Penicillin
B) Cefazolin
C) Vancomycin
D) Daptomycin

PREVIEW QUESTION

1.17

36-year-old female injection drug user with R hip pain, decreased ROM 2/2 pain; 2/2 blood cultures + for MSSA; CXR, right hip x-ray, CT abdomen and pelvis, MRI, TTE all normal.

She was treated with empirical vancomycin, blood cultures sterile after 1 day of therapy, now on day 5 of nafcillin.

Pain much improved on day 7, but she still uses a cane for ambulation.

PREVIEW QUESTION

1.17

Which one of the following antibiotics would you recommend for a 6 week course?

A) Dalbavancin

B) Ceftriaxone

C) Vancomycin

D) Cefazolin

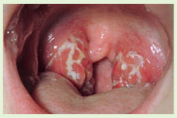
PREVIEW QUESTION

1.18

38-year-old healthy female with 1 day of sore throat and fever.

Childhood history of anaphylaxis to penicillin.

Physical exam
T=102.3
HEENT-tonsillar purulence
Neck-Tender bilateral anterior LAN



Labs:
Rapid strep antigen diagnostic test negative

PREVIEW QUESTION

1.18

What is the most appropriate antimicrobial treatment?

A) Cephalexin

B) None

C) Doxycycline

D) Clindamycin

E) Levofloxacin

PREVIEW QUESTION

1.19

A 42-year-old, previously healthy woman is seen for a bad "sore throat" that began 4 days earlier while attending her sister's wedding in southern Ukraine.

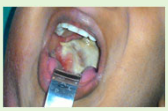
She complains of malaise, odynophagia, and low grade fever.

Today, she noted a choking sensation, prompting medical evaluation.

PREVIEW QUESTION

1.19

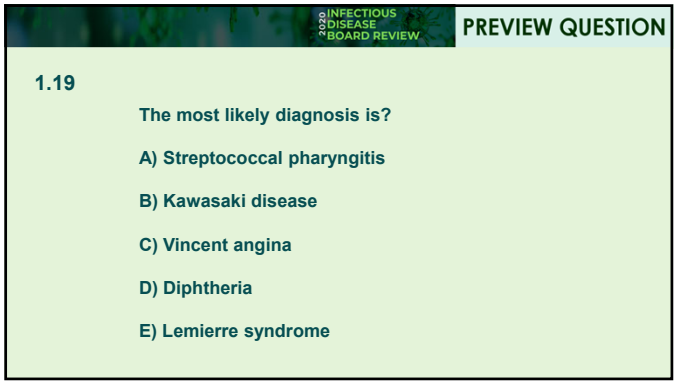
T 100.2F; P 126; BP 118/74.
HEENT: Submandibular swelling
Gray exudate coating posterior pharynx.
An S3 gallop is heard.



CBC is normal.
EKG shows: 1st degree AV nodal block, prolongation, and ST-T wave changes.

01 – Introduction

Speaker: John Bennett, MD and Henry Masur, MD



03

Clinical Immunology and Host Defense

Dr. Steven Holland

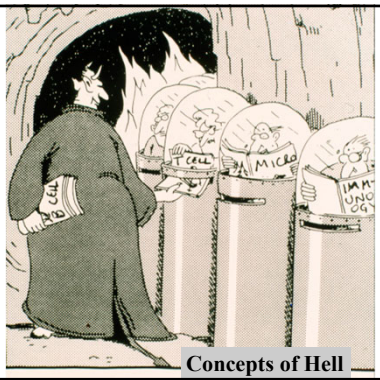
2020 INFECTIOUS DISEASE BOARD REVIEW

Host Defense: Where the Rubber of Immunology Hits the Road of Life

Steven M. Holland, MD
Laboratory of Clinical Immunology and Microbiology
NIAID, NIH

Disclosures of Financial Relationships with Relevant Commercial Interests

- None



Concepts of Hell

Host Immune Defense

Humoral
- Complement
- Mannose binding lectin
- Antibody

Cellular
- Neutrophils
- Monocytes
- Lymphocytes (NK, T, B)
- Other (erythrocytes, platelets)

Basic Principles

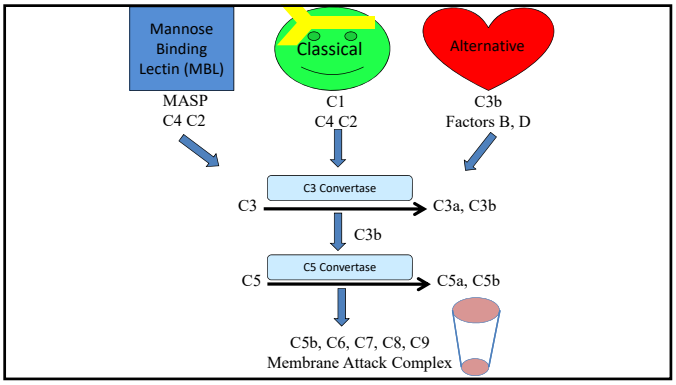
Patients with impaired inflammation:
- may be unable to tell you they are sick (feel fine)
- are often sicker than they look
- often have more extensive disease than is apparent
- may require longer treatment than normals
- may have unusual infections

Who's Got a Problem?

Abnormal frequency of infections
- recurrent *Neisseria* bacteremia
- recurrent pneumonia

Abnormal presentation of infections
- necrotic cutaneous ulcers (not anthrax)
- *Aspergillus* pneumonia

Specific unusual infections
- *Pneumocystis jiroveci*
- *Burkholderia cepacia*
- *Nontuberculous mycobacteria*



Complement Deficiencies

Classical Pathway (C1-C9) (AR)
- Antibody *de*pendent bacterial lysis
- Deficiency leads to recurrent bacteremia and meningitis

Alternative Pathway (Factors I, H, Properdin, C3) (Properdin X-linked, others AR)
- Antibody *in*dependent bacterial lysis
- More severe than classical defects

Mannose Binding Lectin (MBL) Pathway
- Very modest IF ANY defect, mild effect in infancy

Complement Defects

C5-C9 Defects
- recurrent *Neisseria* bacteremia and meningitis
- average age of onset 17 y, milder CNS sequelae
- high rates of relapse and reinfection

C1-C4 Defects
- Autoimmune disease (SLE, DLE) more common

Dx- CH_{50} (Classical), AH_{50} (Alternative)

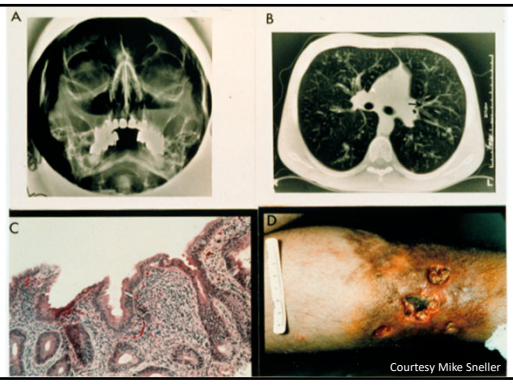
Rx- treat infections, prophylaxis if needed, hypervaccination?

Antibody Deficiencies

IgA Deficiency (AR)
- common (1/700 adults)
- probably not a pathologic condition *per se*
- frequently associated with other deficits, such as common variable immunodeficiency (CVID), Ig subclass deficiencies

Dx- low IgA

Rx- none



Common Variable Immunodeficiency (CVID)

- recurrent sino-pulmonary bacterial infections
- chronic enteric infections with *G. lamblia, Campylobacter, Salmonella, Shigella*
- severe echoviral meningitis/encephalitis/myositis

Dx- ↓ IgG (total and subclasses 1,3 or 2,4), IgA, IgM, isohemagglutinins, DTH, response to new or recall immunization
↑ autoimmunity and cancer

Rx- treat infections, Ig replacement

47 year old woman

Recurrent episodes of bronchitis, recently more exacerbations. Tired.

One episode of documented bacterial pneumonia and sinusitis.

Immunoglobulin levels:

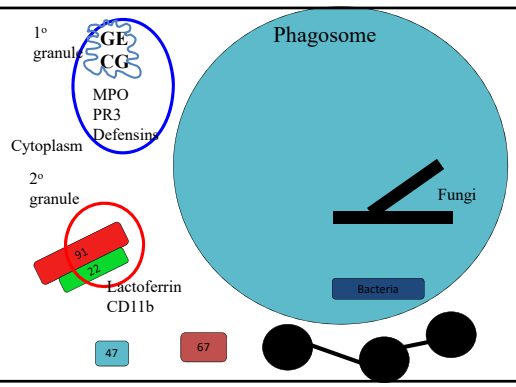
IgG 500 (normal 523-1482)

IgA <10 (normal 51-375)

IgM 165 (normal 37-200)

Next step?

a) IgG subclasses and titers against tetanus and pneumococcus. If low consider IVIG
b) Repeat IgG levels. If low, consider IVIG.
c) Skin tests for DTH. If anergic, consider IVIG.
d) Titers against tetanus and pneumococcus, immunize, and repeat. If low, consider IVIG.
e) Check MBL levels. If low, consider IVIG.



52 year old man

referred from his Family Practitioner.

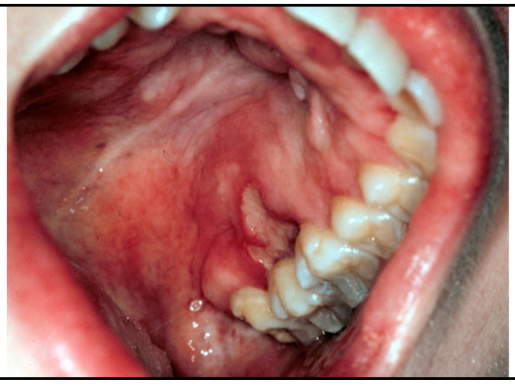
Recurrent digital and oral ulcers occurring every month or so for the last 4 months.

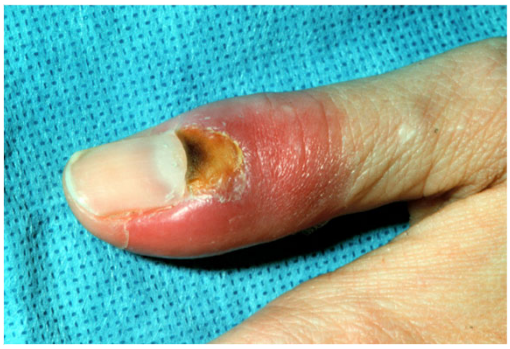
One CBC showed an ANC of 100, but on repeat several days later was normal.

Previous health good.

Took "some antibiotic for a cold a few months ago".

Spleen tip felt.





Cyclic or Acute Neutropenia

-drug induced (chemoRx, sulfa, nucleosides, clozapine)

-hereditary **cyclic** and chronic neutropenia (AD) due to neutrophil elastase (ELA2) mutations. Childhood.

- digital, oral, perineal infections, usually self-healing with recovery of counts, bacteremia uncommon
- relatively low baseline PMN count with valleys of profound neutropenia, about every 3-4 weeks

Dx- molecular; demonstration of periodicity, family history.

Rx- G-CSF lifts both nadir and baseline

Acquired Neutropenia in Adults

-Drugs, lupus, etc.

-acquired cyclic neutropenia

(Large Granular Lymphocytosis, LGL)

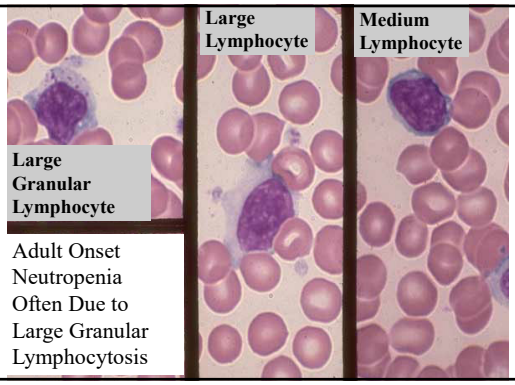
splenomegaly, often associated with rheumatoid arthritis (Felty Syndrome)

Dx- clonal CD3+/8+/57+ lymphs (LGL)

(Gain of Function mutations in STAT3)

Rx- treatment of the abnormal clone is curative (cyclosporine, MTX, steroids)

G-CSF may lift both nadir and baseline



Adult Onset Neutropenia Often Due to Large Granular Lymphocytosis

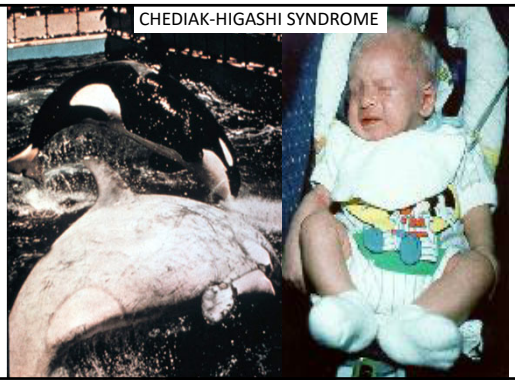
Myeloperoxidase (MPO) deficiency (AR)

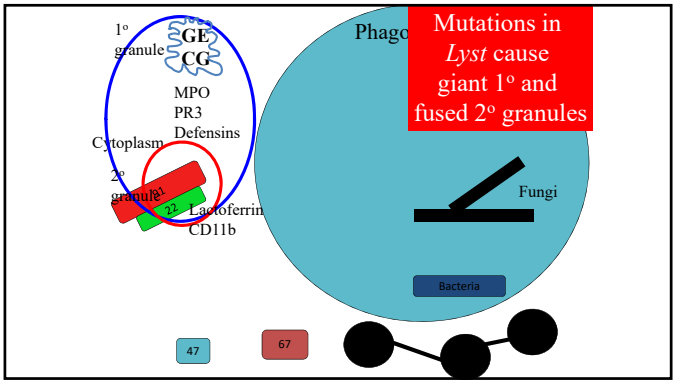
most common neutrophil disorder (1/2000)

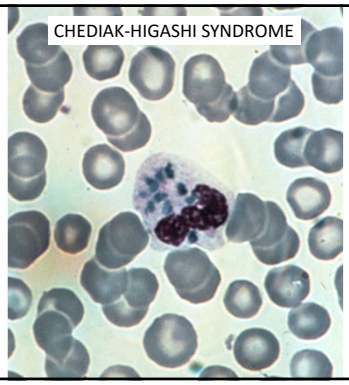
- not a pathologic condition *per se*
- failure of H_2O_2 -----MPO-----> HOCl
- compensated by increased H_2O_2 production
- appears to need another condition to potentiate, such as diabetes mellitus

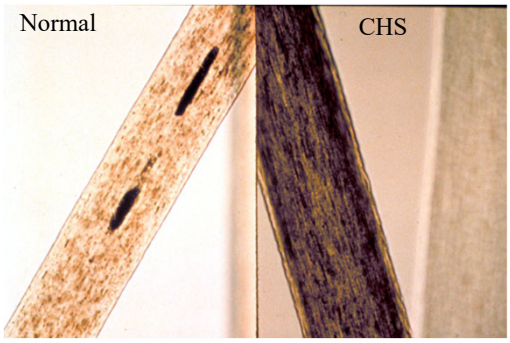
Dx- absence of peroxidase positive granules due to mutations in *MPO* gene

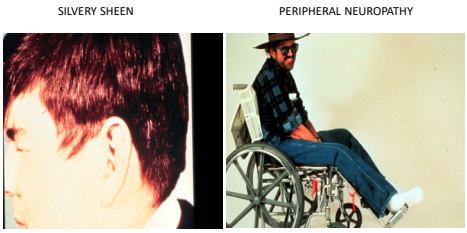
Rx- treat invasive infections (*Candida*), no specific therapy











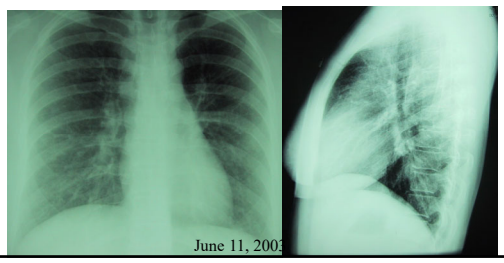
Chediak-Higashi Syndrome (AR)

recurrent cutaneous, sino-pulmonary infections
  GNR, staph, strep, no fungi
  mild neutropenia (intramedullary destruction)
partial oculocutaneous albinism,
mental retardation, neuropathy (late),
lymphoma or HLH-like "accelerated phase" (late)

Dx- giant blue granules; killing and chemotactic defects due to mutations in *CHS1*, encodes LYST
Rx- prophylaxis, treatment of infections, BMT

23 yo woman; athletic coach

Previously healthy; short of breath 4 hours after 3 mile run



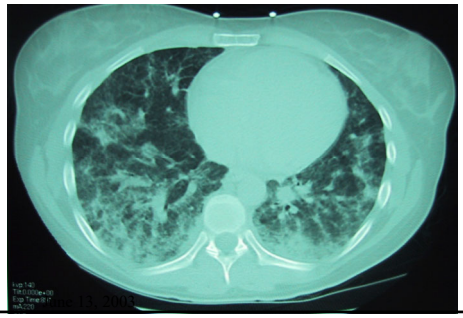
ER presentation

Recent weekend with friends in NYC
Anxious, chest pressure, febrile
acute mononucleosis?

PMH
Respiratory infections in infancy
Cat scratch disease 8 yo: resolved with antibiotics

Family History
1 brother with two episodes Cat scratch cervical nodes
2 sibs well

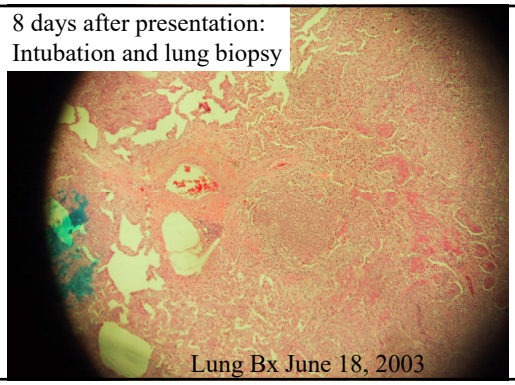
2 days later, hypoxia and fever



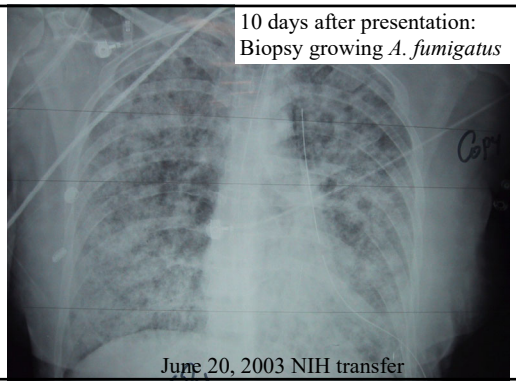
Hospital Course

- Progressive dyspnea, fever, leukocytosis
- Refractory to antibiotics and steroids
- Bronchoscopy uninformative
- Visually Assisted Thoracoscopic Surgery (VATS)
  necrotizing granulomata and hyphae

8 days after presentation:
Intubation and lung biopsy



10 days after presentation:
Biopsy growing *A. fumigatus*



Differential Diagnosis?

Invasive aspergillosis in an <u>otherwise normal host</u>

a) Allergic bronchopulmonary aspergillosis

b) Cystic fibrosis

c) Lymphocyte dysfunction (SCID)

d) Phagocyte defect

e) Acute HIV

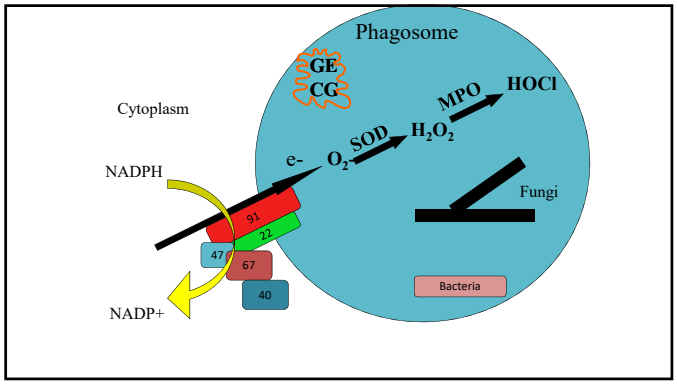
What is so special about phagocytes?

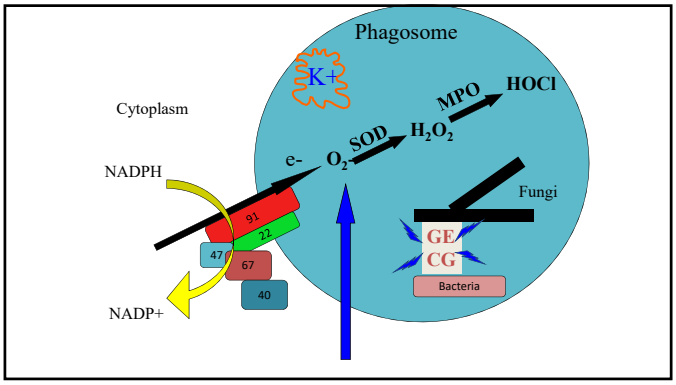
neutrophils, monocytes, macrophages, eosinophils, basophils

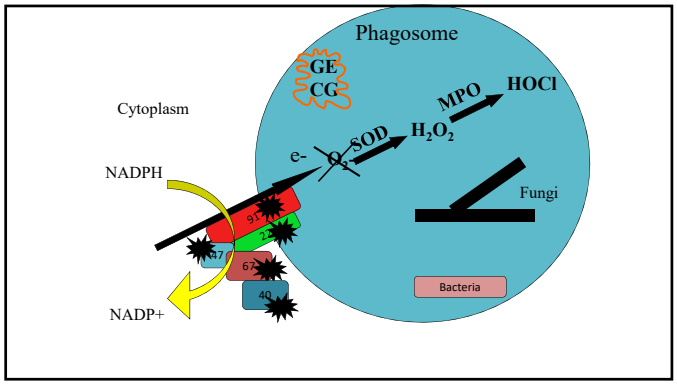
Preformed cytoplasmic granules with stored enzymes

Normal humans make how many neutrophils/d?
10^{11}

Half life of neutrophils in the circulation?
7 hours







Chronic Granulomatous Disease
(X, AR)

frequency 1/100,000 - 1/200,000 live births
- presentation usually in childhood, but more adult cases being recognized

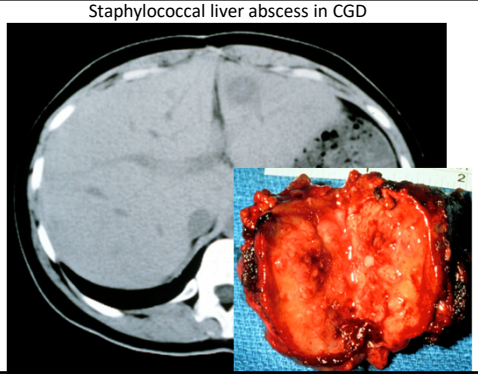
recurrent life-threatening infections
- catalase-positive bacteria, fungi
- tissue granuloma formation
  - **infections**: lung, liver, lymph nodes, skin, bone
  - **Bacteremia:** uncommon but bad

Infections in CGD

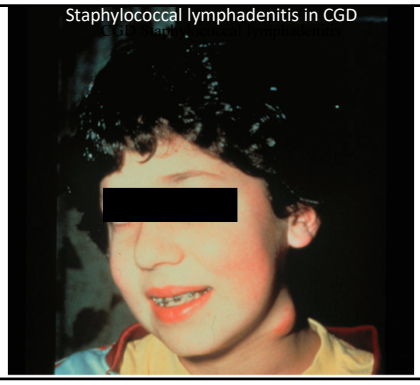
S. aureus	(liver, lymph nodes, osteo)
S. marsescens	(skin, lung, lymph nodes)
B. cepacia	(pneumonia, bacteremia)
Nocardia spp.	(pneumonia, brain, liver)
Aspergillus spp.	(lung, esp. miliary, spine)
Salmonella	(enteric, bacteremia)
BCG	(local/regional infections)

Chromobacterium violaceum *(warm brackish water, soil, e.g., Disney World)*
Francisella philomiragia *(brackish water, Chesapeake Bay, Sounds)*
Burkholderia gladioli *(causes onion rot)*
Granulibacter bethesdensis *(necrotizing LN, hard to grow, likes CYE)*
Paecilomyces spp.

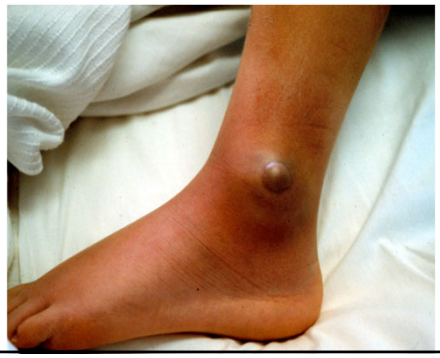
Staphylococcal liver abscess in CGD



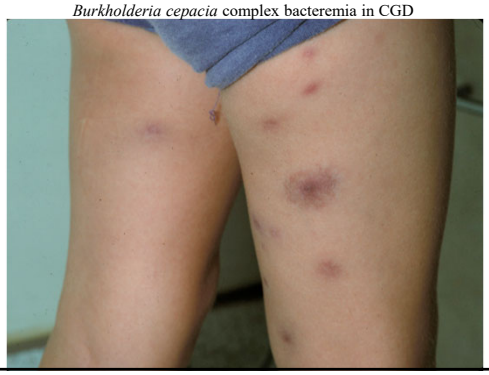
Staphylococcal lymphadenitis in CGD



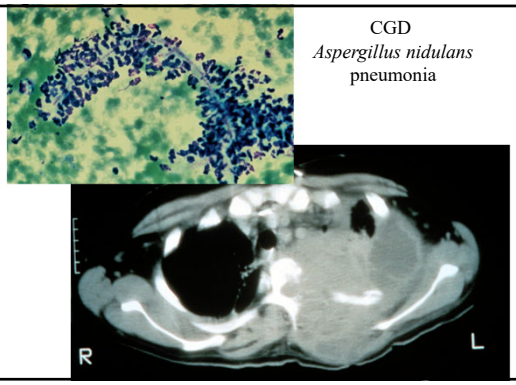
Staph aureus osteomyelitis in CGD



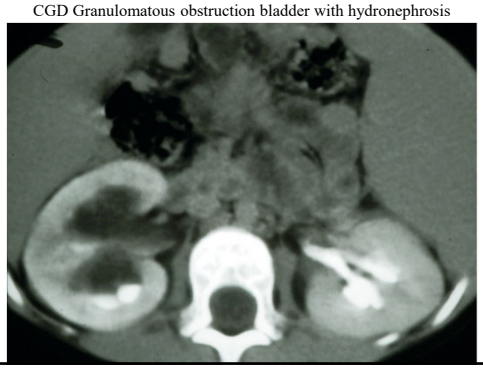
Burkholderia cepacia complex bacteremia in CGD



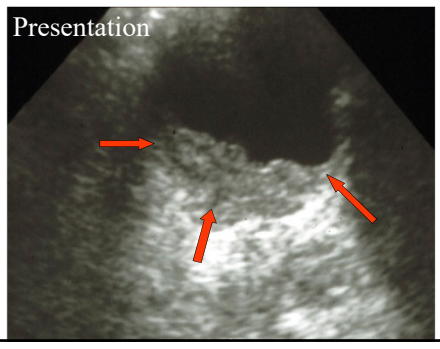
CGD
Aspergillus nidulans
pneumonia

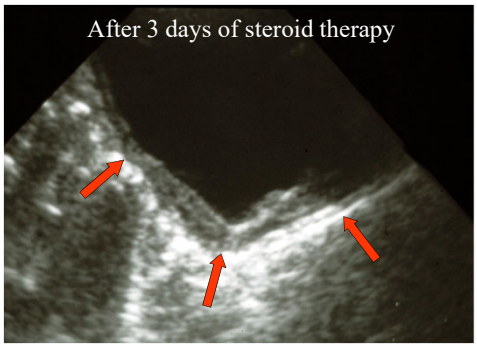


CGD Granulomatous obstruction bladder with hydronephrosis

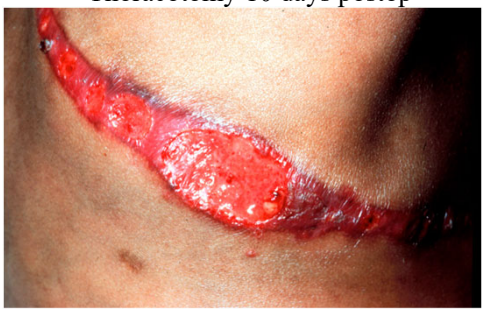


CGD Granulomatous cystitis

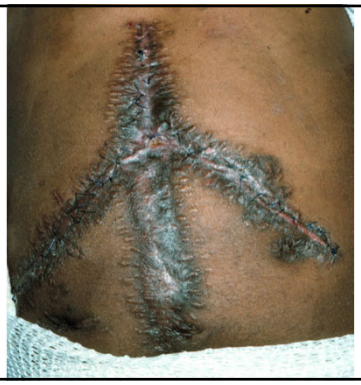




Thoracotomy 10 days postop

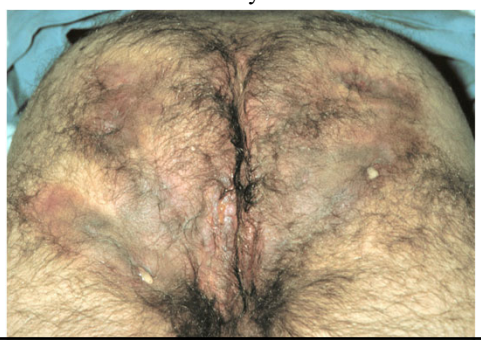


CGD granulomatous wound dehiscence



CGD granulomatous esophageal obstruction

CGD Inflammatory Bowel Disease



Chronic Granulomatous Disease

frequency 1/100,000 - 1/200,000
- presentation usually in childhood, but more adult cases being recognized

failure to produce superoxide and its metabolites

Dx- PMN <u>dihydrorhodamine 123 oxidation (DHR),</u>
PMN nitroblue tetrazolium reduction (NBT)
(MPO Deficiency gives a FALSE ABNORMAL DHR)
BE CAREFUL ABOUT THE LAB!!!!

CGD Genetics

X-linked, chr. Xp21 (70% of cases)
- carrier females are mosaic (Lyonization)
- 1/2 of offspring of carrier Mom will receive the gene
  - about 1/3 of carriers are sporadic, from sperm
- X-linked male: all daughters carriers, no sons affected

autosomal recessive (30% of cases)
- 1/2000 carry the gene for the most common AR form
  - bad luck happens

CGD Management and Treatment

90% overall long-term survival

follow ESR, radiographs

prophylactic antibiotics and antifungals

TMP/SMX, itraconazole

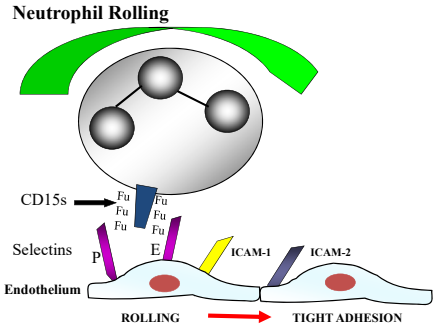
prophylactic interferon gamma

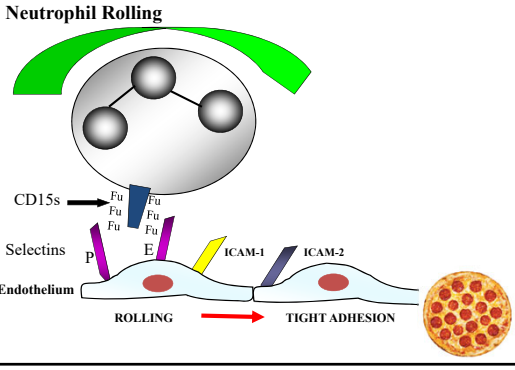
50 µg/m2 subcutaneously three times weekly

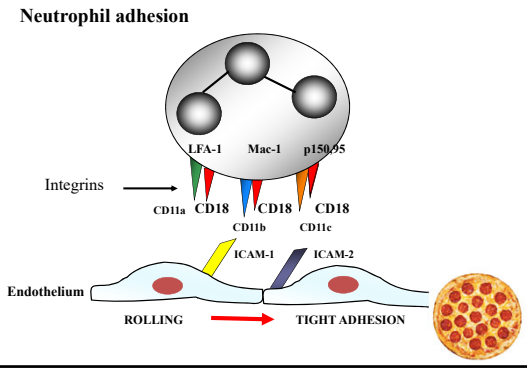
aggressive search for and treatment of infections

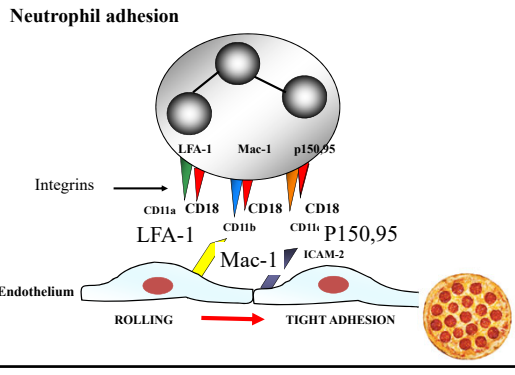
BMT

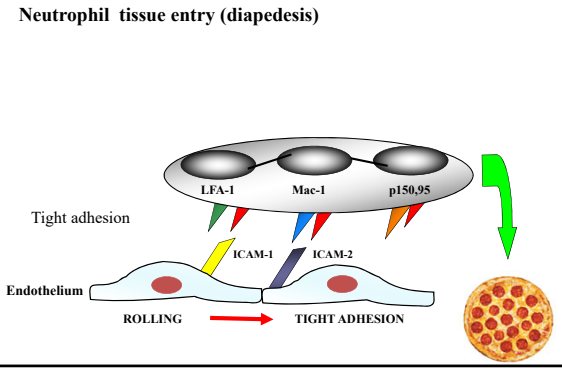
(gene therapy)

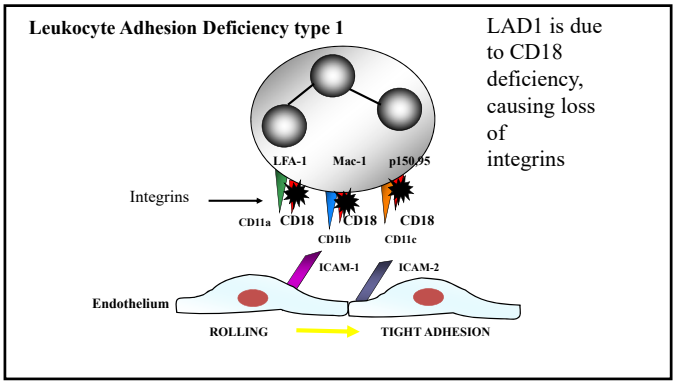












Leukocyte Adhesion Deficiency Type 1 (AR)

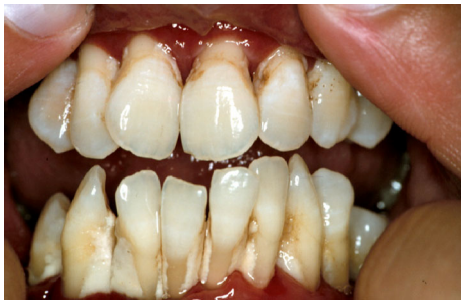
Recurrent necrotizing infections: skin, perineum, lung, gut

Enteric GNR, GPC, NOT fungi or *Candida*

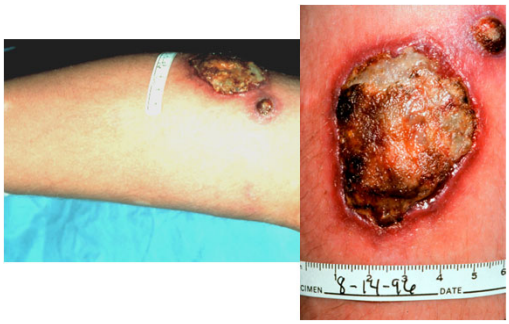
baseline leukocytosis, further WBC increase to infection

rare, consanguinity common

Almost universal tooth loss in LAD1 by adulthood



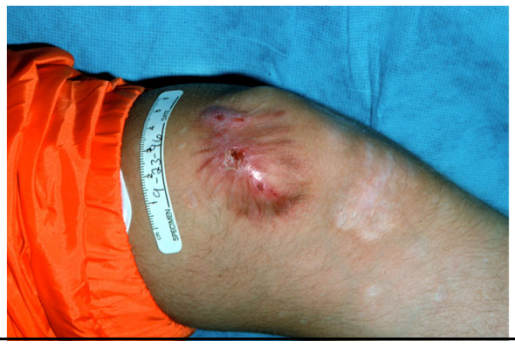
Impaired wound healing in LAD1

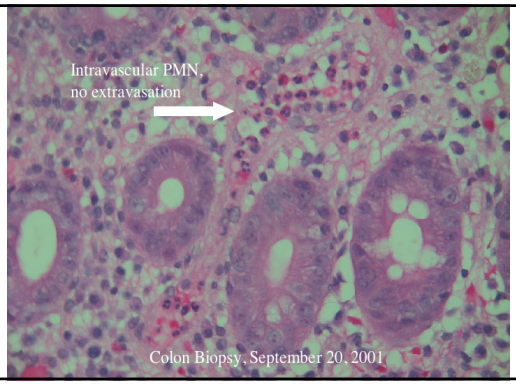


Leukocyte Adhesion Deficiency I

Delayed umbilical stump separation
dystrophic, "cigarette paper" scars
gingivitis with tooth loss, alveolar ridge resorption
Biopsies: no neutrophils at sites of infection,
rare monocytes and eosinophils
Severe and moderate forms of disease

Cigarette paper scarring





Leukocyte Adhesion Deficiency 1

Mutations in CD18, obligatory chain of integrins
Binds to intercellular adhesion molecules (ICAMs)
also serve as receptors for C3bi

Dx- FACS for CD18,
Complement dependent opsonization
Rx- treatment of infections, BMT

19 year old boy with Pneumonia

Admission WBC 43,000, looked OK.
Ceftriaxone, good response.
Medical student: WBC never <11,000/mcl
Left shin ulcer not inflamed
Not healed in > 2 mos
She raises the possibility of
Leukocyte Adhesion Deficiency (LAD1)

Ruling against LAD1 would be:

a) Gingivitis, tooth loss, and alveolar ridge resorption.

b) FACS showing 5% of normal expression of CD18 and CD11a-c on granulocytes.

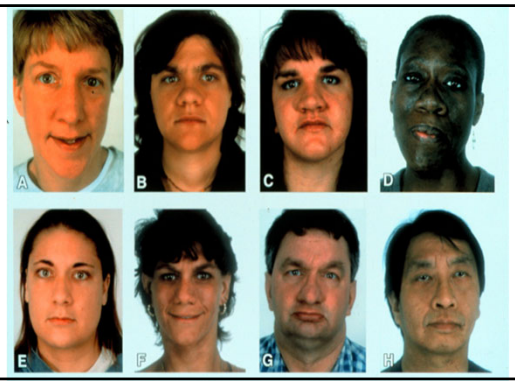
c) He is the product of a first cousin union.

d) Extensive neutrophil infiltration in the left shin ulcer.

e) Multiple dystrophic scars over the legs from previous ulcers

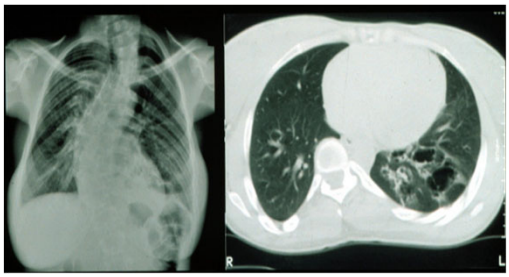
27 year old woman with boils

Referred from her internist for recurrent boils with *S. aureus*
IgE of 12,376 IU.
"Bronchitis and sinusitis at least once a year"
Persistent eczema requiring topical steroids.
Never hospitalized but having "more trouble" lately.



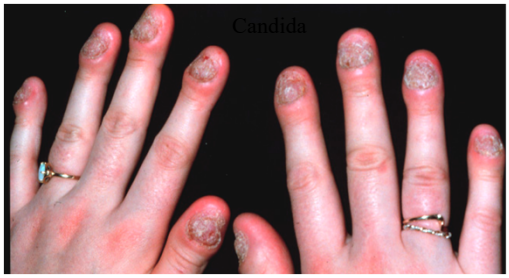
HIE (Job's) Syndrome History and Exam

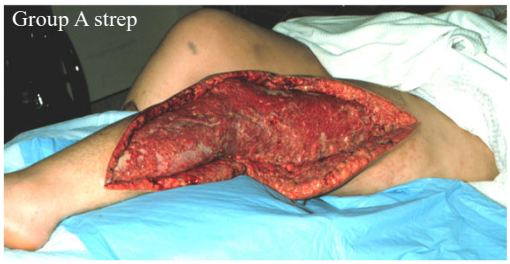
Eczema	100%
Facies	100% (≥16y)
Boils	87%
Pneumonia	87%
Mucocutaneous Candidiasis	83%
Pulmonary Cysts	77%
Scoliosis	76% (≥ 16y)
Delayed dental deciduation	72%
Coronary artery aneurysms	65%
Pathologic fractures	57%

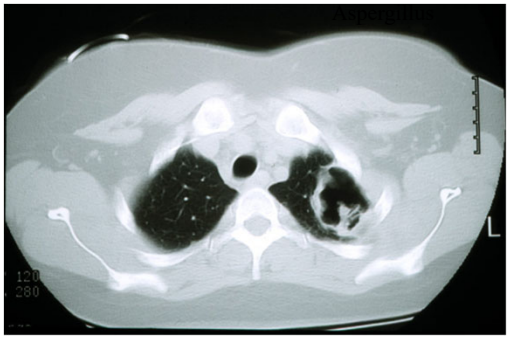


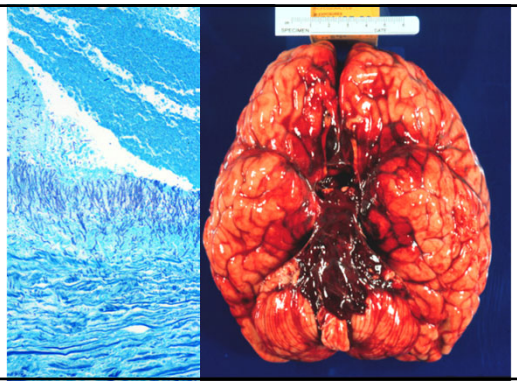
Pulmonary Pathogens in HIE

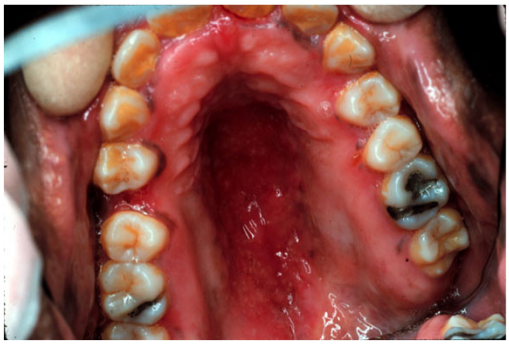
Primary pathogens:
Staphylococcus aureus
Streptococcus pneumoniae
Hemophilus influenzae
Secondary pathogens:
Pseudomonas aeruginosa
Aspergillus fumigatus
Others:
Pneumocystis jiroveci, M. avium complex

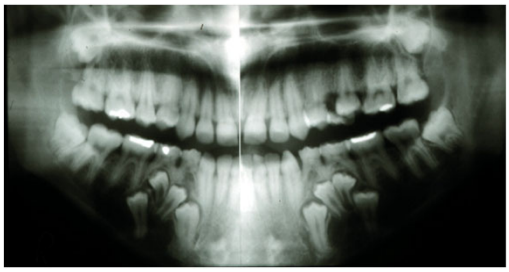








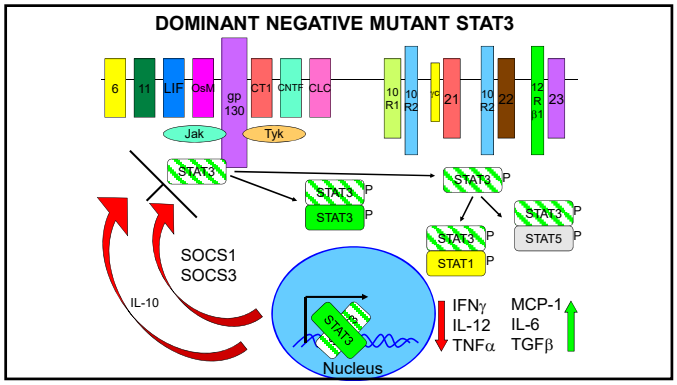




HIE Laboratory Findings

Hyper IgE	97% >2000 IU/ml
Eosinophilia	93% >2SD above mean

No correlation between IgE and eosinophilia
IgE values declined into the normal range in 17%



Hyper IgE Recurrent Infection (Job's)

recurrent sinopulmonary infections *S. aureus, S. pneumo, H. flu*
post-infectious pulmonary cyst formation
recurrent *S. aureus* skin abscesses
characteristic facies, eczema, scoliosis, fractures
very elevated IgE (>2000 IU), eosinophilia

DDx- atopic dermatitis is a close mimic
HIE: onset of rash near birth, pneumonia, lung cysts, skeletal
Mutations in STAT3
Rx- treatment of infections, prophylactic antibiotics, antifungals.
BMT

DOCK8 Deficiency

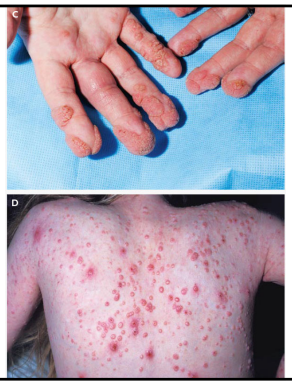
Autosomal Recessive
Eczema, allergies, asthma, high IgE
Staph, Strep, H. flu, Acinetobacter, Pseudomonas

Candida, Cryptococcus, Histoplasma

HPV, HSV, molluscum

Squamous cell carcinomas, lymphoma

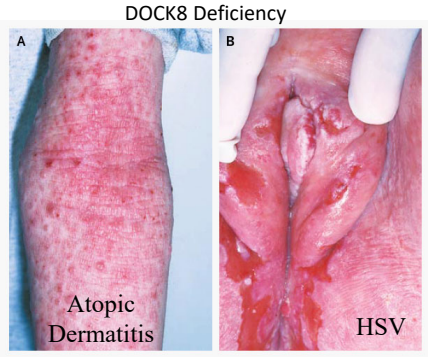
DOCK8 Deficiency



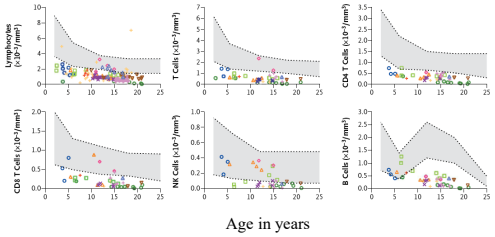
HPV

Molluscum contagiosum

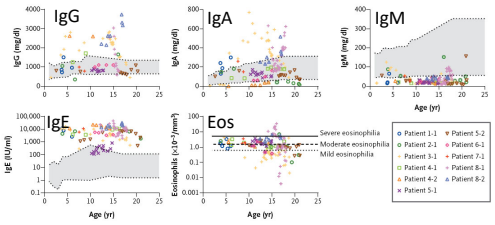
DOCK8 Deficiency



DOCK8: Lymphopenia is common and somewhat progressive



DOCK8: IgE and eosinophils are high, IgM is low



DOCK8 vs. STAT3 Hyper IgEs

	DOCK8 (Recessive)	STAT3 (Dominant)
Pneumonia	+	+++
Pneumatoceles	-	+++
Retained teeth	-	+++
Fractures	-	+++
Viral infections	+++	-
Fungal infections	+	++
Allergies	+++	-
IgM	low	normal
eosinophils	+ to +++	+

15 year old girl with recurrent infections

Infancy: eczema, recurrent pneumonias, skin infections

IgE 14,574 IU/ml

Allergist: use bed covers to avoid dust mites.

Going over the allotted 15 minutes you elicit points trying to establish whether she has hyper-IgE recurrent infection syndrome (Job's).

Which one of the following is not supportive of the diagnosis of Job's:

a) Pneumatoceles
b) Scoliosis
c) Severe warts
d) Retained baby teeth
e) Recurrent fractures

18 year old male with lymph node

Referred from hematologist/oncologist
nodes biopsied for Hodgkin showed granulomata and grew *M. avium.*

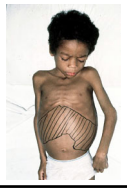
PMH recurrent salmonellosis as a child.

Sibling had tuberculosis but is now cured.

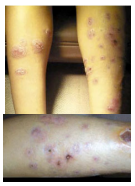
CD4+ number is normal, HIV -

Clinical Spectrum of NTM Infections

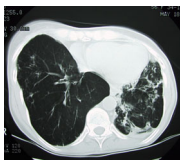
Disseminated
Severe, Young
IFNγ/IL-12 defects
NEMO, STAT1

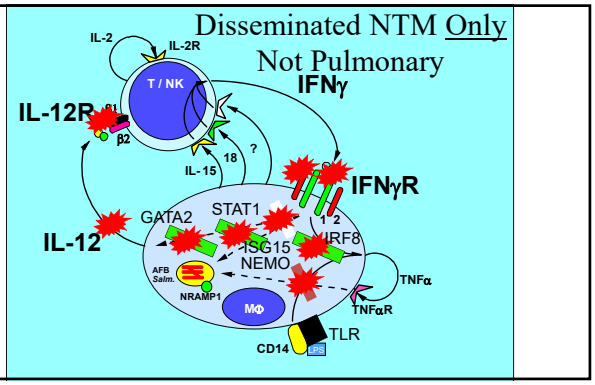


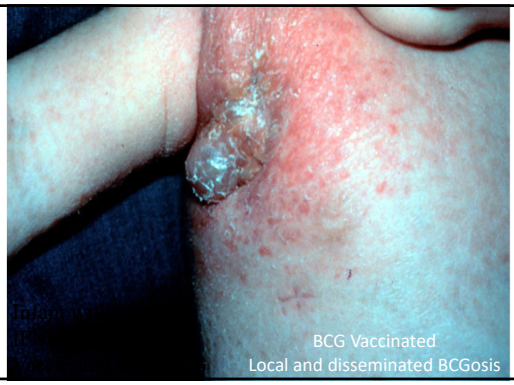
Skin
Exposure
Inoculation

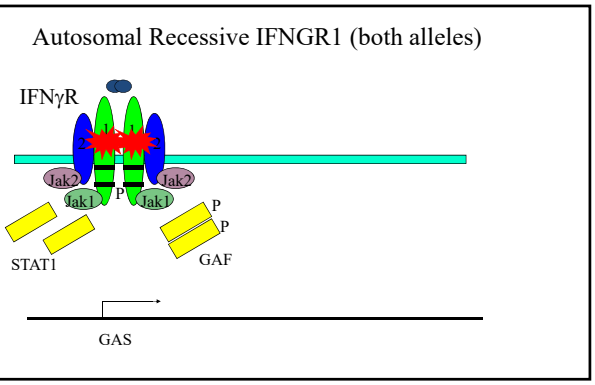


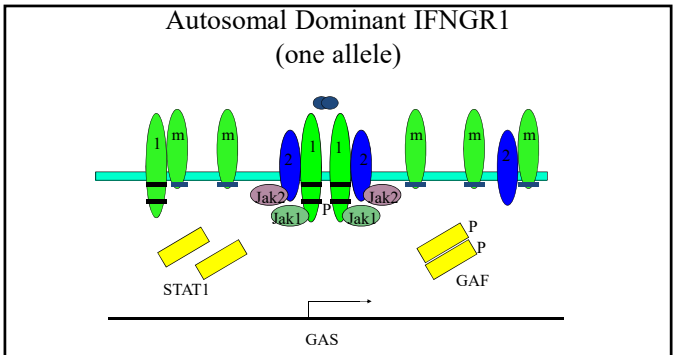
Pulmonary
Chronic, Older
Bronchiectasis
Cystic fibrosis (CF)
Ciliary dyskinesia (PCD)

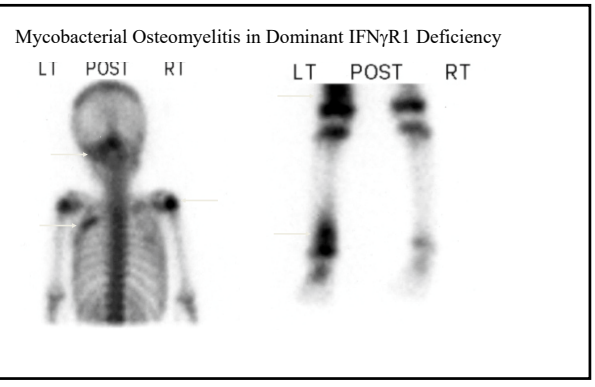












IFNGR1: Dominant vs. Recessive

Characteristic	AD	AR
IFNγR1 display	high	none
IFNγ responsiveness	low	none
Clinical presentation	local	disseminated
Granulomata	present	absent
Osteomyelitis	100%	rare
Survival	excellent	most die

Pathogens in human IFNγR deficiencies

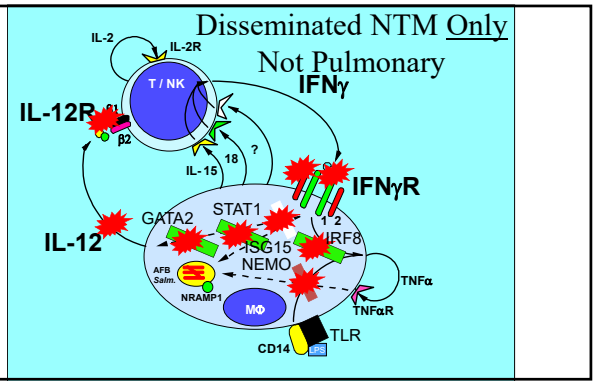
M. avium	*Salmonella*
M. intracellulare	*Listeria*
M. chelonae	
M. abscessus	CMV
M. smegmatis	HSV
M. fortuitum	VZV
M. tuberculosis	RSV
Bacille Calmette Guerin	HHV-8

Coccidioides
Histoplasma

Interferon γ Receptor Deficiencies

Absent or defective IFNγR1
- MAC and other NTM, *Salmonella*, TB, viruses
- complete defects present in childhood
- partial defects present later in life
- may be misdiagnosed as malignancy!
- NOT a cause of isolated lung disease in adults

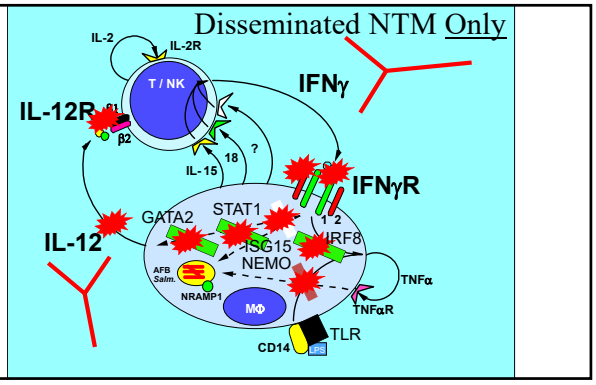
Dx- genetics, flow cytometry for IFNγR1
Rx- antimycobacterials (BMT for recessive)



IL-12βR1 Deficiency

Similar to IFNγR defects
- disease is usually milder and later onset
- residual IFNγ production
- similar pathogens-NTM, TB, *Salmonella, cocci*

Dx- genetics, flow cytometry
Rx- antimycobacterials, IFNγ systemically



Anti-IFNγ autoantibody syndrome

Disseminated NTM later in life
Predominantly female, mostly East Asian
NTM, TB

Dx- autoantibody detection
Rx- antimycobacterials, possibly rituximab

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Adult-Onset Immunodeficiency in Thailand and Taiwan

Sarah K. Browne, M.D., Peter D. Burbelo, Ph.D., Ploenchan Chetchotisakd, M.D., Yupin Suputtamongkol, M.D., Sasisopin Kiertiburanakul, M.D., Pamela A. Shaw, Ph.D., Jennifer L. Kirk, B.A., Kamonwan Jutivorakool, M.D., Rifat Zaman, B.S., Li Ding, M.D., Amy P. Hsu, B.A., Smita Y. Patel, M.D., Kenneth N. Olivier, M.D., Viraphong Lulitanond, Ph.D., Piroon Mootsikapun, M.D., Siriluck Anunnatsiri, M.D., Nasikarn Angkasekwinai, M.D., Boonmee Sathapatayavongs, M.D., Po-Ren Hsueh, M.D., Chi-Chang Shieh, M.D., Ph.D., Margaret R. Brown, B.S., Wanna Thongnoppakhun, Ph.D., Reginald Claypool, R.N., Elizabeth P. Sampaio, M.D., Ph.D., Charin Thepthai, M.Sc., Duangdao Waywa, M.Sc., Camilla Dacombe, R.N., Yona Reizes, R.N., Adrian M. Zelazny, Ph.D., Paul Saleeb, M.D., Lindsey B. Rosen, B.S., Allen Mo, B.S., Michael Iadarola, Ph.D., and Steven M. Holland, M.D.

NEJM 2012;367:725

20 yo with back pain

WBC 12,000/µl, ESR 93 mm/hr, PPD12 mm
2 weeks pain over L2 and a lytic lesion
Biopsy: histiocytic malignancy, chemotherapy started
Father had similar illness, turned out to be MAC

You suspect that she has the autosomal dominant form of IFNγR1 deficiency and you need to prove it before radiation starts.

To confirm the diagnosis, you should:

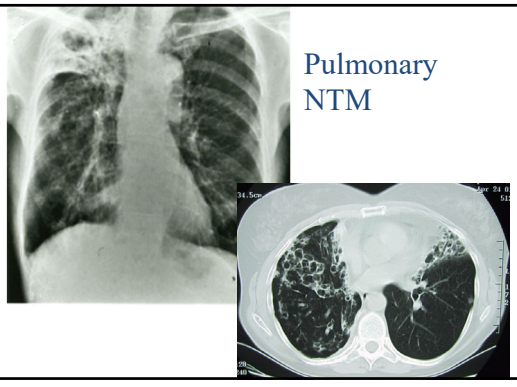
a) Show high TNFα from stimulated cells
b) Show high IL-12 from stimulated cells
c) Show high IFNγR1 on cell surfaces
d) Show high TNFαR on cell surfaces
e) Show low IFNγR1 on cell surfaces

GATA2 Deficiency

Adolescent to adult onset
- HPV (hands, genitals, cervical, vulvar)
- disseminated NTM (mediastinal *M. kansasii*)
- pancytopenia

Labs: profound monocytopenia, low B, low NK
CT: subpleural blebs
Autosomal dominant
Dx: genetic, hypocellular marrow
Rx: antibiotics, BMT

Spinner et al. Blood 2014; 123:809-21



Pulmonary NTM

Pulmonary NTM: Adults

Female predominance
Caucasian predominance
Post menopausal
"Lady Windermere Syndrome"
tall, thin, pectus abnormalities
Association with CFTR mutations
Complex immunologic and somatic genetics

Szymanski Am J Respir Crit Care Med. 2015

Remember

Disseminated NTM means immunodeficiency

Corollary: Isolated Pulmonary NTM Does not

CD4+ T-lymphocytopenia

HIV associated

autoimmune associated

idiopathic CD4+ T-lymphocytopenia (ICL)

- ≤ 300 CD4+/μl
- associated with AIDS-like infections (crypto, PCP, MAC)
  - exclude HIV infection (PCR, bDNA, p24, culture)
  - often older onset than HIV associated OI

Dx- determination of ICL (FACS)

Often due to an underlying defect, so LOOK

Rx- treat infections (follow CD4+, ?cytokines)

Screening Laboratories

For Lymphocytes

- Ig levels
- immunization status (tetanus, pneumovax)
- CD4+ number
- Genetics (exome studies, panels)

Screening Laboratories

phagocytes

- DHR for superoxide
- FACS (CD18, CD11a-c, IFNγR1, IL-12Rβ1)

complement

- CH_{50} (classical pathway)
- AH_{50} (alternative pathway)
- ELISA for individual components

Think about the gene involved!

Use Pubmed OMIM

- sequence gives a solid diagnosis

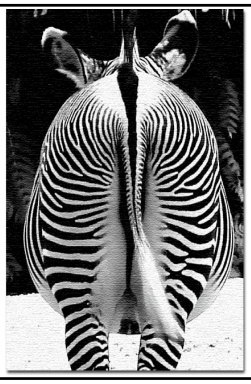
It is the SOS

History

Physical

Imaging

Laboratories
(talk to the lab yourself!!!)



04

Respiratory Viral Infections Including Influenza, Immunocompetent, and Immunocompromised Patients

Dr. Andrew Pavia

4 - Respiratory Viral Infections Including Influenza, Immunocompetent, and Immunocompromised Patients

Speaker: Andrew T. Pavia, MD

2020 INFECTIOUS DISEASE BOARD REVIEW

Respiratory Viral Infections Including Influenza, Immunocompetent, and Immunocompromised Patients

Andrew T. Pavia, MD
Chief of the Division of Pediatric Infectious Diseases
George and Esther Gross Presidential Professor
University of Utah

Disclosures of Financial Relationships with Relevant Commercial Interests

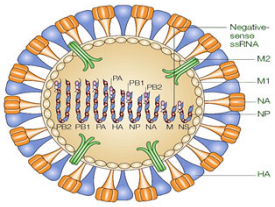
- Commercial Interests: Antimicrobial Therapy Inc, WebMD, Genentech, Merck

What you need to know for the boards

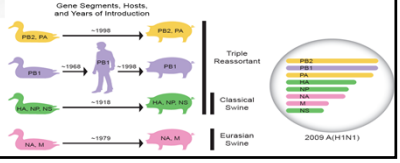
- Minimal virology
- Epidemiology including H5N1 and H7N9
- Diagnosis
- Complications
- Treatment
- Vaccines

Influenza virus

- Orthomyxovirus; 8 gene segments
- Flu A, B and C
- Flu A has 16 HA types, 9 N types
- High error rate leads to point mutations (drift); segment re-assortment leads to shift (pandemics)
- Huge reservoir in wild fowl. Cause disease in poultry, and many mammals
- Mutations in neuraminidase lead to resistance to NAIs



A/California/7/2009 (H1N1)pdm09, the virus formerly known as swine flu



Clinical findings of influenza

- Fever, malaise, cough, sore throat, myalgia, chills, eye pain
- Sudden onset is typical
- During an epidemic, fever with cough has high predictive value
- Fever may be absent in the elderly, immunocompromised
- Minor complications: Croup, bronchiolitis, asthma exacerbation, otitis media, sinusitis, parotitis

4 - Respiratory Viral Infections Including Influenza, Immunocompetent, and Immunocompromised Patients

Speaker: Andrew T. Pavia, MD

Groups at Risk for Complications of Influenza

Group	Example/Comment
Children <5 yrs	Highest hospitalization rate children <1 yr
Persons >65 yrs	Highest among frail elderly
Pregnancy	Highest risk in 3rd trimester **and 2 weeks post partum**
Chronic CVD	Hypertension not seen as independent risk
Chronic lung	Asthma and/or COPD, cystic fibrosis
Metabolic disorder	Diabetes
Renal, Hematologic	Includes sickle cell disease
Neurologic	Neuromuscular, neurocognitive, or seizure disorder
Immunosuppression	Including HIV, organ transplantation, chemotherapy, hypogamm
Morbid obesity	Noted in several studies during H1N1
Am. Indian/Alaskan native	Recently added

Question #1

- A 45-year-old international agricultural researcher presents in June in the US with fever, diarrhea, myalgia, sore throat, and dyspnea. He is hypotensive and hypoxemic.
- CBC shows mild leukopenia, chemistry panel and LFT's are normal.
- Three days prior to the onset of his illness he was inspecting poultry operations Jiangsu Province, China.

Question #1 Continued

Assuming the he acquired his severe respiratory illness from the poultry he was inspecting, the most likely influenza diagnosis would be:

A. H1N1
B. H3N2
C. H5N1
D. H7N9
E. Influenza B

What makes a human influenza strain

- Despite increasing study anticipating changes difficult
- Many genes interacting in complex ways determine virulence species specificity and transmissibility (e.g. 1918 H1N1 virus)
- Influenza risk assessment tool (IRAT)
  - https://www.cdc.gov/flu/pandemic-resources/national-strategy/risk-assessment.htm

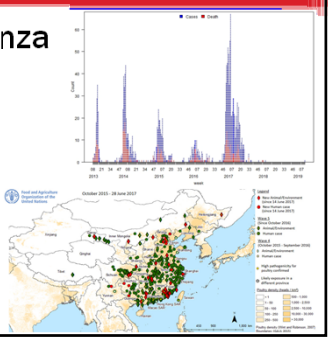
Influenza A viruses infecting humans

- H1N1*: Emerged in 1918. Re-emerged in 1977
- H2N2: 1956-1977 but replaced by H3N2
- H3N2*: Emerged in 1968 (Hong Kong flu)
- H3N2v: Assorted swine associated variants
- H5N1*: Emerged 2003 in Hong Kong. Persists
- H7N9*: Caused >130 cases of severe disease 2013; >200 in second wave; ongoing
- H7N3: Isolated cases in farm workers
- H7N7: Human cases associated with outbreak in Netherlands. H7 viruses associated with conjunctivitis
- H9N2: Sporadic cases associated with poultry

* Currently causing human disease

H7N9 Avian influenza

- > 1500 cases in 5 years
- 22% case fatality
- Avian to human transmission
- Family clusters with human to human documented
- Some intrinsic and some emergent oseltamivir resistance
- Exported cases
  - US x 2, Canada, Hong Kong, Taipei



4 - Respiratory Viral Infections Including Influenza, Immunocompetent, and Immunocompromised Patients

Speaker: Andrew T. Pavia, MD

Source: CDC Public Health Image Library

Influenza Transmission

- Incubation period: 1-4 days (average: 2 days)
- Serial interval: estimated 3-4 days among household contacts
- Shedding:
  - Adults: day before symptoms; 5-7days after illness onset
  - Young children: 1-2 days before illness onset; 10 or more days after symptom onset
  - Immunocompromised or severely immunosuppressed persons: weeks to months has been documented
- Large droplets (up to 6 feet) most important. Fomite and small droplet (true airborne) may contribute.
- Standard plus droplet precautions recommended
- "Use caution" for aerosol generating procedures
- Monitor and manage ill health care personnel

Question #2

- Five days ago (January), a healthy 25 year old woman developed fever, myalgia, sore throat and malaise which was diagnosed as influenza. She was slowly improving.
- Sixteen hours ago, she became hypotensive and hypoxemic, complained of diarrhea, abdominal pain, had a diffuse erythematous rash.

Question #2

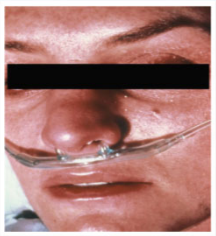
On exam she was slow to respond and had diffuse rales and mild abdominal tenderness that was non focal.

- Chest xray shows diffuse infiltrates
- WBC =5500/mm3 (60% polys, 30% bands)
- Platelets = 40,000/mm3 with PTT 2 x normal
- Creatinine 1.9
- ALT and AST 2 x normal with normal serum ammonia level

Question #2 Continued

What is the most likely cause of this influenza complication?:

A. Reye's syndrome
B. *Staph aureus* pneumonia with Toxic shock syndrome
C. Gram negative sepsis with ARDS
D. Pneumococcal meningitis
E. Viral encephalitis



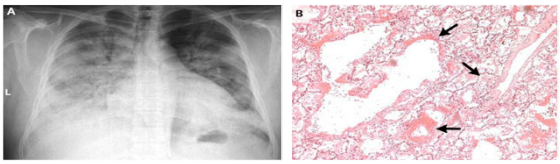
Severe complications of influenza

Complication	Comment
Exacerbation of underlying illness	COPD, asthma, CHF
Ischemic heart disease	Ecologic association
Viral pneumonia	May be mild or severe hemorrhagic pneumonitis/ARDS
Secondary bacterial infection	*Strep pneumoniae*, GAS, *S. aureus*. Classically marked worsening after initial improvement. Account for large proportion of pandemic deaths
Toxic Shock Syndrome	Staphylococcal TSS most commonly described but GAS also reported
Invasive aspergillosis	Clusters in Belgium and Netherlands. Rare reports worldwide

4 - Respiratory Viral Infections Including Influenza, Immunocompetent, and Immunocompromised Patients

Speaker: Andrew T. Pavia, MD

Influenza associated hemorrhagic pneumonitis



Question #3

An 18 year old high school student develops chills, fever, cough, myalgia in January. She is prescribed azithromycin, rest and NSAIDS. Fever and cough continue and she becomes progressively dyspneic and weak. On admission T 39, P 150, RR 24-30, BP 120/50. She has crackles throughout both bases and a gallop. Influenza PCR positive

- WBC =9000/mm3 (60% polys, 30% bands)
- Creatinine 1.9
- BNP markedly elevated
- CXR shows diffuse bilateral infiltrates and cardiomegaly
- Requires V-A ECMO

Question #3 Continued

What is the most likely cause of this influenza complication?:

A. Pneumococcal pneumonia
B. Staph aureus pneumonia with purulent pericarditis
C. Influenza cardiomyopathy
D. MIS-C due to recent SARS-CoV-2 infection
E. Viral pericarditis with effusion

Non-respiratory complications of influenza

Complication	Comment
Neurologic	
Seizures	
Encephalopathy/Necrotizing encephalitis	Viral particles and RNA are rarely found. More common in children but higher mortality in adults
Guillan Barre Syndrome	Up to 10 fold more common with infection than estimated association with vaccine
Musculoskeletal	
Myositis, Rhabdomyolysis	Can be severe and lead to AKI
Cardiac	
Pericarditis	
Myocarditis	
Reyes Syndrome	Acute onset vomiting, altered mental status, seizures. Labs include elevated LFTs, ammonia. Only half of cases associated with ASA before warnings

Question #4

- A 20 year old woman is 18 days out from HSCT in January on and engrafted 3 days ago.
- She develops fever, hypoxemia, bilateral lung infiltrates and is intubated.
- A nasal swab is negative by rapid test for influenza.

Question #4 Continued

Which of the following is the most appropriate course of action (regardless of other actions you may take)?

A. Do not initiate anti-influenza therapy due to result of rapid test. The timing suggests idiopathic pulmonary syndrome (engraftment)
B. Initiate anti-influenza therapy empirically and send tracheal aspirate or BAL for influenza PCR
C. Send IgG and IgM for influenza
D. Send RSV EIA and initiate empiric IV ribavirin

4 - Respiratory Viral Infections Including Influenza, Immunocompetent, and Immunocompromised Patients

Speaker: Andrew T. Pavia, MD

Diagnosis



Diagnosis of influenza

- Performance of all tests depends on prevalence of virus in community and specimen quality
- Clinical diagnosis: up to 80% PPV during peak
- Rapid influenza detection tests have low-moderate sensitivity 10-70% (less for H1N1); reasonably specific
- Positive test in peak season high PPV; negative test should not be used for decisions
- PCR/NAAT recommended by IDSA Guidelines, rapid platforms expanding
- Serology useless for clinical diagnosis

Influenza in transplant pearls

- Typical flu symptoms less common
- Lower respiratory tract disease is common
- Spread on transplant units can be explosive - High mortality
- Virus may not be present in nasopharynx in patients with influenza pneumonia – lower tract specimens should also be tested.
- Prolonged shedding is common
- Resistance may develop on oseltamivir therapy especially in HSCT patients

Question #5

- A 32 year old nurse is 34 weeks pregnant during influenza season. She develops influenza symptoms and is seen at an instacare where a rapid test is positive and she is given azithromycin.
- 72 hours after the onset she presents to the ED with fever, tachypnea, hypoxemia and decreased urine output.
- CXR shows bilateral hazy infiltrates. She is hospitalized.

Question #5 continued

Which of the following is correct?

A. She should get supportive care only since she has had symptoms for >48 hours
B. Oseltamivir is relatively contraindicated in pregnancy
C. Zanamivir is clearly preferred because of low systemic absorption
D. Oseltamivir should be started as soon as possible

ACIP and IDSA Guidelines for Antiviral Use 2020

- Antiviral treatment is recommended for patients with confirmed or suspected influenza as soon as possible for:
  - Who are hospitalized, or have severe, complicated or progressive illness regardless of duration of symptoms
  - Outpatients with confirmed or suspected influenza who are at higher risk for influenza complications based on their age and/or medical conditions

https://www.cdc.gov/flu/professionals/antivirals/index.htm
Uyeki. IDSA Guidelines Clin Infect Dis 2019;68(6):895

ACIP Guidelines for Antiviral Use 2020 (con't.)

- Recommended medications: oseltamivir and zanamivir
- Oseltamivir should be used, when indicated to provide treatment or chemoprophylaxis for infants younger than one year old

https://www.cdc.gov/flu/professionals/antivirals/index.htm
MMWR 2011 59: RR-1

CDC Antiviral Treatment Recommendations

- Empiric antiviral therapy should be offered to pregnant women and women up to 2 weeks postpartum
- Pregnancy should not be considered a contraindication to oral oseltamivir or zanamivir use.
- Treatment duration for NAIs should be 5 days
- Initiating treatment within 2 days of symptoms results in improved outcomes
  - Substantial reduction in morbidity and mortality

https://www.cdc.gov/flu/professionals/antivirals/avrec_ob.htm

Baloxavir

- Cap-dependent polymerase inhibitor
- Non inferior to oseltamivir in two phase 3 studies
- Superior for influenza B in patients with risk factors
- Shorter duration of shedding
- Resistance mutations emerge on treatment in 10-20%
- ? Testable

Hayden NEJM 2018; 379:913-923
Ison Lancet Infect Dis 2020:Jun 8;S1473-309
Uehara JID 2019; 221:346

Antiviral Prophylaxis

- Chemoprophylaxis should not replace vaccination
- Oseltamivir, zanamivir, baloxavir 70-90% effective in trials
- Prophylaxis may increase selection of resistant viruses
- PEP is recommended to control influenza outbreaks in nursing homes
- PEP can be considered for high risk persons with unprotected close contact with patient with flu
- Post exposure prophylaxis should not be given after 48 hours from exposure
- Post exposure prophylaxis for otherwise healthy persons is generally discouraged; prompt empiric therapy is preferable

Influenza antiviral pearls

- Antivirals not effective after 48 hours in outpatients with uncomplicated flu but are effective later in hospitalized patients
- Double dose oseltamivir not more effective
- Resistance to oseltamivir occurs most often through a specific point mutation H275Y in H1N1 viruses (functionally same as H274Y in N2). This confers partial resistance ~40-fold to peramivir but not baloxavir

More influenza antiviral pearls

- Zanamivir remains active against H275Y mutant influenza and most oseltamivir resistant viruses
- Peramivir licensed (600 mg IV x 1) but only for acute uncomplicated
- Inhaled zanamivir can exacerbate asthma, not approved under 5 years
- Using commercial powder of zanamivir in ventilator circuit has caused catastrophic ventilator failure

4 - Respiratory Viral Infections Including Influenza, Immunocompetent, and Immunocompromised Patients

Speaker: Andrew T. Pavia, MD

Vaccines

ACIP Recommendations for Influenza vaccination 2020-2021

- Routine influenza vaccination is recommended for all persons aged 6 months and older.
- "During the COVID-19 pandemic, reducing the overall burden of respiratory illnesses is important to protect vulnerable populations at risk for severe illness, the healthcare system, and other critical infrastructure."
- QIIV (Quadrivalent inactivated influenza vaccine) H1N1, H3N2, B Yamagata, B Victoria

Vaccine pearls

- Efficacy varies by year and group
- Generally 50-70%; lower in elderly, children < 2, renal disease, immunosuppressive therapy and transplant pts.
- In HIV, response related to CD4 count
- Major mismatch occurs at least every 10 years

Vaccine pearls (con't.)

- All influenza vaccines can be given to those with egg allergy.
- Recombinant influenza vaccine (RIV, FluBloc) is available and contains no egg protein.
- For those with anaphylaxis to egg, consultation with allergist no longer recommended. Anaphylaxis to flu vaccine is still a contraindication

Newer flu vaccines

- Quadrivalent vaccines (IIV4) largely replacing IIV3
- High dose (60mcg HA) vaccine is available for persons > 65 years. More immunogenic and more effective
- Adjuvanted vaccine available for persons > 65. More immunogenic, possibly more effective
- Recombinant vaccine contains no egg antigen. Cell culture grown vaccine (Flucellvax) has minimal to no egg antigen

Egg Allergy

- Persons with a history of egg allergy who have experienced only hives after exposure to egg should receive flu vaccine. Any licensed and recommended flu vaccine (i.e., any form of IIV or RIV) that is otherwise appropriate for the recipient's age and health status may be used.
- Persons who report having had reactions to egg involving symptoms other than hives... or who required epinephrine or another emergency medical intervention, may similarly receive any licensed and recommended flu vaccine (i.e., any form of IIV or RIV) that is otherwise appropriate for the recipient's age and health status. The selected vaccine should be administered in an inpatient or outpatient medical setting. Vaccine administration should be supervised by a health care provider who is able to recognize and manage severe allergic conditions.
- A previous severe allergic reaction to flu vaccine, regardless of the component suspected of being responsible for the reaction, is a contraindication to future receipt of the vaccine.

https://www.cdc.gov/flu/prevent/egg-allergies.htm

4 - Respiratory Viral Infections Including Influenza, Immunocompetent, and Immunocompromised Patients

Speaker: Andrew T. Pavia, MD

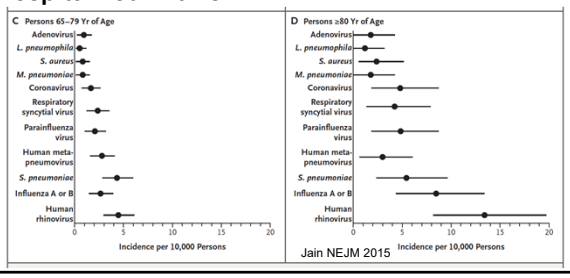
Other important respiratory viruses

Adenovirus, RSV, hMPV, parainfluenza, coronaviruses, hantaviruses (and more)

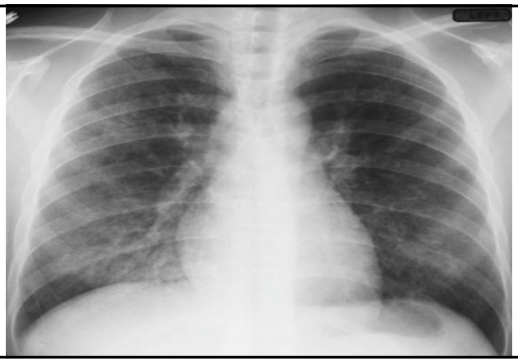
What you may be tested on

- **Focus on lower respiratory tract disease in immunocompetent and compromised hosts, *including* the elderly**
- **RSV, adenoviruses, hMPV are fair game**
- **Parainfluenza viruses possibly**
- **Coronaviruses including MERS (possible) and SARS (unlikely) NOT SARS-CoV-2**
- **Hantavirus is a popular zebra**

Incidence of pathogens in older adults hospitalized with CAP



Jain NEJM 2015



Findings which may suggest viral vs bacterial CAP: beware the overlap!

Characteristic	Viral	Bacterial
Onset	Gradual	Sudden
Season	Winter, associated with viral outbreaks	Slightly less seasonal
Host	Older age, more cardiac and pulmonary disease	Any age
Exam	Wheezing	Consolidation
CBC	Leukopenia	Leukocytosis
Procalcitonin	< 0.1	>0.5
CRP	Lower	Higher
CXR (big overlap)	Interstitial, multilobar	Consolidated, effusion

Diagnosis of respiratory viruses in adults

- Generally shed less virus than children
- Sensitivity depends on test and specimen. Flocked swab and swabbing nose and throat may be better
- Virus may be present in lower respiratory tract (TA/BAL) but not upper in patients with pneumonia
- PCR most sensitive. FDA cleared multiplex platforms available
- Testing is critical in immunocompromised transplant patients with respiratory symptoms

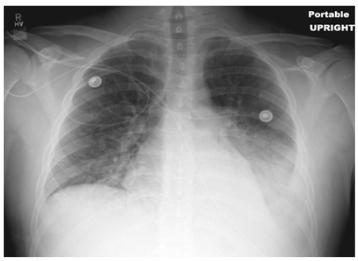
4 - Respiratory Viral Infections Including Influenza, Immunocompetent, and Immunocompromised Patients

Speaker: Andrew T. Pavia, MD

Respiratory Viruses in HSC Transplant Patients

Virus	Mortality for pneumonia	Treatment	Comment
RSV	7-33%	IVIG, ribavirin	LRI associated with severe outcomes
Influenza	25-28%	Oseltamivir, zanamivir, peramivir	Antiviral resistance may develop
Parainfluenza	35-37%	IVIG? DAS181? (invest)	
Adenovirus	30-50%	Cidofovir, CMX 001 (invest)	May disseminate
hMPV	33-40%	IVIG?	27-41% progress from URI to LRI
Coronavirus	?	?	Progression to LRI less common
Rhinovirus	<5	?	Severity unclear

Falsey, Walsh. Clin Microbiol Rev 2000;13: 371
Nichols. Blood 2001;98:573
Englund. Ann Intern Med 2006;144:344
Reynaud. Curr Opinion Infect Dis 2011:333
Boeckh. Br J Haematol. 2008; 143: 455
Larosa. Clin Infect Dis 2001;32:871
Ison. Clin Infect Dis 2003;36:1139



Case

An 18 yo man presents in March in Portland OR with several days of fever, cough, chest pain, tachypnea, hypoxia and conjunctivitis with this CXR.

WBC 3.0, platelets 160, CRP 2.5, AST 75

Question #7

2 days later he is in ICU on high levels of support. You suspect:

A. Pneumococcal pneumonia
B. *Borrelia hermsii* with capillary leak and ARDS
C. Adenovirus
D. Hantavirus pulmonary syndrome
E. MRSA pneumonia
F. Group A streptococcus with TSS

Adenovirus

- DS DNA; 7 species, 50 serotypes
- Associated with URI, pharyngitis, pneumonia, conjunctivitis, hemorrhagic cystitis, gastroenteritis, hepatitis, disseminated disease
- Outbreaks of pneumonia in day care, closed settings, stressed populations e.g. military barracks
- No real seasonality
- Cidofovir, Brincidofovir have been used for Rx

Adenovirus in transplant patients

- More common with Campath (alemtuzumab)
- URI progresses to LRI in about half, with high mortality
- May disseminate and cause severe hepatitis, encephalitis
- May cause hemorrhagic cystitis, tubulointerstitial nephritis
- May lead to loss of graft in SOT patients
- Diagnosis by PCR of **respiratory secretions, blood**, pathology of organ biopsy

Question #8

- A 71 yo man with COPD, history of MI is admitted in January with progressive dyspnea, cough, tachypnea, low grade fever. ROS is positive for rhinitis.
- He has been spending time with young grandchild who has bronchiolitis
- CXR shows bilateral perihilar infiltrates consistent with pneumonia..

Question #8 Continued

The recommended strategy, pending more lab results, regarding isolation should be:

A. Put him in a regular two bedded room with standard precautions
B. Put him in a single room with standard precautions
C. Put him in a single room with contact/droplet precautions
D. Put him in an airborne isolation room with airborne isolation

Question #9

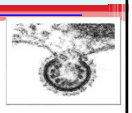
- Multiplex PCR of his nasal swab shows RSV. Which of the following is correct

A. RSV is an incidental finding which might cause URI symptoms
B. RSV likely accounts for infiltrate. He should be immediately started on palivizumab (Synagis) and ribavirin
C. RSV likely accounts for infiltrate. Supportive care is appropriate
D. He has high risk CAP and should be started on vancomycin and piperacillin tazobactam

RSV, hMPV in older adults

- Viruses are common as cause of CAP in elderly
- COPD and heart disease are risk factors
- May also present as exacerbation of COPD or CHF
- Exposure to children probably a risk factor
- Nosocomial transmission has been documented and testing and use of appropriate precautions may be important

RSV



- Most common cause of LRTI in children
- Common cause of URI with rhinitis in adults. AE-COPD, worsened CHF, asthma exacerbation and pneumonia in elderly and immunocompromised
- Transmitted by large droplet and contact; nosocomial transmission in hospitals and ECF
- Late fall to spring (usually December- April)
- As common as influenza among hospitalized persons > 65

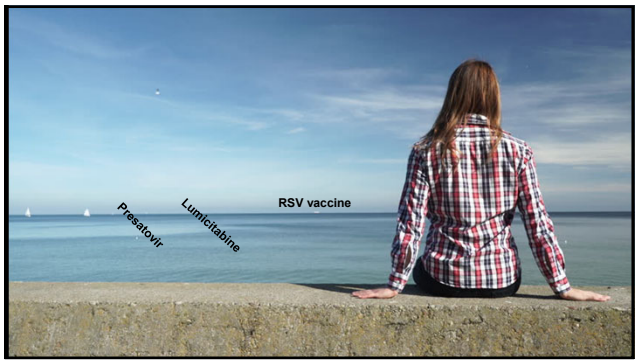
Falsey NEJM 2005, Widmer 2012

RSV

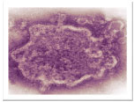
- Long incubation period 2-8 days
- Diagnosis by antigen detection, PCR
- No indications for palivizumab (Synagis)in adults
- Inhaled ribavirin controversial
  - Limited efficacy, high cost, occupational risk
- Case series suggest benefit aerosolized RBV +/- IVIG in HSCT patient with LRTI; no good data in SOT.
- Oral ribavirin appears equally effective

4 - Respiratory Viral Infections Including Influenza, Immunocompetent, and Immunocompromised Patients

Speaker: Andrew T. Pavia, MD



Human Metapneumovirus



- "Discovered' in the last decades
- Nonsegmented, single stranded, negative sense RNA virus: Paramyxoviridae family, Pneumovirinae subfamily
- Causes URI, bronchiolitis, pneumonia similar to RSV
- Winter/Spring in temperate climates
- In younger adults, URI common with sore throat, hoarseness, wheezing, asthma exacerbation, AE-COPD, and CAP
- More severe in elderly, more wheezing; ECF outbreaks
- Mortality among HSC transplant similar to RSV

Parainfluenza virus

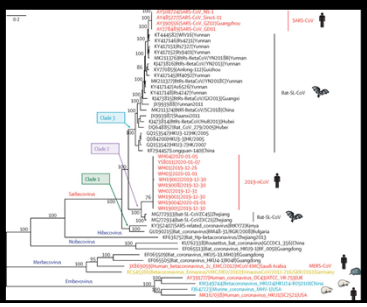
- Paramyxovirus with 4 subtypes 1-4
- Spring and fall seasonality
- Causes URI, bronchiolitis, croup, pneumonia in children. Parainfluenza 3 more severe.
- Causes URI, cough illness and viral pneumonia in adults
- May cause severe disease in transplant patients and all respiratory viruses be associated with COP (formerly known as BOOP)

Other Human Coronaviruses

- HuCoV 229e, HuCoV OC43
  - "Older" associated predominantly with URI
- HuCoV HKU1, HuCoV NL63
  - Recently described using molecular techniques. Associated with URI and some pediatric and adult pneumonia
- May be detected on newer multiplex platforms (Luminex, FilmArray). Do not cross react with SARS-CoV-2
- Can cause severe disease in HSCT population

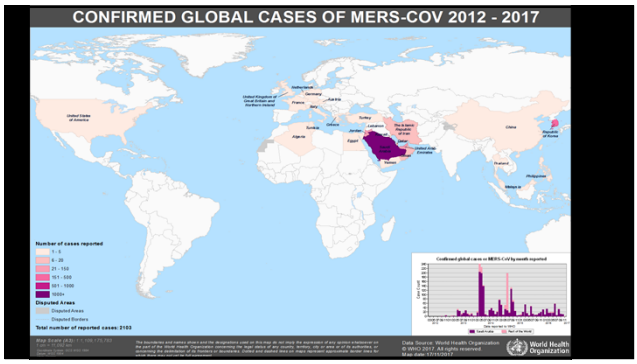
MERS coronavirus

- Discovered April 2012
- > 600 cases in or with contact with Gulf area, predominantly Saudi Arabia
- Transmission documented in health care settings and families but to date, super spreaders suspected in Korea
- Mortality 56% with small number of asymptomatic
- Closest relative is a bat virus
- Camels play important role



4 - Respiratory Viral Infections Including Influenza, Immunocompetent, and Immunocompromised Patients

Speaker: Andrew T. Pavia, MD



Question #10

- A 35 yo man is admitted to the ICU in July with fever, respiratory failure, hypotension.
- 5 days PTA he complained of having the "flu;" fever, malaise, myalgia, mild abd pain.
- History: Recently camped in cabins at Yosemite National Park which has had rodent infestations issues.
- Has parakeet, dogs, cat had kittens recently, owns a hot tub. 2 kids in daycare have URI.

Question #10 (con't.)

- Labs: Hct 52; WBC 6.0 (20% bands, 45% polys, 2+ atypical lymphs), platelets 90K,
- AST 105, PT 18, PTT 25
- CXR: Rapidly progressing bilateral infiltrates leading to white out

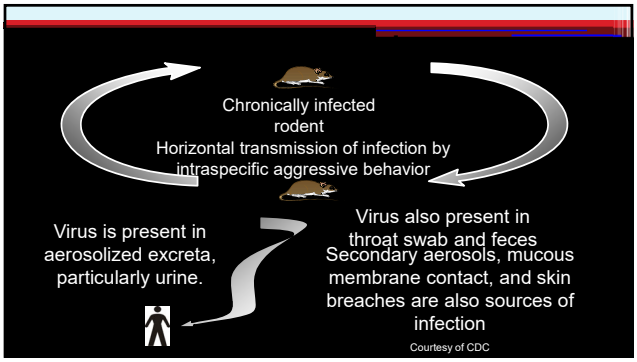
Question #10 (con't)

Which of the following is the most likely cause of his illness?

A. Adenovirus
B. Influenza
C. Anthrax
D. Coxiella burnetii
E. Hantavirus Pulmonary Syndrome

Hantavirus Pulmonary Syndrome HPS

- First described in a 1993 outbreak in the 4 Corners
- Recent outbreak in Yosemite. Endemic cases of HPS in much of US, Chile, Argentina
- Caused by specific North American and Latin American hantaviruses – member of Bunya virus family.
  - Previously unrecognized viruses cause HPS, Sin Nombre virus, Black Creek Canal, New York virus
  - Prior to the HPS outbreak, the only known hantaviruses were those that caused HFRS



4 - Respiratory Viral Infections Including Influenza, Immunocompetent, and Immunocompromised Patients

Speaker: Andrew T. Pavia, MD

Stages of Hantavirus Pulmonary Syndrome (HPS)

- Incubation (4-30 days)
- Febrile phase
  - Fever, myalgia, malaise occasionally N, V, abd pain
- Cardiopulmonary phase
- Diuretic phase
- Convalescent phase

HPS-Cardiopulmonary Phase

- Acute onset of cough an dyspnea
- Presentation and rapid progression of shock and pulmonary edema (4-24h non-productive cough and tachypnea (shortness of breath)
- Hypovolemia due to progressive leakage of high protein fluid from blood to lung interstitium and alveoli, decreased cardiac function

HPS-Cardiopulmonary Phase

- Hypotension and oliguria
- *Critical clues*:
  - Thrombocytopenia (98%),
  - Hemoconcentration
  - left shift with atypical lymphs
  - elevated PT, abnormal LFTs

Good Luck on the Exam!

andy.pavia@hsc.Utah.edu
@AndrewPaviaMD

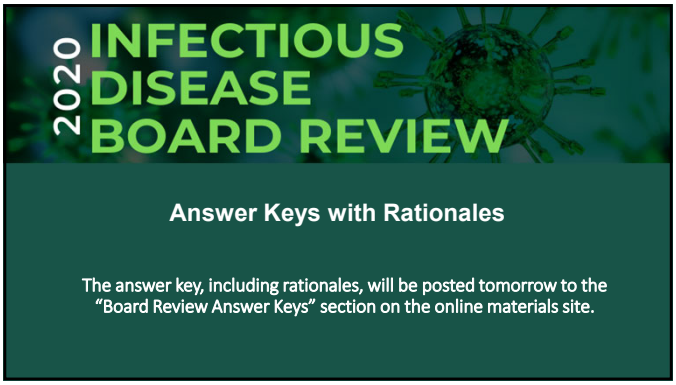
05

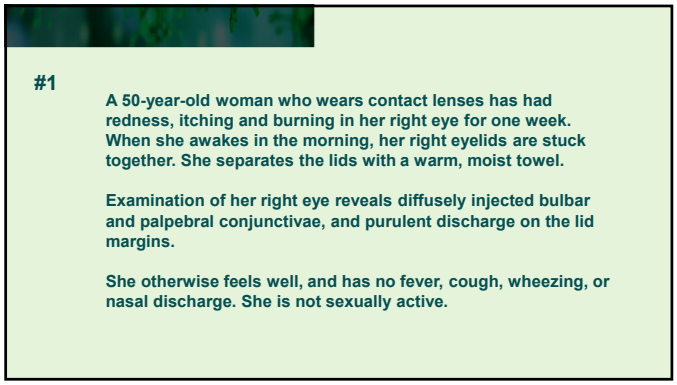
Board Review Session 1

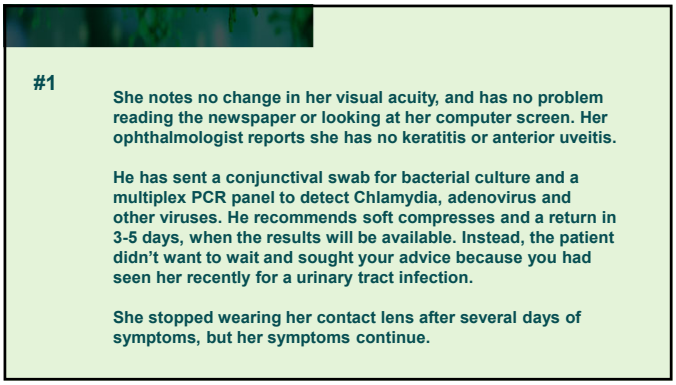
Drs. Pavia (Moderator), Bennett, Bloch, Chambers, Gandhi, and Nelson

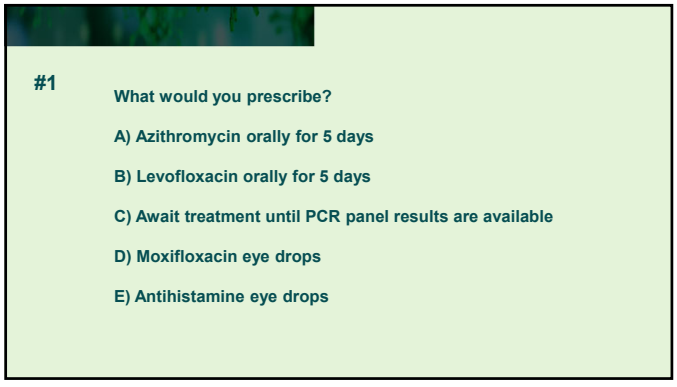
05 – Board Review Session 5

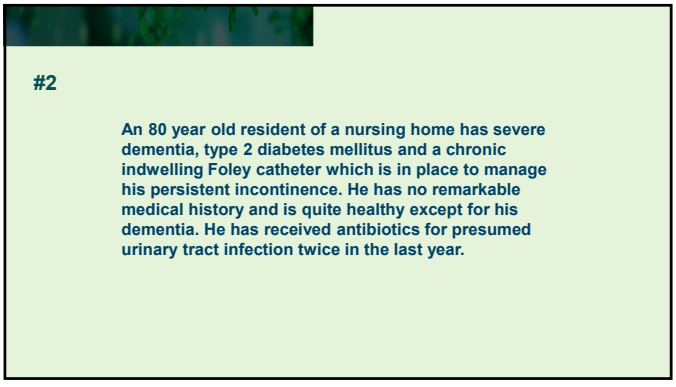
Drs. Pavia (Moderator), Bennett, Bloch, Chambers, Gandhi, and Nelson











#2

The nursing home staff decided to obtain a urinalysis and urine culture: they call you because the urine culture is growing Candida albicans with a colony count of 100,000 cfu/ml. His UA shows 30-40 WBC and 10-20 RBC per HPF, with a 1+ leukocyte esterase

He is in his usual state of health with no fever, no urinary symptoms that you can elicit from him, and no flank tenderness.

#2

What would you recommend?

A) Observe and do nothing more unless the patient becomes symptomatic

B) Observe but obtain repeat urinalysis and culture in one week

C) Change Foley catheter and give oral fluconazole for 1 week

D) Change Foley catheter and IV caspofungin for 1 week

E) Change the Foley catheter and order Amphotericin B deoxycholate bladder washes daily for 5-7 days

#3

In the month of January in Chicago, a 30 year old woman in excellent health has had purulent nasal drainage, fevers to 38.5 C, sore throat, and chills for the past 14 days.

She has been able to work and to exercise on the tread mill as usual, but she feels tired in addition to her other symptoms.

She saw her primary care physician after 3 days of symptoms, who was insistent that she did not need antibiotics because her symptoms were of short duration and likely would resolve without antibiotics.

#3

She comes to you as an ID physician for another opinion a week after seeing her primary care physician.

On exam she has a temperature of 38.3C with intermittent chills, moderate pain over her sinuses, and purulent looking nasal discharge. Her CBC is still normal.

She has no drug allergies.

#3

What would be the best choice for management?

A) Cephalexin (Keflex)

B) Nasal decongestant and nasal irrigations with saline twice daily for 3-5 days but no antibiotics unless her clinical symptoms worsen

C) Clindamycin (Cleocin)

D) Amoxicillin-clavulanate (Augmentin)

E) Ciprofloxacin

#4

A 45 year old male is 10 days post-chemotherapy with cytarabine plus daunorubicin for acutemyeloidleukemia. He presents to the ED with profound weakness, fever, and watery diarrhea.

Due to a known absolute neutrophil count of <500 cells/mcL, he has been taking prophylactic once daily levofloxacin since starting chemotherapy.

Three days prior to admission, WBC was 0.1 K/mcL, hgb 9 gm/dL and platelets 26,000/mcL.

In the ED, T 103°F, BP 79/42 mm Hg, P 144/min. Immediate empiric therapy was started with meropenem and vancomycin.

#4

The lab was unable to measure hgb due to massive hemolysis.

Peripheral smear shows "ghost" RBCs (RBCs without a cytoplasm).

Lactic acid 14 mmol/L

Total bilirubin 13.6 mg/dl, creatinine 48 mg/dL and LDH 17,000 units/L.

#4

Which one of the following is the most likely pathogen causing the clinical syndrome?

A) Clostridium perfringens

B) Clostridium sordellii

C) Escherichia coli shiga toxin

D) Group A Streptococcus

E) Bacteroides fragilis

#5

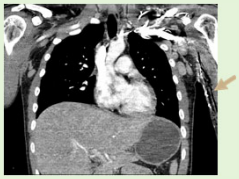
A 56-year-old man was admitted to the ICU with sepsis. His family notes that the previous day he complained of diffuse myalgias and chills and he stayed home from work. The next morning, he was unarousable. EMS was called and patient was intubated at the scene.

Physical exam was pertinent for T=34.7 C, BP=77/42 (unresponsive to fluid resuscitation), HR=126. He was unresponsive to voice, but grimaced with palpation of left upper extremity, and bilateral lower extremities. Scleral icterus was present. Extremity exam was without erythema, swelling or fluctuance, but note was made of left upper extremity crepitus on palpation.

#5

Labs revealed WBC=28.9 (96% seg), H/H=6.9/20.3, platelets=50, Cr=2.7, AST/ALT=521/312, Bil=7.2, LDH=842

CT scan of the chest is displayed below:



#5

What is the most likely predisposing factor for his illness?

A) Colon cancer

B) Poorly controlled diabetes

C) Hypogammaglobulinemia

D) Tick bite

E) Tinea pedis

#6

A 57 year old female is admitted for alcohol intoxication.

She has symptoms of an upper respiratory tract infection, is mildly tremulous, but otherwise has no complaints.

Temperature is 37°C, heart rate 110, blood pressure 145/95, respiratory rate 16. The exam is normal except for tremulousness.

Admission labs include serum sodium 132 mEq/L, serum potassium 3.2 mEq/L, serum chloride 98 mEq/L, bicarbonate 23 mEq/L, blood urea nitrogen 30 mg%, serum creatinine 1.6 mg%.

#6

CXR is normal.

She responds well to fluids and lorazepam.

After 3 days labs have normalized and she is ready for discharge.

Two blood cultures obtained on admission grew nothing, urine culture from admission 10^4 cfu/ml of pan-susceptible MSSA (contemporaneous urinalysis 10-20 WBCs, 1+ protein, trace ketones, and a few squamous cells).

You are asked by the primary team to provide recommendations on antimicrobial therapy.

#6

Which is the following would you recommend?

A) No antimicrobial therapy

B) A 7-day course of cefazolin 1 g IV q8H

C) A 7-day course of cephalexin 500 mg po q6h

D) TMP/SMX 160/800 mg po twice daily for 3 days

E) Penicillin VK 500 mg po q6h for 7 days

#7

A 28 year old male who injects drugs is admitted for fever and left hip pain. On physical examination the temperature is 39.5°C , heart rate 130, blood pressure 110/60, respiratory rate 22.

He has a 2/6 systolic murmur at the left sternal border and difficulty moving his left hip because of pain. Renal function is normal.

#7

CXR is normal and CT of the left hip shows a large left gluteal abscess. The abscess is drained with Gram-stain of the pus showing Gram-positive cocci in clusters.

He is empirically started on vancomycin. The next day 2 of 2 blood cultures from admission are positive for Gram-positive cocci in clusters. A transthoracic echocardiogram is normal.

#7

What empirical therapy would you recommend for this patient?

A) Continue vancomycin

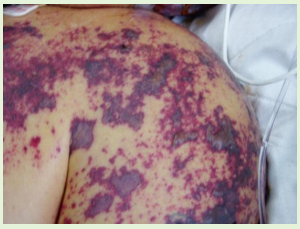
B) Continue vancomycin and add rifampin

C) Continue vancomycin and add nafcillin

D) Discontinue vancomycin and start daptomycin

E) Discontinue vancomycin and start linezolid

#8



This rash was found on a stuporous adult one morning. He had appeared well the night before other than some “flu like” symptoms.

#8

Blood cultures of this patient are likely to grow which of the following:

A) Gram negative cocci

B) Gram positive cocci

C) Gram negative bacilli

D) Gram positive bacilli

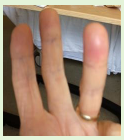
#9

A 74-year-old female presented with a 4-month history of fatigue and one month of dull, non-radiating lumbar back pain.

She had low-grade fever four months ago which resolved with three weeks of amoxicillin-clavulanate, given for sinusitis.

She has lost 10 pounds of weight, has sweating at night and recently noticed a tender swelling on her finger.

#9



She had a mitral valve repair with a prosthetic ring implanted 20 years prior and has mitral regurgitation on transthoracic echocardiogram, unchanged from 8 months prior.

#9

The finger nodule in the above photo, is suggestive of which of the following:

A) Staphylococcal felon

B) Osler's node

C) Rheumatoid nodule

D) Polymyalgia rheumatic

E) Janeway lesion

#10

A 55-year-old male carpenter consulted his orthopedic surgeon about increasing pain and stiffness in his right shoulder over the past three months.

Fifteen months previously the surgeon had performed a right shoulder arthoplasty because of severe arthritis in the shoulder. The patient had been able to return to work and reported no fever, redness or swelling.

#10

The surgeon aspirated about a milliliter of cloudy fluid from the joint which had a WBC of 2500 and a negative Gram stain, routine aerobic and anaerobic culture.

Because of concern for infection in the prosthetic joint, the surgeon plans on a two-stage joint replacement and seeks your advice about intraoperative cultures.

#10

You recommend which of the following:

A) Obtain 3-5 pieces of tissue from the infected site and request the lab hold aerobic and anaerobic cultures for 14 days

B) Inoculate any fluid found in the joint into aerobic and anaerobic blood cultures for routine processing

C) Send swabs of the prosthetic ball and socket for aerobic and anaerobic culture

D) Request that all intraoperative cultures be stained for acid fast organism and cultured for Mycobacteria as well as routine aerobic and anaerobic cultures

E) Ask the lab to hold some of the intraoperative specimen for possible PCR testing in case the routine cultures are negative

#11

A 20-year-old woman presents with progressive pain and swelling over her right medial clavicle.

She first noticed discomfort several weeks ago that was most apparent when she used her right arm. Over the last week she became aware of swelling in this area. She has had occasional low-grade fevers over this period of time which respond to ibuprofen.

When she was 18 years old, she developed subacute osteomyelitis of her left femur. Blood cultures and bone cultures were negative. She received a course of oral antibiotics and reports that the pain in her leg improved over several months.

#11

She lives on an organic dairy farm. She denies any history of injection drug use.

On exam she is well appearing. The medial clavicle is prominent with tenderness and erythema overlying the sternoclavicular junction. ESR is 32 and CRP 14.6 mg/dL.

Plain films demonstrate lytic areas within the medial clavicle with periosteal thickening and areas of sclerosis. The sternum was normal.

#11

What do you suggest next?

A) MRI of the clavicle and bone scan

B) Percutaneous needle biopsy of the clavicle for histopathology and culture

C) Open surgical debridement of the clavicle with cultures and biopsy

D) Administer vancomycin and ceftriaxone for a six-week course

E) Administer ciprofloxacin and doxycycline for a 12-week course

#12

A 59 year old male is being treated for MSSA sternal osteomyelitis after undergoing coronary artery bypass grafting. He has been home receiving outpatient parenteral antimicrobial therapy (OPAT) with IV oxacillin.

Two weeks after discharge, fever develops. On OPAT laboratory surveillance, the following results are noted:

WBC: 18.4
neutrophils: 32%
eosinophils: 18%

#12

HCT: 31.3
PLT: 512
BUN: 24
Creatinine: 1.4 (baseline 1.1)
AST: 380
ALT: 475
Alk Phos: 166
Bili: 1.0

Oxacillin is stopped, but fever persists, and he develops a diffuse erythematous maculopapular rash on his torso and limbs.

#12 What is your best management option?

A) Start nafcillin; advise oral diphenhydramine and continue outpatient monitoring

B) Start cefazolin and IV diphenhydramine; continue outpatient monitoring

C) Start vancomycin; hospitalize and consider corticosteroid therapy

D) Test dose cefazolin; if tolerated start IV cefazolin

E) Penicillin skin testing and test dose of nafcillin; if negative start nafcillin

#13

A 31-year-old male first grade school teacher developed fever, rhinorrhea, and malaise for several days, followed by a progressively worsening dry cough. He has now been sick for 12 days.

His chest x-ray was normal.

An empirical 5 day course of azithromycin treatment was begun on day three of his illness (he has now completed treatment 4 days ago), but he has continued to cough.

A nasopharyngeal swab, sent for Bordetella pertussis PCR, was positive. He was previously in excellent health. He received all of his childhood immunizations but nothing subsequently.

#13 The best advice for this patient would be which one of the following:

A) His clinical syndrome is not due to pertussis if his chest x-ray is normal.

B) He should not return to the classroom until his PCR is negative.

C) His students should be offered chemoprophylaxis. Students who refuse should be excused from school for 21 days.

D) If the teacher was immunized as a child, this is likely a false positive PCR.

E) All his household contacts, regardless of age and vaccine status, should receive prophylaxis.

#14

A 70-year-old male presents to the Emergency Room with confusion, slurred speech and a right sided weakness of 3 hours duration.

He had previously been healthy except taking methotrexate and infliximab for rheumatoid arthritis.

He has no history of headaches and no pain on palpation of his forehead.

MRI with gadolinium contrast showed restricted diffusion in the left posterior basal ganglia extending to the internal and external capsule, compatible with an acute stroke.

#14 LP showed:

- 90 wbc (90% mononuclear)
- 5 rbcs
- Glucose: 50 mg/dl
- Protein: 60 mg/dl

The patient's wife reports that he had shingles on his left forehead and around his eye 7 weeks ago. This began while he was on a Mediterranean cruise, delaying medical attention. While extremely painful, the rash had improved over three weeks with famciclovir and prednisone.

#14 If this lesion were caused by an infectious agent, which of the following would be the most likely etiologic agent?

A) West Nile Virus

B) CMV

C) HSV

D) VZV

E) Tick borne encephalitis virus

#15

A 29-year-old man is referred to you for evaluation of fever and a rash, which have lasted 5 days. He returned from vacationing in South Africa 3 days ago. While there he spent most of his time at the beaches around Capetown.

On the last day of his vacation, he had the onset of fever, mild headache, and myalgias. These symptoms persisted and were accompanied by photophobia and the development of a diffuse papular rash last night. He was sexually active while on vacation with two different female partners. His past medical history is unremarkable and he is taking no medications.

#15

On examination, temperature is 100.6°F, BP 110/78 mm Hg, pulse 94/min, respirations 14. There is a diffuse, papular erythematous rash on the trunk that extends onto the extremities.

There are five dark red, 0.5–1.0-cm lesions on the right lower extremity. A few shotty cervical and inguinal lymph nodes are palpable bilaterally.

The conjunctivae are mildly injected. The oropharynx is normal as are the ears and nose. The remainder of the examination is normal.

#15

Which of the following is the most likely cause of this patient's current illness?

A) Rickettsia prowazekii

B) Rickettsia rickettsia

C) Rickettsia africae

D) Measles

E) Treponema pallidum

06

Bone, Joint and Musculoskeletal Infections

Dr. Sandra Nelson

2020 INFECTIOUS DISEASE BOARD REVIEW

Bone, Joint and Musculoskeletal Infections

Sandra B. Nelson, MD
Director, Musculoskeletal Infectious Diseases
Division of Infectious Diseases
Massachusetts General Hospital

Disclosures of Financial Relationships with Relevant Commercial Interests

- None

Osteomyelitis:

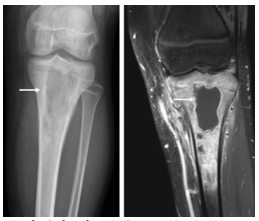
- Hematogenous Osteomyelitis
  - Metaphyseal long bone (more common in children)
  - Vertebral spine (Spondylodiscitis)
  - Usually monomicrobial
- Contiguous Osteomyelitis
  - Trauma / osteofixation
  - Diabetic foot ulceration
  - Often polymicrobial

Osteomyelitis: General Principles

- MRI and CT are the best radiographic studies
  - Bone scan has good negative predictive value but lacks specificity
  - MRI and CT not useful as test of cure
- Diagnosis best confirmed by bone histopathology and culture
  - Identification of organism improves outcomes
  - Swab cultures of drainage are of limited value
- Optimal route and duration of therapy an evolving target
  - 6 weeks of IV antimicrobial therapy commonly employed
  - Longer oral suppression considered in setting of retained hardware

Brodie's Abscess (Subacute hematogenous osteomyelitis)

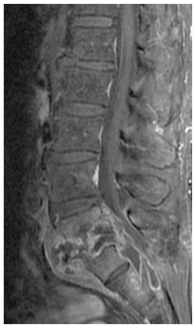
- More common in children and young adults
- Bacteria deposit in medullary canal of metaphyseal bone, become surrounded by rim of sclerotic bone → intraosseous abscess
- "Penumbra sign" on MRI
  - Granulation tissue lining abscess cavity inside bone gives appearance of double line
- *Staph aureus* most common



Simpfendorfer Infect Dis Clin N Am 2017;31:299

Case #1

- 57 year old male presented with a 3 month history of progressive lower back pain
- On ROS denied fevers or chills but wife noticed weight loss
- Originally from Cambodia, emigrated as a child. Employed at a seafood processing plant
- ESR 84 CRP 16
- MRI with discitis and osteomyelitis at L5-S1
- Blood cultures grew *Staph epidermidis* in 2 of 4 bottles



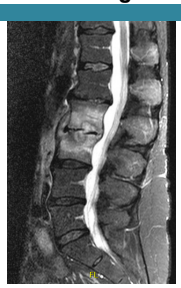
Case #1: Vote

What is the best next step in management?

A. Repeat 2 sets of blood cultures
B. Initiate vancomycin; place PICC for six week treatment course
C. Obtain interferon gamma release assay
D. Percutaneous biopsy of disc space
E. Empiric treatment with rifampin, isoniazid, ethambutol, and pyrazinamide

MASSACHUSETTS GENERAL HOSPITAL HARVARD MEDICAL SCHOOL 7

Pyogenic Vertebral Osteomyelitis: diagnosis

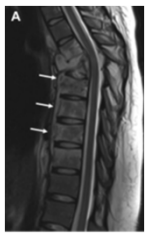


- Blood cultures (positive in 60%)
  - No further diagnostics if *Staph aureus* or *Staph lugdunensis*
- Brucella serologies, PPD/IGRA
  - In appropriate epidemiological setting
- Percutaneous biopsy (paraspinal or bone/disc space)
  - When blood cultures and serology negative
  - Yield 36-65%
  - In absence of sepsis and/or neurologic compromise, withhold antibiotics 1-2 weeks if feasible
  - If negative repeat percutaneous or consider open procedure (open procedure higher yield)

MASSACHUSETTS GENERAL HOSPITAL HARVARD MEDICAL SCHOOL 9

Pott's Disease

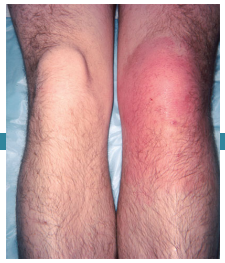
- Clinically:
  - More indolent than pyogenic osteomyelitis
  - Constitutional symptoms common
  - Anterior collapse may lead to gibbus deformity
- Radiographic:
  - Thoracic>lumbar with anterior involvement
  - Relative sparing of the disc space until later
  - Multi-level disease, large paraspinal abscesses
- Treatment:
  - Conventional TB therapy, 6-12 months
  - Surgery often not necessary



Simpfendorfer Infect Dis Clin N Am 2017;31:299

MASSACHUSETTS GENERAL HOSPITAL HARVARD MEDICAL SCHOOL 10

Septic Arthritis



MASSACHUSETTS GENERAL HOSPITAL HARVARD MEDICAL SCHOOL 11

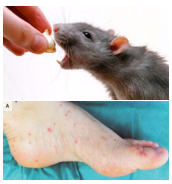
Septic Arthritis: Clinical Pearls

- Synovial fluid cell counts: No diagnostic threshold
  - Higher probability of SA if WBC >50,000/mm^3
  - Lower cell counts do not exclude septic arthritis
- More subtle presentations in immunocompromised hosts and with indolent organisms
  - Subacute history
  - Lower synovial fluid cell counts
- Negative cultures and/or delayed culture positivity:
  - think Gonococcus, HACEK, Lyme, Mycoplasma

MASSACHUSETTS GENERAL HOSPITAL HARVARD MEDICAL SCHOOL 12

Polyarthritis

- 10-20 % of septic arthritis is polyarticular:
- Associated with bacteremia/sepsis
  - Staph aureus most common (look for endocarditis)
- *Streptobacillus moniliformis*
  - Rat bite fever (fever/rash)
  - Polyarthritis, usually symmetric
  - If bitten in Asia – *Spirillum minus*
  - Rx: penicillin
- Consider also:
  - gonococcal, viral, non-infectious

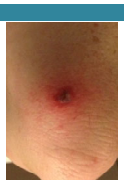


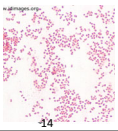
Giorgiutti NEJM 2019: 381:1762

MASSACHUSETTS GENERAL HOSPITAL HARVARD MEDICAL SCHOOL 13

Gonococcal Arthritis

- Tenosynovitis, arthralgias, skin lesions
  - Especially extensor surface tenosynovitis
  - Migratory arthralgias
- Purulent arthritis
  - May be polyarticular; knees most common
  - Lower synovial fluid cell counts more common
- Asymptomatic mucosal phase predisposes
  - Dissemination more common in women
- Highest yield diagnosis: mucosal site sampling (cervical, urethral)
  - Blood (<30%) and synovial fluid (<50%) cultures lower yield
  - Compatible clinical syndrome





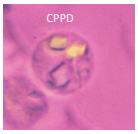
Viral arthritides

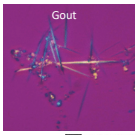
- Symmetric polyarthritis, often involving small joints, often associated with fever and rash
- Diagnose serologically (+IgM or 4 fold rise in IgG titer)

Most common viruses to cause arthritis	Clinical and Epidemiologic Clues
Rubella	Non-immune (non US born). See cervical lymphadenopathy, fever, rash.
Parvovirus B19	More common in women. History of exposure to young children, often a teacher or parent. Hands most common; can be severe.
Hepatitis B Virus	Serum-sickness like reaction, resolves with development of jaundice; also polyarteritis nodosa (PAN)
Hepatitis C Virus	Immune complex arthritis associated with cryoglobulinemia
Alphaviruses (esp Chikungunya)	Travel to endemic areas

Crystalline arthritis: clinical pearls

- Acute gout flare mimics septic arthritis (fever)
  - Clues: rapid onset (hours), history of gout, alcohol, CKD, diuretics, elevated uric acid
  - Synovial WBC 10,000-100,000/mm^3
- Crystalline disease and septic arthritis can coexist (esp. CPPD)
  - CPPD rarely has cell count >30,000





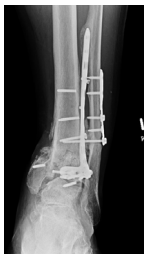
Images: Taljanovic RadioGraphics 2015;35:2026

Masquerading as Infection…

- Other noninfectious causes of arthritis:
  - Reactive arthritis
    - Following enteric or genitourinary infection
    - Asymmetric mono or oligo-arthritis affecting knees/ankles
    - Associated features: enthesitis (tendon insertion), dactylitis (sausage digits), mucosal lesions, urethritis, conjunctivitis/uveitis, skin lesions (keratoderma blennorhagica)
  - Still's disease
  - Sarcoid (Lofgren's)
  - Polymyalgia rheumatica
  - Many others….

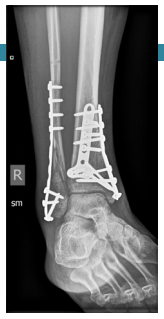
Coelho BMJ Case Reports 2017-222475

Osteofixation Infections



Case #2

- 44 year old woman, previously healthy, suffered a right ankle closed pilon fracture
  - Open reduction and internal fixation
- Impaired wound healing
  - Chronically discharging wound despite courses of cephalexin and trimethoprim-sulfamethoxazole
- 3 months after ORIF, wound culture grows methicillin-susceptible *Staph aureus*



Case #2: Vote

What are your next steps?

A. Nafcillin followed by long-term trimethoprim- sulfamethoxazole
B. Hardware removal; six weeks of oxacillin
C. Hardware removal; six weeks of oxacillin and rifampin
D. Debridement without hardware removal; six weeks of oxacillin and rifampin
E. Debridement and hardware replacement; six weeks of oxacillin and rifampin

MASSACHUSETTS GENERAL HOSPITAL HARVARD MEDICAL SCHOOL 20

Osteofixation Infections

- Infection risk as high as 25% and varies based on:
  - Open fractures (type and inoculum of bacterial contamination)
  - Severity of fracture (Gustilo grade)
  - Severity of soft tissue injury
  - Fracture location (lower extremity higher risk)
  - Timely antibiotic prophylaxis for open fractures
  - Usual host risk factors

MASSACHUSETTS GENERAL HOSPITAL HARVARD MEDICAL SCHOOL 20

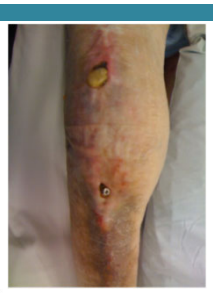
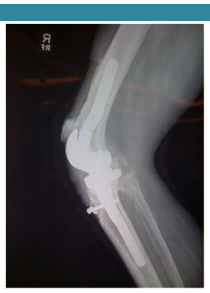
Osteofixation Infections

- Goals: fracture consolidation and infection eradication
  - Removal of hardware depends upon fracture healing

	Early or delayed infections prior to fracture union	Late nonunion
Microbiology	*Staph aureus* most common	Indolent organisms (coagulase-negative Staphylococcus, *Cutibacterium acnes*)
Surgical Strategy	Debride and retain (assuming implants well fixed)	Hardware removal Revision fixation (1 or 2 stage) Or external fixation
Antimicrobial Management	Pathogen-directed therapy Add rifampin if Staph species Consider suppression until fracture consolidates, especially if *Staph aureus*	Pathogen-directed therapy

MASSACHUSETTS GENERAL HOSPITAL HARVARD MEDICAL SCHOOL 23

Prosthetic Joint Infection

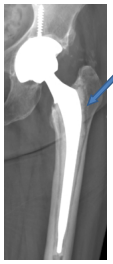
MASSACHUSETTS GENERAL HOSPITAL HARVARD MEDICAL SCHOOL 24

Prosthetic Joint Infection (PJI): Clinical presentations

- Early surgical site infection (< 3months)
  - Acute onset of fever, joint pain, swelling
  - Caused by virulent organisms (*Staph aureus*)
- Delayed / Subacute infection (3 – 24 months)
  - Insidious onset of pain; fever is uncommon
  - Less virulent organisms: e.g. Coagulase-negative Staph, Cutibacterium
- Acute hematogenous infection
  - Acute onset of fever, joint pain, swelling in previously healed and pain-free joint
  - Hematogenous seeding, virulent organisms (*Staph aureus, Streptococcus)*

MASSACHUSETTS GENERAL HOSPITAL HARVARD MEDICAL SCHOOL 25

Chronic PJI: diagnostic pearls



- ESR/CRP may be minimally elevated
- Plain films often normal or may show periprosthetic lucency
- Synovial fluid aspiration the best test
  - Lower cell counts than in native joints or acute PJI (> 3000 WBCs per µL)
  - Yield of synovial fluid culture 50-60%
    - » Reduced by prior antibiotics
  - Coagulase-negative Staph can be considered pathogenic if in >1 culture and compatible cell counts

MASSACHUSETTS GENERAL HOSPITAL HARVARD MEDICAL SCHOOL 26

Case #3

- A 57 year old woman with a history of diabetes, hypothyroidism, and anxiety has undergone total hip replacement. Three weeks postoperatively, she developed erythema, swelling, and incisional drainage. She was taken back to the operative room, where she was found to have purulent infection within the joint pseudocapsule. The polyethylene liner was exchanged but acetabular and femoral components were secure and maintained in place. Operative cultures have grown methicillin-sensitive Staph aureus.

MASSACHUSETTS GENERAL HOSPITAL HARVARD MEDICAL SCHOOL 27

Case #3: Vote

You are asked to provide recommendations about antimicrobial management

A. Nafcillin for six weeks
B. Cefazolin and rifampin for six weeks
C. Cefazolin for four weeks followed by minocycline for two months
D. Cefazolin and rifampin for four weeks followed by minocycline and rifampin for two months
E. Vancomycin for six weeks followed by doxycycline for six months

MASSACHUSETTS GENERAL HOSPITAL HARVARD MEDICAL SCHOOL 28

PJI Management

Surgical Procedure	Most appropriate for:	Antimicrobial Therapy
Debride and retain with exchange of polyethylene liner	Acute infections (early and late); well fixed components	2-6 weeks IV antibiotics 3-6 months oral*, including rifampin if Staph
1 stage exchange (hips)	Acute infections; subacute infections with healthy soft tissues, sensitive organisms	2-6 weeks IV antibiotics 3-6 months oral*, including rifampin if Staph
2 stage exchange "Spacer" utilizing antibiotics in cement	Chronic infections Sinus tracts Resistant organisms	6 weeks IV or highly bioavailable oral

*3 months for hips; 6 months for knees

MASSACHUSETTS GENERAL HOSPITAL HARVARD MEDICAL SCHOOL 30

Case #4

- A 63 year old woman with rheumatoid arthritis is anticipating knee arthroplasty. She takes methotrexate, hydroxychloroquine and low dose prednisone (2.5 mg daily). She has a history of recurrent urinary tract infections. She asks how she might prevent infection after knee replacement.

MASSACHUSETTS GENERAL HOSPITAL HARVARD MEDICAL SCHOOL 31

Case #4: Vote

What do you advise?

A. Stop methotrexate and prednisone two weeks preoperatively
B. Screen for Staph aureus colonization; decolonize if present
C. Screening UA and urine culture, treat if positive
D. 48 hours perioperative prophylaxis with cefazolin
E. Amoxicillin prior to dental procedures for 2 years postoperatively

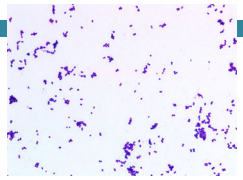
MASSACHUSETTS GENERAL HOSPITAL HARVARD MEDICAL SCHOOL 32

Prevention of PJI

- Immunosuppressives:
  - Stop TNF agents, no need to stop DMARDs or low dose prednisone
- Surgical antibiotic prophylaxis: one dose prior to surgery
- Urinary tract infections:
  - Diagnose and treat symptomatic UTI; no role to screen for asymptomatic bacteriuria
- Dental prophylaxis: No more!
- *Staph aureus* decolonization reduces surgical site infection

MASSACHUSETTS GENERAL HOSPITAL HARVARD MEDICAL SCHOOL 34

Microbiology of Musculoskeletal Infections



MASSACHUSETTS GENERAL HOSPITAL HARVARD MEDICAL SCHOOL 35

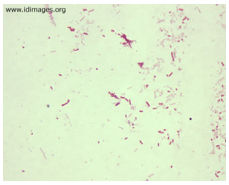
Case #5

- 56 year old man presents to ED with 1-2 week history of atraumatic right knee pain and swelling and low grade fevers; weight bearing is now very uncomfortable.
- He has poorly controlled diabetes. One month ago he travelled to the Dominican Republic where he swam in the ocean, recalls receiving several insect bites. He owns a pet kitten, last saw a dentist three months ago, and denies injection drug use.
- On exam, he has pain with passive range of motion and a moderate effusion.
- ESR 68 CRP 17 mg/dL
  Synovial fluid: 45,000 WBCs (82% neutrophils)
  Negative gram stain

MASSACHUSETTS GENERAL HOSPITAL HARVARD MEDICAL SCHOOL 36

Case #5: Vote

Culture growth at 3 days incubation



What is the most likely organism?

A. *Stenotrophomonas maltophilia*
B. *Salmonella heidelberg*
C. *Staphylococcus aureus*
D. *Kingella kingae*
E. *Pasteurella canis*

MASSACHUSETTS GENERAL HOSPITAL HARVARD MEDICAL SCHOOL 33

Microbiology of Bone and Joint Infections: clinical and epidemiologic clues (1)

Gram Negative Organisms	Clinical Clues
Pseudomonas aeruginosa	Immunocompromised host, indwelling line, history of injection drug use (IDU)
HACEK organisms	Human bite wounds (*Eikenella corrodens*) Recent dental procedure or infection
Kingella kingae (K in HACEK)	Common in children <4yo. Grows poorly in routine culture (diagnose by pcr)
Pasteurella species	Cat or dog bite
Salmonella species	Sickle cell disease, diabetes, immunocompromise. Reptile exposure. Travel to developing world or unsafe food hygiene. +/- antecedent GI illness
Brucella species	Consumption of unpasteurized dairy; travel to endemic areas (Latin America, Mediterranean and Middle East). Sacroiliitis and spondylodiscitis
Streptobacillus moniliformis	Rat bite

MASSACHUSETTS GENERAL HOSPITAL HARVARD MEDICAL SCHOOL 39

Microbiology of Bone and Joint Infections: clinical and epidemiologic clues (2)

Other bacteria and mycobacteria	Clinical Clues
Neisseria gonorrhoeae	Triad of Tenosynovitis, Dermatitis, Arthritis.
Mycoplasma species	Humoral immunodeficiency (CVID, XLA) Postpartum women. Difficult to grow in routine culture. "Fried egg" morphology in culture
Borrelia burgdorferi (Lyme)	Northeast and Upper Midwest with tick exposure. Subacute monoarthritis of large joints (knee most common) with large effusions.
Tuberculosis	Subacute to chronic infections including vertebral osteomyelitis (Pott's) and septic arthritis
Non-tuberculous mycobacteria	Environmental water exposure (fishermen, fish tanks). Tenosynovitis of hands

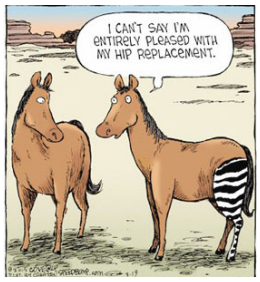
MASSACHUSETTS GENERAL HOSPITAL HARVARD MEDICAL SCHOOL 40

Microbiology of Bone and Joint Infections: clinical and epidemiologic clues (3)

Fungal Infections	Clinical Clues
Candida species	Seen in immunocompromised hosts, IDU
Molds	Madura Foot (barefoot walking) Environmental contamination (e.g. open fracture with soil contamination) Immunocompromised hosts (neutropenia)
Coccidioides species, Blastomyces dermatitidis (Histoplasma capsulatum less frequent)	Subacute to chronic monoarthritis, long bone osteomyelitis, and vertebral disease. Usually associated with symptomatic or asymptomatic pulmonary findings (esp. cocci). Immunocompromised host

MASSACHUSETTS GENERAL HOSPITAL HARVARD MEDICAL SCHOOL 41

Thank you!



MASSACHUSETTS GENERAL HOSPITAL

HARVARD MEDICAL SCHOOL

42

07

Syndromes that Masquerade as Infections

Dr. Karen Bloch

07 – Syndromes that Masquerade as Infections

Speaker: Karen C Bloch, MD, MPH, FIDSA, FACP

2020 INFECTIOUS DISEASE BOARD REVIEW

Syndromes that Masquerade as Infections

Karen C. Bloch, MD, MPH, FIDSA, FACP
Associate Professor, Division of Infectious Diseases
Vanderbilt University Medical Center

*Special Thanks to Dr. Bennett Lorber!

Disclosures of Financial Relationships with Relevant Commercial Interests

- None

Mimics

- Many conditions masquerade as infections.
- Often with fever
- Sometimes focal abnormality
  - Cellulitis
  - Pneumonia
  - Lymphadenopathy
  - Splenomegaly

VS

2018 ID Board Content

Medical Content Category	% of exam
Bacterial Diseases	27%
HIV Infection	15%
Antimicrobial therapy	9%
Viral Diseases	7%
Travel and Tropical Medicine	5%
Fungi	5%
Immunocompromised Host (non HIV)	5%
Vaccinations	4%
Infection Prevention and Control	5%
General Internal Medicine, Critical Care & Surgery	**18%**
Total	100%

Test taking tip

- Just as for infections, look for "buzz words" and "hooks"
- For infections:
  If I say "rabbit", you say…..

Test taking tip

- For infections:
  If I say "rabbit", you say…..

TULAREMIA

Test taking tip

I say ”Chitlins”

You say…..

Test taking tip

I say ”Chitlins”

You say…..

YERSINIA

Test taking tip

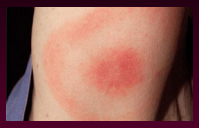
I say ”Bull’s-eye rash”

You say…..

Test taking tip

I say ”Bull’s-eye rash”

You say…..

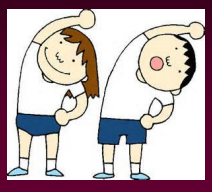


Lyme disease
(or Erythema migrans or STARI)

My Approach to Mimics

- Think like an Internist.
- The key is recognition, not treatment.
- This talk will emphasize illustrative case
- Goal is to cover lots of non-infectious diseases rather than in-depth discussion

Quick Warm Up!



Question 1

A young man has oral and genital ulcers. You suspect Behçet's disease. Which of the following is most consistent with that diagnosis?

A. Evanescent, salmon-colored rash
B. High ferritin
C. Saddle nose deformity
D. Pustule at site of venipuncture
E. Posterior cervical adenopathy

Question 2

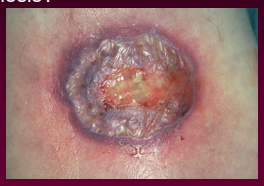
Sweet Syndrome is *most* likely to occur in a patient with which of the following illnesses?

A. Ulcerative colitis
B. Adult onset Still's Disease
C. Acute leukemia
D. Systemic lupus
E. Ankylosing spondylitis

Question 3

A patient has a slowly enlarging ulcerated skin lesions on his shin after being hit by a soccer ball. Which of the following is the most likely diagnosis?

A. Pyoderma gangrenosum
B. Ecthyma gangrenosum
C. Erythema nodosum
D. Sweet Syndrome
E. Behçet's disease



Now on to our discussion, starting with a case.

Case 1

- 26yo man presents with a 1-month h/o fever, night sweats and fatigue. He was evaluated by his PCP with normal bloodwork and a positive monospot test. He was diagnosed with mononucleosis, but symptoms have persisted. He lives in Indiana with his wife and 2 yo son. They have 2 cats.

Case 1

- Exam:
  - Vitals:
    - T=38.4ºC, HR=118bpm
  - No lymphadenopathy
  - Palpable spleen tip
  - No rash
- Labs
  - CBC
    - WBC=2.7, plt=53
    - Normal H/H
  - Normal Cr
  - AST/ALT=38/200
  - Alk phos=494, bili=1.9
  - Ferritin=35,148 mg/ml

Question 4

- What is the most appropriate next study?
  - A. Flow cytometry of whole blood
  - B. ANA profile
  - C. EBV serologies
  - D. Soluble IL-2 receptor alpha level
  - E. Toxoplasma titer

Hemophagocytic Lymphohistiocytosis

- Immune activation syndrome
  - Primary: Familial due to genetic mutation
  - Secondary: Most commonly triggered by infections (EBV or other herpes group viruses, HIV, histoplasmosis, *Ehrlichia*, etc) or malignancy (lymphoma, leukemia)

HLH: Diagnostic Criteria

- Requires >=5/8
  - Fever
  - Splenomegaly
  - Cytopenias (any line)
  - Hypertriglyceridemia
  - Ferritin >500 mg/mL
  - Elevated soluble IL-2 receptor alpha (aka CD25)
  - Low NK cell activity
  - Hemophagocytosis on pathology

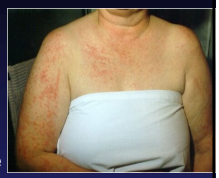
HLH Clues

- EBV or other infection with progressive symptoms
- Massively elevated ferritin
- Cytopenia with negative ID evaluation

Case 2

- A 39-year-old woman is seen on day 4 of hospitalization for high fever and leukocytosis. The fever had been present for 3 ½ weeks and was accompanied by severe arthralgias of the knees, wrists and ankles as well as myalgias. A severe sore throat was present during the first week of the illness.

- Exam: T=104.2º F.
- Tonsilar swelling and erythema is present, with tender cervical LN.
- Spleen tip is palpable.
- The R wrist is swollen and painful.
- A rash present on the trunk and extremities, most prominently under the breasts and in the area of her underwear waistband.



Adult Still's Disease (Adult Onset JRA)

Yamaguchi Criteria: (5 features with 2 major criteria)

Major:	Minor:
1. Fever >39ºC for ≥1week	1. Sore throat
2. Arthritis/arthralgia >2 wks	2. Lymphadenopathy
3. Typical rash (during febrile episodes)	3. Lg Liver or spleen
4. Leukocytosis ≥10K with >80% PMNs.	4. Abnl LFTs
	5. Negative ANA & RF

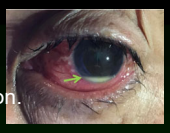
Adult Still's

- Buzz words and associations:
  evanescent, **salmon-colored** rash

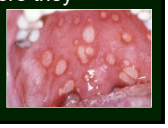
- Other clues:
  - Multi-system illness
  - Elevated ferritin
  - Pharyngitis
  - Koebner phenomenon = rash elicited by stroking skin or areas of pressure.

Case 3

- A 24-year-old man is referred from the ED for ulcers of the mouth and penis. Three months ago he came to the U.S. from Japan to attend graduate school.
- He has a history of intermittent, painful oral ulcers for 3-4 years. Four days ago he developed a painful ulcer on the penile shaft. He recalls a similar lesion 2 months earlier. He takes no medicines and denies sexual contact for the past 5 years.



- Exam: afebrile.
- Left eye is inflamed and there is a hypopyon. Numerous ulcers on the oral mucosa.
- There is a 0.5cm ulcer on the penis.
- A 6mm papulo-pustular lesion is present in the right antecubital fossa; the patient says that is where they drew blood yesterday in the ED.



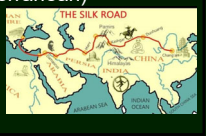
- Labs: Hb 12.1; WBC 13,750. HIV negative

Question 6

- The most likely diagnosis is?
  - A. Syphilis
  - B. Behçet's disease
  - C. Herpes simplex virus infection
  - D. Sarcoidosis
  - E. Cytomegalovirus infection

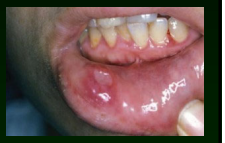
Behçet's disease

- Pleomorphic vasculitis with clinical diagnosis
  Recurrent oral ulcers (≥3 per year) PLUS 2 of the following
  - recurrent genital ulcers
  - eye (uveitis, retinitis, hypopion) or skin lesions (EN, papules)
  - pathergy (red papule developing 24-48 hrs after needlestick)
- Think "silk road" ancestry (Asia->Mediterranean)
- Less common manifestations
  - GI disease (abdo. Pain, bloody diarrhea)
  - CNS disease (aseptic meningitis)
  - Arterial and venous thrombosis
- Treatment: colchicine



Behçet's disease

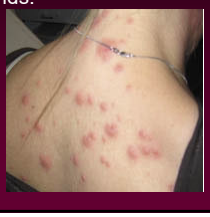
- Buzz words and associations:
  - Mucosal ulcers on mouth and/or genitals PLUS….
    - GI symptoms (vs CMV)
    - Aseptic meningitis (vs HSV)
    - Visual changes
    - Pathergy (needle or IV site)
  - Asian or Mediterranean ancestry



Case 4

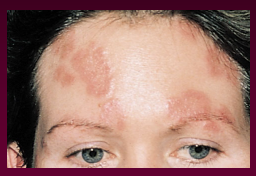
- A 38-year-old woman with AML is admitted with fever. She underwent induction chemotherapy 2 weeks prior, complicated by neutropenic fever. Following marrow recovery, she was d/c to home. The day of admit she developed fever without localizing symptoms. CBC showed a white blood cell count of 12,250 with 20% bands.
- Exam: T 101.4; P 98; otherwise unremarkable.
- Blood cultures were sent, and she was admitted and started on broad spectrum empiric antibiotics.

- HD 2: Fever persists, with interval development of raised, red-purple, tender, non-pruritic papules and nodules on her face, neck and the dorsum of her hands.



HD 3: Fever persists; some of the papules develop a plaque-like appearance

HD 4: biopsy: dense dermal perivascular infiltrates of neutrophils without evidence of vasculitis; stains for organisms negative.



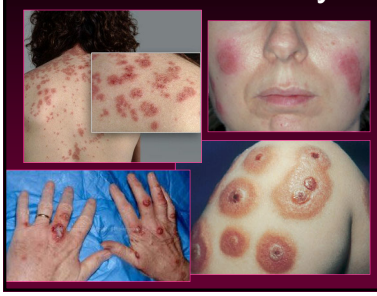
Question 7

- Which of the following is the most likely diagnosis?
  - A. Ecthyma gangrenosum
  - B. Pyoderma gangrenosum
  - C. DRESS
  - D. Leukemic infiltrates
  - E. Sweet syndrome

Sweet Syndrome

- AKA acute febrile neutrophilic dermatosis
- Three variants:
  - Idiopathic or "classical"->50% (IBD, post viral illness, preg, etc)
  - Malignancy associated~20% (may precede dx, AML most frequent)
  - Drug induced-G-CSF most common, usually 2 wk after exposure
- Fever universally present
- Rarely oral ulcers or extra-cutaneous disease characterized by neutrophilic infiltrate on path
- Labs notable for leukocytosis with left shift, inc ESR & CRP
- Path diagnostic—Neutrophilic infiltrate without vasculitis

Sweet Syndrome



- Lesions appear **abruptly** and usually **tender**.
- May be single or multiple, often involving **dorsum of hand**.
- Red, violaceous, or yellow center
- Nodular or **plaque-like**
- Central umbilification with **target appearance**

Sweet Syndrome

- Buzz words and associations:
  - Acute
  - Febrile
  - Neutrophilic (peripheral and on path)
  - Dermatosis

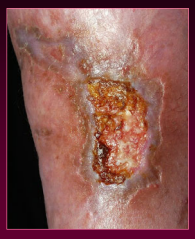
Be suspicious in patients with malignancy (esp AML, past or present), IBD, recent URI, vaccination, pregnancy, or colony stimulating factor use in preceding 2 weeks

Case 5

- A 33-year-old recent immigrant from Central America is seen for a chronic ulcer of the leg.
- The ulcer has progressively enlarged over 3 months. after he bumped his leg on a table. Several courses of oral antibiotics have been given with no response.
- For the past year he has been troubled by an "upset stomach" = intermittent abdominal cramps, frequent diarrhea; and, on 2 occasions, blood in the stool. He has also had intermittent fever, sometimes accompanying diarrhea, sometimes not.

- Exam:
  - T 100.2; skin lesion on leg (see image)
  - Slight, diffuse abdominal tenderness.
  - Otherwise unremarkable.
- Labs:
  - Hb 12.4; WBC 11,150, ESR=79, CRP=110
  - UA normal
  - Basic metabolic panel normal
  - Chest x-ray normal

Leg lesion



Painful and irregularly shaped ulcer with undermined borders

Question 8

Which one of the following is the most likely diagnosis?

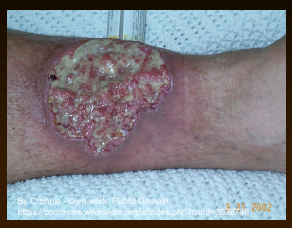
A. Ulcerative colitis
B. Cutaneous leishmaniasis
C. Amebic colitis
D. Necrotizing fasciitis
E. Squamous cell cancer

Pyoderma gangrenosum

- *Another* neutrophilic dermatosis
  - Indolent, fever rare (vs Sweet)
- Papule at site of often trivial trauma, progressing to a **painful** ulcer with violaceous or red border and necrotic base
- >50% of cases occur with systemic illnesses (but may precede dx, or occur independent of flares)
  - IBD (MOST COMMON COMORBIDITY; UC>Crohn's)
  - Inflammatory arthritis
  - Solid organ or heme malignancy

Pyoderma Gangrenosum

- Buzzwords & Hooks
  - Minor trauma (Pathergy) frequent
  - Painful, progressive **undermined ulcer** with violaceous edges and **necrotic base**
  - Concomitant IBD, arthritis, neoplasm



Case 6

A 79-year-old woman is seen for 3 weeks of fever and fatigue. Except for hypertension, she has no medical problems. Has noted jaw discomfort when chewing food, and 1 week ago had a brief episode of double vision. One week before she became ill she attended a wedding at which she ate pork from a whole pig that was roasted on a spit over an open fire.

Question 9

Which of the following is most likely to yield a diagnosis?

A. Anti-neutrophil cytoplasmic antibody (ANCA)
B. *Taenia solium* serology
C. Blood cultures
D. Arteriography
E. Temporal artery biopsy

Giant Cell Arteritis

- GCA (AKA temporal arteritis)= pan-arteritis of extracranial branches of the carotid.
- A disease of the older adult: Almost all >50years
- Clinical findings: Fever, HA, scalp or TA tenderness, jaw claudication, amaurosis fugax
- Marked inc ESR/CRP suggestive, TA biopsy diagnostic
- Immediate steroid therapy indicated if visual changes to prevent blindness (won't affect biopsy yield for up to two weeks).

Giant Cell Arteritis

Buzz words and associations:

Age >50 years; fever (FUO) and:

scalp or TA tenderness

diplopia or transient visual loss

jaw or tongue fatigue or pain while chewing

high sedimentation rate

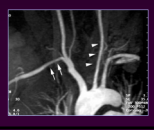
Polymyalgia Rheumatica (PMR)

Buzz words and associations:

- Half of all patients with polymyalgia rheumatic (PMR) have concomitant GCA
- Fever not prominent (may be low grade) in absence of GCA
- Aching and **morning stiffness** in proximal muscles of shoulder and hip girdle
- Gel phenomenon

Takayasu Arteritis

- Another large vessel vasculitis involving aorta, branches and pulmonary arteries.
- Buzz words and associations:
  - Young woman (>80%), Asian ancestry
  - Subacute onset of fever, weight loss, arthralgias and myalgias
  - Carotidynia (pain with palpation), decreased pulses
  - Extremity claudication; visual changes; TIAs
- Dx: Arteriography



Case 7

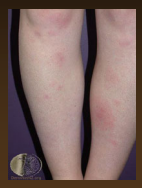
- A 37-year-old female presents with fever and joint pain. She is a long-distance runner and in excellent health.
- Three weeks prior she noted R knee pain after a long run. She was treated with steroid injection with transient improvement, but subsequently developed bilateral ankle pain and redness. She notes subjective chills and sweats.
- She does recall several tick bites over the last 2 months

Exam:

T 101.2; Pulse 72; BP 110/70

Bilateral synovial thickening of ankles with warmth and tenderness to passive movement

Skin exam with painful pre-tibial nodules



Labs:

WBC 8.8 (76% segs)

CRP=167

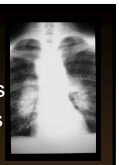
Uric acid=4.4, RF <15, CCP negative

Question 10

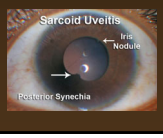
Which of the following is most likely to be diagnostic?

A. Chest x-ray
B. Serology for *Borrelia burgdorferi*
C. Urine *Histoplasma* antigen
D. Arthrocentesis
E. Skin biopsy

Sarcoidosis

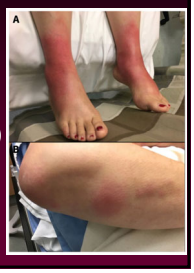


- A common mimicker with protean presentations
- Extra-pulmonary presentations in ~1/3 of cases
- Lofgren Syndrome
  - Clinical diagnosis: Triad of hilar LAN, acute arthritis, EN
  - Women, ankles (>90%), fevers common
- BUZZ WORDS
  - Hilar LAN, EN, parotid enlargement, uveitis
  - Aseptic meningitis with basilar enhancement
  - Non-caseating granulomas



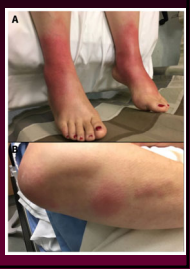
Erythema nodosum

- NO cause >50% of cases
- Drugs: sulfonamides, Penicillins
- Oral contraceptives
- Sarcoid (Lofgren's syndrome)
- Ulcerative colitis (or Crohn's or Bechet's)
- Microbes:
  - EBV, Hep B/C
  - *Streptocci*, *Bartonella,* TB
  - Endemic fungi



Erythema nodosum

- NO cause >50% of cases
- Drugs: sulfonamides, Penicillins
- Oral contraceptives
- Sarcoid (Lofgren's syndrome)
- Ulcerative colitis (or Crohn's or Bechet's)
- Microbes:
  - EBV, Hep B/C
  - *Streptocci*, *Bartonella,* TB
  - Endemic fungi



Case 8

- A 19-year-old recent immigrant from Iraq is hospitalized for 2 day history of fever and severe abdominal pain
- He says he has had similar episodes on at least 3 previous occasions over the past 7 years. At the first episode he underwent appendectomy; the removed appendix was normal. Other episodes resolved spontaneously after 2-3 days.

- Exam:
  T 102.2; pulse 114; no rash
  Abdominal guarding, rebound tenderness, hypoactive bowel sounds.
- Labs:
  Hb 12.4; WBC 16,650; UA normal
  Basic metabolic panel normal
  no occult blood in stool
  CT of abdomen and pelvis normal

Question 11

The most likely diagnosis is:

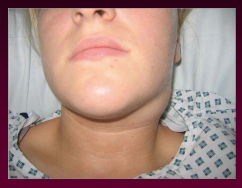
A. Hereditary angioneurotic edema
B. Familial Mediterranean fever
C. Systemic lupus erythematosus
D. Crohn's disease
E. Acute intermittent porphyria

Familial Mediterranean Fever

- Hereditary auto-inflammatory disease
- Sporadic, recurrent attacks of fever & serositis (peritonitis, pleuritis, arthritis) manifesting as pain.
- Dx: Genetic testing
- Buzz words and associations:
  - Periodic episodes (fever PLUS…)
  - Colchicine responsive illness
  - Mediterranean ethnicitiy

Case 9

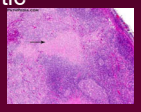
- A 26-year-old medical student presents with fever and cervical adenopathy.
- She was completely well until 9 days ago when she had the acute onset of fever and vague neck discomfort. She had no sore throat and no dental or scalp problems.



- Exam:
  T 101.4; unilateral anterior and posterior cervical enlarged lymph nodes, firm, and mildly tender. Otherwise unremarkable.
- Labs:
  Hb 13.9; WBC 4,900 (9% atypical lymphocytes)
  Basic metabolic panel normal
  Chest x-ray normal
  ESR=72
  Monospot: Negative

- Serologic studies:
  EBV consistent with prior infection
  CMV, *Toxoplasma*, *Bartonella* titers negative
  RF, ANA, ds-DNA negative
- Lymph node pathology:
  necrotizing lymphadenitis with histiocytic infiltrate and phagocytosed debris.

  Stains for AFB and fungi negative.



Question 12

Which one of the following is the most likely diagnosis?

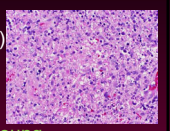
A. Cat Scratch Disease
B. Adult Still's Disease
C. Sarcoidosis
D. Kikuchi Disease
E. Non-Hodgkin Lymphoma

Kikuchi Disease

- AKA acute necrotizing histiocytic lymphadenitis
- Self-limited condition of unknown cause
- Typically young women
- No racial or ethnic proclivity (more common in Asia)
- fever & cervical LAN (esp posterior, usually unilateral).
- May also see morbiliform exantham, rarely extra cervical LAN, aseptic meningitis, uveitis.
- Variably leukopenic and atypical lymphocytes (25% of cases).

Kikuchi's Disease

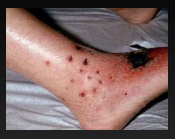
- Diagnosis by lymph node biopsy:
  - necrotizing histiocytic infiltrate (not neutrophils) and fragments of nuclear debris.
- Buzz words and associations:
  - Acute onset fever and cervical adenopathy in young woman
  - Atypical lymphocytes (mono-like syndrome)
  - Path: necrotizing adenitis with histiocytosis

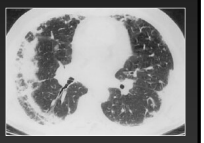


Case 10

- A 41-year-old woman is seen for fever, worsening respiratory symptoms, and a rash.
- She has long-standing asthma with frequent exacerbations
- She uses an inhaler several times a day and was recently placed on a leukotriene receptor antagonist. She is being tapered off steroids which she has taken for several months.

- Exam: Temp 101.5; RR 24
- Diffuse wheezing; palpable purpura with nodules on elbows and legs.
- Labs: WBC 15,230 (22% eosinophils).
- CT scan: bilateral peripheral infiltrates.
- Skin nodule biopsy: granulomas





Question 13

Which one of the following is the most likely diagnosis?

A. Strongyloidiasis
B. Disseminated histoplasmosis
C. Sarcoidosis
D. Allergic bronchopulmonary aspergillosis
E. Churg-Strauss syndrome

Churg-Strauss Syndrome

- AKA eosinophilic granulomatosis with polyangiitis (EGPA)
- Multisystem, small vessel vasculitis with allergic rhinitis, asthma, peripheral and lung eosinophilia.
- Most often involves lung and skin, but can involve heart, GI tract, and nervous system.
- Presence of blood eosinophilia and peripheral pulmonary infiltrates in setting of difficult to control asthma
- Tapering of steroids often "unmasks" EGPA
- May be p-ANCA positive.

Churg-Strauss Syndrome

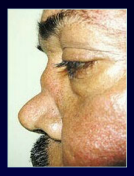
- Buzz words and associations:
  - Longstanding asthma
  - New infiltrates and eosinophilia (>10%) as steroids tapered.
  - Rash (tender nodules on extensor surfaces, purpura, ecchymosis, necrosis)
  - Fever UNCOMMON (until late)

Case 11

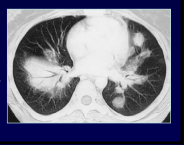
- A 38-year-old man is seen for a 6-week history of cough, intermittent fever and night sweats.
- He has had nasal stuffiness for 4-5 months with occasional epistaxis.
- He lives in Philadelphia, and 6 months ago traveled to Cincinnati, OH on business.
- He has no pets and takes only an OTC decongestant

Exam:
- T 100.2; RR 18;

Nasal deformity with perforation of septum
Lungs clear; rest of exam normal.



- Labs:
  WBC 6,900 with normal differential;
  UA 30-50 RBC; BMP normal
  Chest CT: bilateral nodules with cavitation.



Question 14

- The diagnosis will most likely be supported by which one of the following?
  - A. c-ANCA
  - B. Anti-glomerular basement membrane Ab
  - C. Histoplasma urine antigen
  - D. Angiotensin converting enzyme (ACE)
  - E. Pulmonary angiogram

Granulomatosis with polyangiitis (GPA) (formerly Wegener's)

- Systemic vasculitis of medium and small arteries.
- Primarily involves the upper and lower respiratory tracts and kidneys (Pulmonary-Renal Syndrome).
- Limited to upper respiratory tract or lungs in 25% (most often young women).
- Variably involves joints, eyes, skin, and nervous system.

Granulomatosis with polyangiitis

- Dx:
  Suggestive: Pos ANCA (~85%)
  IFA: c-ANCA.
  ELISA: anti-proteinase 3 (PR3-ANCA)
  Diagnostic: Biopsy

Buzz words and associations:
Nasal symptoms (Saddle nose and perforation)
CT nodules
Respiratory and renal findings (hematuria)

Case 12

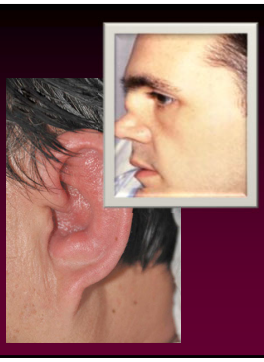
- A 42-year-old man is seen for his third episode of cellulitis of the external ear.
- Two previous episodes involving the same ear, 2 and 5 months ago, responded very slowly to antibiotics.
- He has a several year history of chronic nasal stuffiness and had an episode of knee arthritis in the past year but is otherwise well.

Case 12

Exam:
Afebrile
Left auricle is inflamed and tender, ear lobe is spared.

He has a saddle-nose deformity; the nasal mucosa is normal.

Labs: normal



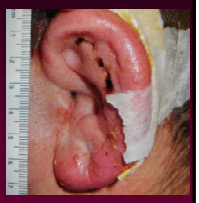
Question 15

The most likely diagnosis is?

A. Invasive external otitis
B. Leprosy
C. Granulomatosis with polyangiitis
D. Relapsing polychondritis
E. Congenital syphilis

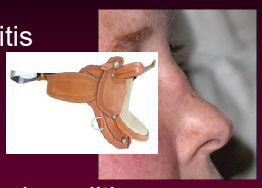
Relapsing Polychondritis

--Immune-mediated condition.
--Inflammation of cartilaginous structures, particularly ears, but also nose, eyes, joints, and airways.
--Clinical diagnosis.



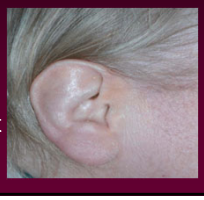
Saddle-nose Deformity

Relapsing polychondritis
Lepromatous leprosy
Congenital syphilis
Leishmaniasis
Granulomatosis with polyangiitis
Cocaine use



Relapsing Polychondritis

- Buzz words and associations:
  - Recurrent "cellulitis" (cartilage inflammation)
  - Saddle-nose
  - Cauliflower ear
  - Sparing of ear lobe
  - Parasternal joint involvement



That's all!

Karen.bloch@vumc.org

08

Endocarditis of Native and Prosthetic Devices, and Infections of Pacers and Ventricular Assist Devices

Dr. Henry Chambers

08 - Endocarditis of Native and Prosthetic Devices, and Infections of Pacers and Ventricular Assist Devices

Speaker: Henry Chambers, MD

2020 INFECTIOUS DISEASE BOARD REVIEW

Endocarditis of Native and Prosthetic Devices, and Infections of Pacers Ventricular Assist Devices

Henry F. Chambers, MD
Professor of Medicine, Emeritus
San Francisco General Hospital
University of California San Francisco

Disclosures of Financial Relationships with Relevant Commercial Interests

- None

Topics for Discussion

- Diagnosis
- Native valve endocarditis
- Culture-negative endocarditis
- Prosthetic valve and device-related endocarditis

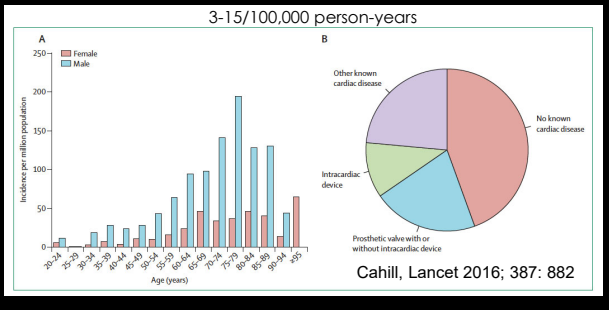
Diagnosis

Q1. Which one of the following statements is correct?

1. Staphylococcus aureus is the most common cause of bacterial endocarditis
2. Dental procedures carry a substantial risk for streptococcal endocarditis for patients with predisposing cardiac lesions
3. Three-quarters of patients with endocarditis have a known underlying cardiac predisposing condition
4. Fever and a new cardiac murmur are present in the majority of patients with endocarditis

Epidemiology

3-15/100,000 person-years



Cahill, Lancet 2016; 387: 882

08 - Endocarditis of Native and Prosthetic Devices, and Infections of Pacers and Ventricular Assist Devices

Speaker: Henry Chambers, MD

Clinical Signs and Symptoms

Finding	Approximate Prevalence, %
Fever	90
Murmur	70-85
New murmur	50
Worsening old murmur	20
Peripheral stigmata (e.g., Osler's)	20% or less
Heart failure, cardiac complications	20-50
CNS complications	20-40

Arch Intern Med. 2009;169:463-473

Microbiology

Organisms	Approximate % of Total
Staphylococci	**40-50**
S. aureus	30-40
Coag-neg	10
Streptococci	**25-30**
Viridans group	20
S. gallolyticus	5
Groups B, C, D	5
Enterococcus	**10**
HACEK	**1-2**
Culture-negative	**3-5**

Arch Intern Med. 2009;169:463; Antimicrob Agents Chemother. 2015;60:1411; Clin Infect Dis. 2018;66:104; Lancet 2016; 387: 882

Modified Duke Criteria for Diagnosis of Endocarditis

Definite pathologic diagnosis	Definite Clinical Diagnosis	Possible Clinical Diagnosis
Organisms on histology or culture of vegetation, intracardiac abscess or peripheral embolus OR Evidence of a vegetation or intracardiac abscess, confirmed by histology showing active endocarditis	Two major criteria OR Five minor criteria OR One major plus three minor criteria	Three minor criteria OR One major plus one minor criteria

If criteria either for definite or for possible endocarditis are not met, the diagnosis of infective endocarditis is rejected.

Duke Major Clinical Criteria for Diagnosis of Endocarditis

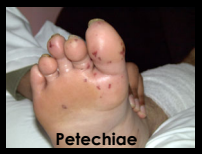
Positive blood cultures	Positive Echocardiogram	Regurgitant murmur
Typical microorganisms* from 2 separate blood cultures OR Persistently positive blood cultures (two > 12h apart, all of 3 or majority of ≥ 4) OR Single positive blood culture for Coxiella burnetii or phase I IgG antibody titer >1:800	Vegetation, defined as an oscillating intracardiac mass on a valve or supporting structure OR Abscess OR New partial dehiscence of a prosthetic valve	New (worsening old murmur does not count)

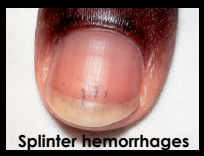
**Staphylococcus aureus*, viridans groups streptococci, *Streptococcus gallolyticus*, HACEK species (*Hemophilus* species, *Aggregatibacter*, *Cardiobacterium*, *Eikenella*, *Kingella*), and community-acquired enterococci in absence of a primary focus.

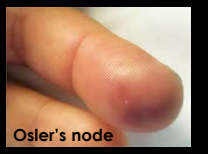
Duke Minor Clinical Criteria for Diagnosis of Endocarditis

- Presence of predisposing cardiac condition or intravenous drug use
- Temperature ≥38.0ºC (100.4ºF)
- Vascular phenomena: systemic arterial emboli, septic pulmonary emboli, mycotic aneurysm, intracranial hemorrhage, conjunctival hemorrhages, or Janeway lesions
- Immunologic phenomena: glomerulonephritis, Osler nodes, Roth spots, or rheumatoid factor
- Positive blood cultures that do not meet major criteria, OR serologic evidence of active infection with organism consistent with infective endocarditis

Microvascular/Immunologic Phenomena


Petechiae


Splinter hemorrhages


Osler's node


Roth spots

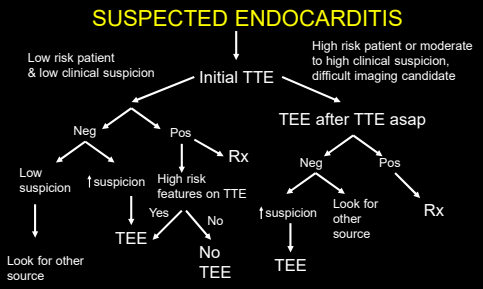

Subconjunctival hemorrhages


Janeway lesion

08 - Endocarditis of Native and Prosthetic Devices, and Infections of Pacers and Ventricular Assist Devices

Speaker: Henry Chambers, MD

Role of Echocardiography



What is High Risk?

- High risk patients (examples)
  - Prosthetic valve
  - Congenital heart disease
  - Previous endocarditis
  - New murmur, heart failure, heart block, stigmata of IE
- High risk TTE (examples)
  - Large or mobile vegetations, anterior MV leaflet veg
  - Valvular insufficiency, perivalvular extension, valve perforation
  - Ventricular dysfunction

Risk of Endocarditis Following an At-Risk Dental Procedure

Predisposing condition	Prophylaxis	Risk of Endocarditis
Prosthetic valve	No	1/10,700
Native valve	No	1/46,000
PV or NV	Yes	1/149,000

Duval, Clinical Infectious Diseases 2006; 42:e102–7

AHA Guidelines: Prevention of Endocarditis

Table 3. Cardiac Conditions Associated With the Highest Risk of Adverse Outcome From Endocarditis for Which Prophylaxis With Dental Procedures Is Reasonable

Prosthetic cardiac valve or prosthetic material u… cardiac valve repair
Previous IE
Congenital heart disease (CHD)*
Unrepaired cyanotic CHD, incl… …ve shunts and conduits
Completely repaired congen… …defect with prosthetic material or device, whether place… …y or by catheter intervention, during the first 6 months aft… …edure†
Repaired CHD wi… …ual defects at the site or adjacent to the site of a prosthetic patch or prosthetic device (which inhibit endothelialization)
Cardiac transplantation recipients who develop cardiac valvulopathy

*Except for the conditions listed above, antibiotic prophylaxis is no longer recommended for any other form of CHD.
†Prophylaxis is reasonable because endothelialization of prosthetic material occurs within 6 months after the procedure.

Dental Procedures

- Prosthetic valve
- Previous infective endocarditis
- Congenital heart disease
  - Unrepaired
  - Within 6 mo of repair
  - Incomplete repair
- Transplant cardiac valvulopathy

Circulation. 2007;116:1736-1754

Native Valve Endocarditis

AHA Scientific Statement

Infective Endocarditis in Adults: Diagnosis, Antimicrobial Therapy, and Management of Complications

A Scientific Statement for Healthcare Professionals From the American Heart Association

Endorsed by the Infectious Diseases Society of America

Larry M. Baddour, MD, FAHA, Chair; Walter R. Wilson, MD; Arnold S. Bayer, MD; Vance G. Fowler, Jr, MD, MHS; Imad M. Tleyjeh, MD, MSc; Michael J. Rybak, PharmD, MPH; Bruno Barsic, MD, PhD; Peter B. Lockhart, DDS; Michael H. Gewitz, MD, FAHA; Matthew E. Levison, MD; Ann F. Bolger, MD, FAHA; James M. Steckelberg, MD; Robert S. Baltimore, MD; Anne M. Fink, PhD, RN; Patrick O'Gara, MD, FAHA; Kathryn A. Taubert, PhD, FAHA; on behalf of the American Heart Association Committee on Rheumatic Fever, Endocarditis, and Kawasaki Disease of the Council on Cardiovascular Disease in the Young, Council on Clinical Cardiology, Council on Cardiovascular Surgery and Anesthesia, and Stroke Council

Circulation. 132:1435-86, 2015

08 - Endocarditis of Native and Prosthetic Devices, and Infections of Pacers and Ventricular Assist Devices

Speaker: Henry Chambers, MD

Q2. A 63 y/o. man with no significant past medical history presents with a week of fever, rigors, and progressive dyspnea on exertion.

- Exam : BP 160/40 P110 , 39.5
  - Rales ½ way up bilaterally
  - Loud diastolic decrescendo murmur, lower left sternal border
- Labs and studies
  - WBC 23,000 90% PMNS, HCT 30. Platelets 110.
  - Creatinine 1.6 mg/dl
  - TTE 1.5 cm oscillating mass, on bicuspid AV with severe aortic regurgitation
- 3/3 blood cultures: Gram positive cocci in clusters.

Q2. What antibiotic regimen would you recommend pending further information about Gram-positive cocci?

1. Nafcillin
2. Vancomycin
3. Vancomycin + nafcillin
4. Vancomycin + gentamicin
5. Vancomycin + gentamicin + rifampin

Native Valve S. aureus IE

Regimen	Duration	Comments
MSSA		
Nafcillin or oxacillin	6 wk	2 wk uncomplicated R-sided IE (IDU)
Cefazolin	6 wk	Pen-allergic naf-intolerant patient (equivalent to naf)
MRSA		
Vancomycin	6 wk	For MSSA if beta-lactam hypersensitivity
Daptomycin	6 wk	≥ 8 mg/kg/day, vanco alternative

No gentamicin, no rifampin

Q3. A 63 y/o woman with a history of mitral valve prolapse presents with 3 weeks of low-grade fever, fatigue, generalized weakness, weight loss, arthralgias. She is first chair violinist for the local orchestra

- Exam: BP 135/90 P100 , 38.2°C
  - 3/6 holosystolic murmur, radiating the the axilla
  - Lungs are clear, no peripheral stigmata of endocarditis
- Serum creatinine 1.2 mg/dl
- TTE: mitral valve prolapse with 0.5 cm vegetation on anterior leaflet, moderate regurgitation
- 3/3 blood cultures from admission positive for *Streptococcus mitis*, penicillin MIC = 0.25 μg/ml, ceftriaxone MIC = 0.25 μg/ml.

Q3. What antibiotic regimen would you recommend for definitive therapy of this patient's infection?

1. Penicillin for 6 weeks
2. Penicillin + gentamicin for 4 weeks
3. Ceftriaxone for 4 weeks
4. Penicillin + gentamicin for 2 weeks then penicillin for 2 weeks
5. Ceftriaxone + gentamicin for 2 weeks then ceftriaxone for 2 weeks

Treatment of VGS and Strep. gallolyticus Native Valve Endocarditis

- Pen MIC ≤ 0.12 μg/ml
  - Penicillin or ceftriaxone + gent x 2 weeks
  - Penicillin, ceftriaxone, vancomycin x 4 weeks
- Pen MIC > 0.12 μg/ml, < 0.5 μg/ml
  - Penicillin or ceftriaxone (4 wk) + gent (2 wk)
  - Ceftriaxone or vancomycin (4 wk)
- Pen MIC ≥ 0.5 μg/ml (Gemella and nutritionally deficient species, Abiotrophia and Granulicatella)
  - Penicillin or ceftriaxone + gent
  - Vancomycin
  - Duration 4-6 weeks (two weeks of gent may be sufficient)

Q4. A 72 y/o man type 2 diabetes mellitus, stage II chronic kidney disease (CKD), and a history of mild aortic stenosis is admitted to the hospital with fever, dysuria, and urinary frequency.

- Exam: T38.9°C, Pulse 110 , BP 145/95 mm Hg.
  - Lungs are clear
  - 3/6 systolic ejection murmur at the right upper sternal boarder.
- Lab results
  - Serum glucose 340 mg/dl
  - Serum creatinine 1.7 mg/dl, BMP otherwise normal
  - UA: 3+ protein, 20-50 wbcs/high power field, 4+ glucose.
  - Two blood cultures and a urine culture are positive for ampicillin-susceptible *Enterococcus faecalis*.

Q4. What antibiotic regimen would you recommend for definitive therapy of this patient's infection?

1. Ampicillin for 2 weeks
2. Penicillin + gentamicin for 4 weeks
3. Ampicillin + gentamicin for 4 weeks
4. Ampicillin + ceftriaxone for 6 weeks
5. Daptomycin for 8 weeks

Enterococcal Endocarditis

Regimen	Duration	Comments
Pen or amp + gent	4-6 wk	Pen S, Gent 1 mg/kg q8h, 6 wk for PVE, symptoms >3 mo*
Amp + ceftriaxone	6 wk	Pen S, aminoglycoside susceptible or resistant
Pen or amp + strep	4-6 wk	Gent resistant, strep synergy, ClCr ≥ 50
Vanco + gent	6 wk	Pen resistant or beta-lactam intolerant (toxic!)
Linezolid or dapto	> 6 wk	VRE: Dapto 10-12 mg/kg & combo with amp or ceftaroline

*Limited data that 2 weeks of gent is sufficient

HACEK Organisms

- Haemophilus species
- Aggregatibacter species
- Cardiobacterium hominis
- Eikenella corrodens
- Kingella species

Antimicrobial Therapy of HACEK Endocarditis

Regimen	Comments
Ceftriaxone	Regimen of choice NO GENT: nephrotoxic
Levofloxacin	Levo or FQ as single agent OK as alternative regimen NO GENT: nephrotoxic
Ampicillin	Avoid: assume amp or pen resistant if no reliable MIC NO GENT: nephrotoxic

Culture-Negative Endocarditis

Q5. Which one of the following is not a cause of culture-negative endocarditis?

1. Coxiella burnetii
2. Mycoplasma pneumoniae
3. Tropheryma whipplei
4. Bartonella henselae
5. Chlamydia psittaci

Culture-Negative Endocarditis

- Prior antibiotics
- Fastidious organisms
  - HACEK
  - Abiotrophia defectiva, et al
- "Non-cultivatable" organism
  - *Bartonella quintana > henselae*
  - *Coxiella burnetii*, *Tropheryma whipplei*, *Legionella* spp.
- Fungi (molds)
- Not endocarditis
  - Libman-Sacks, myxoma, APLS, marantic

Q6. A 44 y.o. man presents with a subjective fever for 3 months, diarrhea for over a year, has lost 30 pounds, and complains of intermittent arthralgias, mainly in his hands.

- Exam: BP 172/52 P 92 R 24 T38C
  - Loud decrescendo blowing diastolic murmur at the lower left sternal border, and rales halfway up bilaterally.
- Blood cultures (6 sets): negative after 21 days
- Valvular tissue obtained at valve replacement reveals foamy macrophages by PAS stain.

Q6. Which of the following is the most likely etiologic agent?

1. A member of the HACEK group
2. Coxiella burnetii
3. Tropheryma whipplei
4. Bartonella quintana
5. Abiotrophia defectiva

Culture-Negative Scenarios

- **Coxiella burnetii (Q fever)**: Direct or indirect animal contact, hepatosplenomegaly, abnormal or prosthetic valve. Doxycycline + hydroxychloroquine >1 yr.
- **Bartonella quintana**: Homeless, very indolent, valve normal or abnormal, louse vector. **Rx:** 6 wks doxycycline plus two wks gentamicin or plus 6 wks rifampin

Tools for Diagnosis of Culture-Negative Endocarditis

Organism	Clinical clues	Serology	Specific PCR	Universal 16s/18s rRNA PCR
HACEK, strep, etc	Prior antibiotics			X
Legionella spp.	Immunocompromise, PVE	X	X	X
T. whipplei	Chronic illness		X	X
Brucella spp.	Travel	X		X
Bartonella spp.	Cats, homeless, lice	X	X	X
Mycoplasma		X		X
Q fever	Animal contact, lab	X	X	X
Yeast, molds	Immunocompromised	X		X

Prosthetic Valve IE

Q7. A 70 y.o. male presents with fever, chills, and low back pain for 6 days, s/o bioprosthetic AVR 9 months previously for critical aortic stenosis.

- PE: T38°C BP 104/70 P90
  - Left conjunctival petechiae.
  - Rales 1/3 way up bilaterally.
  - Grade II/VI SEM
- Blood cultures: 3/3 positive at 18 hours for Gram positive cocci in clusters

Q7. While awaiting TEE, which of the following antimicrobial regimens should be started?

1. Vancomycin
2. Vancomycin + rifampin
3. Vancomycin + gentamicin (and later) plus rifampin
4. Linezolid + gentamicin
5. Daptomycin + gentamicin + rifampin

Microbiology of PVE

Organisms	2 mo. Post-op (%)	2-12 mo. Post-op (%)	> 12 mo Post-op (%)
S. aureus	30	13	22
Streptococci	2	13	30
Enterococci	8	11	11
HACEK	0	0	4
CoNS	28	36	12
Gram-neg bacilli	10	4	5
Fungi	9	8	1
Culture-negative	6	6	10

Adpated from Karcher and Chu, UpToDate, 2020

Therapy of PVE

Organism	Regimen	Duration
S. aureus, CoNS	Naf (MS) or vanco (MR) + gent + rif (add later)	Gent x 2 wk, naf/vanco + rif x 6 weeks
Streptococci, MIC ≤ 0.12 μg/ml	Pen or ceftriaxone + gent OR Vancomycin	6 weeks (gent 1st 2 wk) 6 weeks
Streptococci, MIC > 0.12 μg/ml	Pen or ceftriaxone + gent OR Vancomycin	6 weeks 6 weeks
Enterococci	Same as for NVE	6 weeks

Cardiac Implantable Device Infections
(permanent pacemakers, defibrillators)

J Am Coll Cardiol 2008;49:1851; Circulation 2010;121:458; NEJM 2012;367:842; JAMA 2012;307:1727

08 - Endocarditis of Native and Prosthetic Devices, and Infections of Pacers and Ventricular Assist Devices

Speaker: Henry Chambers, MD

Q8. A 71 y.o. male, permanent pacemaker was implanted 2 months ago for sick sinus syndrome/syncope, presents subjective fever

- Exam:
  - T37.8C, P78 (paced), R18, BP 122/80.
  - Generator pocket is slightly tender, swollen, with moderate warmth and erythema; otherwise WNL.
- Cultures
  - Pus aspirated from the pocket: MSSA
  - Blood cultures: negative

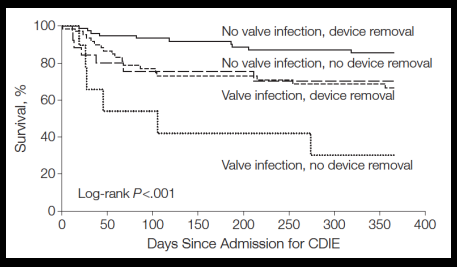
Which of the following is the best management?

1. Cefazolin + rif x 6 wks
2. Remove entire device, then cefazolin x 10 days
3. Remove generator, then cefazolin + rif x 10 days
4. Remove generator, then cefazolin + rif x 6 wks
5. Remove entire device, then cefazolin + rif x 6 wks

Cardiac Implantable Device Infection Types

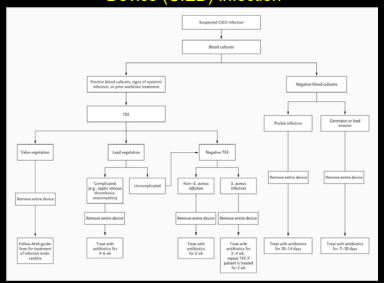
- Pocket site/generator only : ~ 60%
  - Blood culture positive <50%
  - Pocket infection or generator/lead erosion
- Occult bacteremia/fungemia: ~7-30%
- Lead infection +/- endocarditis: ~10-25%

Survival with and without Device Removal



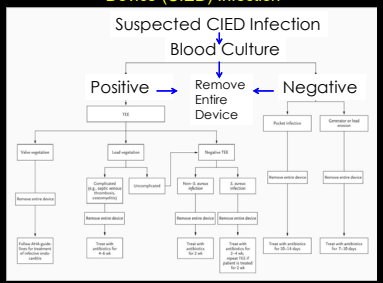
Athan, JAMA. 2012; 307:1727-1735

Algorithm for Management of an Infected Cardiac Implantable Device (CIED) Infection



Baddour LM et al. N Engl J Med 2012;367:842-849 The NEW ENGLAND JOURNAL of MEDICINE

Algorithm for Management of an Infected Cardiac Implantable Device (CIED) Infection



Baddour LM et al. N Engl J Med 2012;367:842-849 The NEW ENGLAND JOURNAL of MEDICINE

AHA Guidelines for Management of Cardiac Implantable Device Infections

- Blood cultures before antibiotics
  - If positive, then TEE
- Gram stain, culture of pocket tissue, lead tips
- Device removal for all infections and occult staphylococcal bacteremia (consider for GNR bacteremia)
- Therapy (antibiotic based on susceptibility)
  - Pocket infection: 10-14 days
  - Bloodstream infection: ≥ 14 days
  - Lead or valve vegetations: 4-6 weeks

Circulation 2010;121:458-77

AHA Guidelines for Reimplantation

- Determine if reimplantation necessary
- New device on contralateral side
- ≥72h negative BC before reimplantation
- If IE: reimplant ≥ 14d after original removal
- Antibiotic prophylaxis: 1h before implantation, none thereafter

Other Management Stuff

Surgical Management NVE/PVE

- Optimal timing of surgery not known
- Early surgery
  - Heart failure due to valvular dysfunction, fistula, shunt
  - Uncontrolled infection
    - MDR, fungal pathogens, persistently pos. BC (5-7d)
    - Paravalvular complication (abscess, heart block, fistula)
  - Prevention of systemic embolization
    - Vegetation > 10 mm, one or more embolic events on therapy

Fever during Therapy of Endocarditis

- Very common, lasts into the second week, a concern in PVE
- Cause (if one is found, when often it is not)
  - Abscess: valve ring or elsewhere
  - Septic pulmonary emboli, pleural effusion)
  - Another infection (e.g., IV site, fungal superinfection)
  - Polymicrobial endocarditis
  - Drug fever
- Work-up:
  - Repeat blood cultures
  - Imaging studies: TEE, abdominal CT, MRI of the spine, etc

Valve Surgery with Stroke

- Stroke is an independent risk factor for post-op mortality
- Early surgery with stroke or subclinical cerebral emboli may be considered if intracranial hemorrhage excluded by imaging and neurological damage is not severe
- For patients with major stroke or hemorrhage, delay valve surgery 4 weeks (although more recent studies have called this into question)

Venn, Am Heart J 2019;216:102-112

Embolic Events in IE

- Systemic embolization in up to 50% and higher
- CNS accounts for 65%
- Highest rates in MV IE (anterior > posterior leaflet)
- 10-fold decrease in rate during first 2-3 weeks of antibiotic therapy
- ~3% of patients suffer a stroke after 1 week of therapy (benefit of early surgery correspondingly less)
- Value of CNS imaging all patients with IE unknown, may be considered as part of pre-op evaluation
- Systemic anticoagulation, antiplatelet therapy is contraindicated.

Anticoagulation

- Management is controversial
- Discontinue all forms of anticoagulation in patients with a mechanical PVE and a CNS embolic event for 2 weeks
  - Reinstitute heparin first then carefully transition to warfarin
- Aspirin or other antiplatelet agents as adjunctive therapy is not recommended
- Continuation of long-term antiplatelet therapy in IE with no bleeding complications may be considered
- Thrombolytic therapy not recommended

Pan-Scanning

- If done, perform prior to surgery
- No recommendations for routine evaluation of patients with IE for metastatic foci of infection
- Cerebrovascular imaging may be considered in all patients with L-sided IE

Questions

09

Penicillin Allergy

Dr. Sandra Nelson

09 - Penicillin Allergy

Speaker: Sandra Nelson, MD

2020 INFECTIOUS DISEASE BOARD REVIEW

Penicillin Allergy

Sandra B. Nelson, MD
Director, Musculoskeletal Infectious Diseases
Division of Infectious Diseases
Massachusetts General Hospital

Disclosures of Financial Relationships with Relevant Commercial Interests

- None

Penicillin (PCN) Allergy: Premise

- 10% of the US population (32 million persons) have documentation of penicillin allergy
  - Rash (38%) > unknown (26%) > hives (18%) > angioedema (9%) > GI symptoms (6%) > itching (5%)
  - More common in older adults and hospitalized patients
- Vast majority of patients with penicillin allergy can be made to tolerate penicillin
  - Reactions are mild drug rashes that do not always recur
  - Reactions wane with time
  - Some reactions are not allergic

PCN Allergy: Consequences

- Alternative antimicrobial use
  - Less effective, more toxic, more broad spectrum
- Associated with:
  - increased risk of MRSA infections
  - increased risk of C difficile colitis
  - increased risk of surgical site infection
  - increased mortality
- An important target of stewardship efforts

Case #1

67 year old woman is hospitalized with nosocomial meningitis due to MSSA. She has a history of allergy to penicillin that is listed in the records as rash; the family recalls that she went to the ED when the rash occurred. She is not able to corroborate history. She has not received penicillin or cephalosporin antibiotics since the rash occurred a few years ago. Two of her daughters have allergies to penicillin.

Case #1: Vote

You are asked about optimal antibiotic treatment. What do you advise?

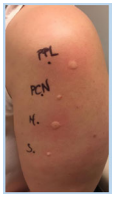
A. Administer nafcillin without prior testing
B. Administer nafcillin after test dose
C. Skin test for penicillin reaction; if negative then administer nafcillin after test dose
D. Administer vancomycin
E. Desensitize to nafcillin

09 - Penicillin Allergy

Speaker: Sandra Nelson, MD

Options for Approaching PCN Allergy

- Monitored oral challenge
  - Useful for outpatients with low risk reactions (remote rash, pruritus) without imminent need of beta-lactam therapy
- Penicillin skin testing
  - Useful for inpatients and outpatients with a history of IgE mediated reaction, or sick patient with unknown reaction
  - Pre-Pen (benzylpenicilloyl polylysine) and penicillin G
  - Avoid in unstable patients



Shenoy JAMA 2019;321:188

Options for Approaching PCN Allergy

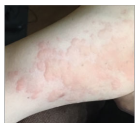
- Graded Challenge (1/10th test dose)
  - As a first step if suspicion for immediate reaction is low
  - After negative PCN skin testing when a related drug is desired (e.g. nafcillin)
- Desensitization
  - Positive skin test and/or confirmed immediate reaction, when a penicillin is the best therapy for an important infection
  - Desensitization wanes with missed doses (3 half-lives)
- Use of alternate therapy

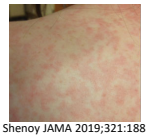
Classification of Drug Allergy (Gell and Coombs)

Type	Immune mechanism	Clinical example	Management
I: Immediate (within one hour)	IgE-mediated	Anaphylaxis, Urticaria, Angioedema, Bronchospasm	Penicillin skin testing
II:	Antibody-dependent	Hemolytic Anemia Thrombocytopenia Neutropenia	No testing; generally avoid re-use
III	Immune Complex	Serum Sickness Vasculitis	No testing; generally avoid re-use
IV delayed	Cell mediated	Cutaneous drug reactions Interstitial nephritis Hepatitis	Varies; for severe reactions and organ involvement avoid re-use

Deciphering Cutaneous Reactions

- IgE Mediated Reactions (hives)
  - Occur within minutes to hours
    - ➡ skin testing appropriate
  - if positive – desensitize or use alternate therapy
- Benign T-cell mediated
  - morbilliform or maculopapular
  - Usual onset days to weeks; persists >24 hours and resolves over days to weeks
    - ➡ test dose appropriate

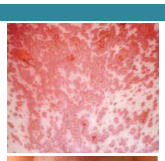


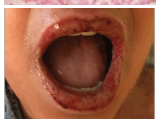


Shenoy JAMA 2019;321:188

Deciphering Cutaneous Reactions

- Severe cutaneous reactions
  - DRESS and SJS/TEN
  - Usual onset days to weeks
  - Blistering, mucosal involvement, severe skin desquamation, organ involvement
    - ➡ avoid any beta-lactam
- Unknown Reaction
  - If hospitalized and/or critical illness:
  - Assume possibly IgE mediated
    - ➡ skin test then test dose





Stern NEJM 2012;366:2492
Shenoy JAMA 2019;321:188

Case #2

A 43 year old man with diabetes is hospitalized with a closed tibial fracture. Three years ago when he was being treated for a foot infection with piperacillin-tazobactam he developed a very itchy rash after several weeks of treatment. The anesthesiologist calls to ask advice about surgical antibiotic prophylaxis prior to operative fixation.

Case #2: Vote

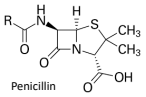
What do you do counsel?

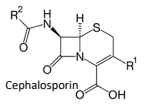
A. Administer clindamycin
B. Administer cefazolin
C. Administer cefazolin after intraoperative test dose
D. Administer ceftriaxone
E. Administer vancomycin

MASSACHUSETTS GENERAL HOSPITAL HARVARD MEDICAL SCHOOL 14

PCN Allergy and other beta-lactams

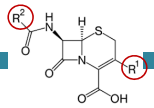
- Cephalosporins:
  - Significant cross reactivity 2%
  - Higher risk with earlier generation cephs
  - If suggestive type I PCN allergy:
    - use 3rd/4th gen (graded challenge preferred)
    - use 1st/2nd after PCN skin testing
  - If mild type IV reaction:
    - any cephalosporin OK
  - Avoid if severe reaction to PCN
- Carbapenems <1%
- Aztreonam: no cross reactivity





MASSACHUSETTS GENERAL HOSPITAL HARVARD MEDICAL SCHOOL 16

Cephalosporin Allergy



- Allergy often arises from side chains
  - More common than beta-lactam ring
- Probability of reaction higher when cephalosporins with similar side chains used (R1 > R2)
- Testable point:
  - Cefazolin has different side chains from all other cephalosporins

MASSACHUSETTS GENERAL HOSPITAL HARVARD MEDICAL SCHOOL 17

Thank you and good luck!

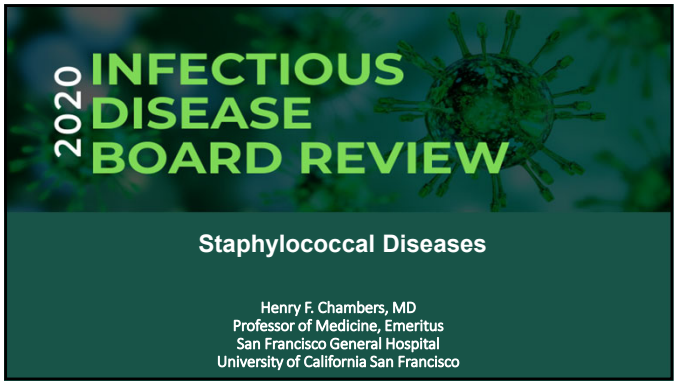
"The penicillin looks good."

MASSACHUSETTS GENERAL HOSPITAL HARVARD MEDICAL SCHOOL 18

10

Staphylococcal Diseases

Dr. Henry Chambers



Disclosures of Financial Relationships with Relevant Commercial Interests

- None

Outline of the Talk

- Risk factors for poor outcome, complicated bacteremia
- Echocardiography
- Treatment of MSSA bacteremia
- Treatment of MRSA bacteremia
- Combination therapy

Q1. 45 year old man, one week of back pain. He is afebrile and vital signs are normal; normal exam except for tenderness to palpation of the lower back. MRI shows L3-L4 discitis, hyperemic marrow; 1 of 3 blood cultures is positive for coagulase-negative staphylococci.
Which one of the following would you recommend?

A. Bone biopsy with culture as the blood isolate is likely a contaminant
B. Request a slide-coagulase test of the blood isolate
C. PET-CT to look for another focus of infection for biopsy
D. Fungal serologies, PPD

Staphylococcus lugdunensis

- Coagulase negative….
  - The tube "free" coagulase test is negative
  - The latex "bound" coagulase (i.e., clumping factor) test may be positive and confuse physicians
- Virulent, aggressive, similar to *S. aureus*.
  - Bacteremia, NV and PV endocarditis
  - Bone and joint infection
  - Pacemaker, other device-related infections
- Susceptible to many antibiotics (rarely *mecA* positive)

Risk factors for poor outcome, complicated S. aureus bacteremia

Q2. Which one of the following risk factors is most predictive of complicated Staph. aureus bacteremia?

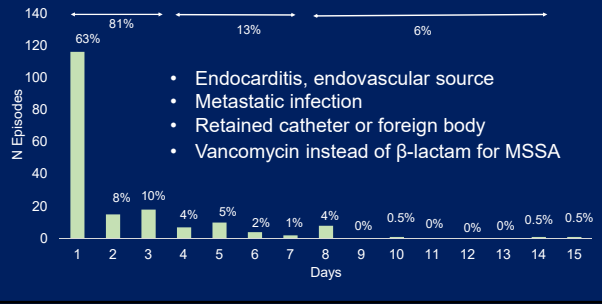
A. MRSA infection
B. Hospital-onset infection
C. Positive blood cultures on appropriate therapy
D. Community-onset infection

Clinical features of complicated Staph. aureus bacteremia

- Positive blood cultures >48-72h on therapy (Odds ratio = 5.6)
- Community-onset (OR 3.1)
- Fever > 3 days on therapy (OR 2.2)
- Skin findings c/w systemic infection (OR 2.0)
- Persistent or secondary focus of infection
- Endocarditis, prosthetic valve
- (Elderly patient: age > 60 years?)
- (MRSA?)

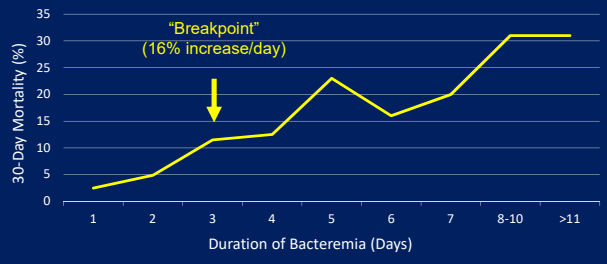
Adapted from Fowler, Ann Intern Med 163:2066, 2003

Duration of MRSA bacteremia on therapy San Francisco General 2008-12



- Endocarditis, endovascular source
- Metastatic infection
- Retained catheter or foreign body
- Vancomycin instead of β-lactam for MSSA

Longer durations of Staph. aureus bacteremia (SAB) are associated with higher the mortality



Clin Infect Dis. 2019 Apr 5. pii: ciz257. doi: 10.1093/cid/ciz257. [Epub ahead of print]

Risk factors for longer durations of Staph. aureus Bacteremia

- Factors predictive of longer duration of bacteremia
  - ➢MRSA
  - ➢Delayed source control
- Factors **NOT** associated with longer durations of bacteremia
  - ➢MIC
  - ➢Choice of antimicrobial (specific agent, single or combo)
  - ➢Switching from vancomycin to daptomycin

Clin Infect Dis. 2019 Apr 5. pii: ciz257. doi: 10.1093/cid/ciz257. [Epub ahead of print]

Q3. In patients with S. aureus bacteremia follow-up blood cultures should be obtained until negative.

A. True
B. False

Duration of therapy for SAB

Duration	Indications
14 days	• Fever resolves by day 3 • Sterile blood culture after 2-3 days • Easily removed focus of infection • No metastatic infection (e.g., osteo) • Negative echo, no evidence of endocarditis • No predisposing valvular abnormalities • No implanted prosthetic devices • (No DM, immunosuppression)
4-6 weeks +	• Failure to meet one or more of above criteria • Osteomyelitis, endocarditis, epidural abscess, septic arthritis, pneumonia, complicated UTI

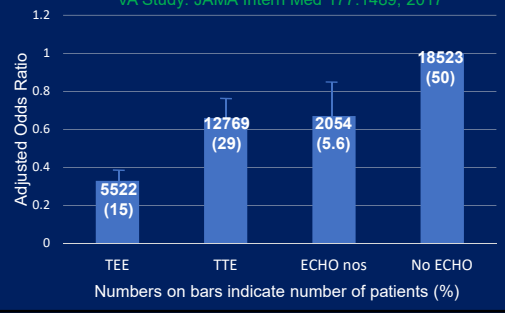
Echocardiography

Q4. For patients with Staph. aureus bacteremia which one of the following statements about echocardiography is true?

A. Echocardiography is not associated improved outcomes of patients with Staph. aureus bacteremia
B. Transesophageal ECHO should be obtained in all patients with S. aureus bacteremia
C. Transthoracic and transesophageal ECHOs have comparable sensitivities for diagnosis of Staph. aureus endocarditis
D. Transthoracic and transesophageal ECHOs have comparable specificities for diagnosis of Staph. aureus endocarditis

ECHO and mortality in S. aureus Bacteremia

VA Study: JAMA Intern Med 177:1489, 2017



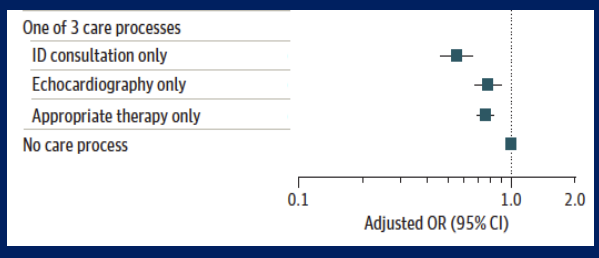
Role of echocardiography and what modality used for S. aureus bacteremia

Depends on the pre-test probability

- Consider TTE in all patients with SAB
  - Possible exception: HCA + no intracardiac devices + no signs IE + negative BC @ 48-72h
- Obtain TEE in high risk patients
  - Embolic events, intracardiac device, IVDU, prior IE

Heriot, OFID Nov 24, 4:ofx261, 2017; Bai, Clin Micro Infect 23:900, 2017

ID Consultation is Better than ECHO!



JAMA Intern Med 177:1489, 2017

Treatment of MSSA Bacteremia

Q5. On day 9 of nafcillin therapy for complicated methicillin-sensitive S. aureus bacteremia the patient has developed new neutropenia (1,000 neutrophils). MICs (µg/ml) of the blood isolate are penicillin 0.12 (S), cefazolin 0.5 (S), vancomycin 1 (S), daptomycin 0.5 (S), ceftaroline 0.5 (S). **Which one of the alternative agents would you recommend?**

A. Penicillin
B. Cefazolin
C. Vancomycin
D. Daptomycin

Beta-lactam vs. Vancomycin for MSSA Bacteremia (122 VA hospital study) – Multivariable Analysis

Variable	Mortality, Hazard Ratio (95% CI)
Beta-lactam vs vancomycin	0.65 (0.52-0.80)
ASP or cefazolin vs vancomycin	0.57 (0.46-0.71)

Clin Infect Dis 61:361, 2015

Penicillin for treatment of Staph. aureus endocarditis per AHA guidelines

…the current laboratory screening procedures for detecting penicillin susceptibility may not be reliable.

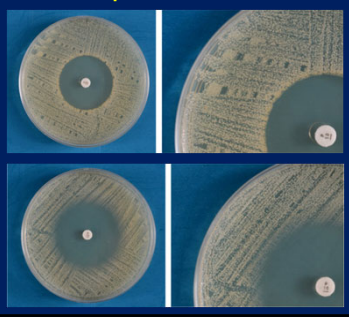
Pen MIC (µg/ml)	No. (%) of strains	
	Tested for blaZ	PCR + for blaZ
0.015	1 (100)	0
0.03	24 (100)	0
0.06	370 (100)	14 (3.4)
0.12	53 (100)	17 (32.1)

J Clin Micro 54:812, 2016

Zone edge test for β-lactamase

Positive

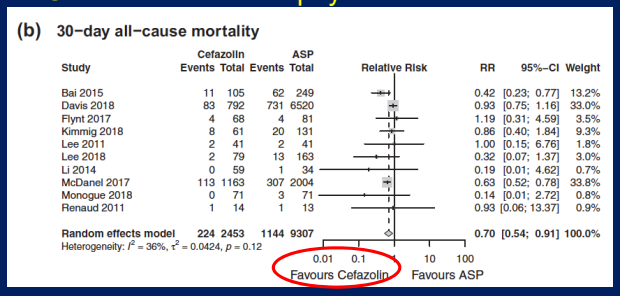
Negative



MSSA Bacteremia: Cefazolin vs. Antistaphylococcal Penicillins

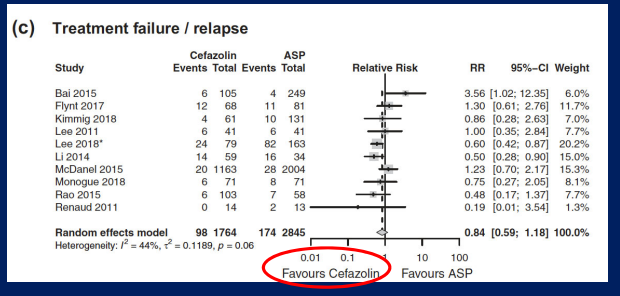
- Efficacy:
  - Penicillinase inoculum effect on cefazolin MICs – does it matter?
- Safety :
  - Adverse events due to ASPs

Cefazolin vs Anti-staphylococcal Penicillins



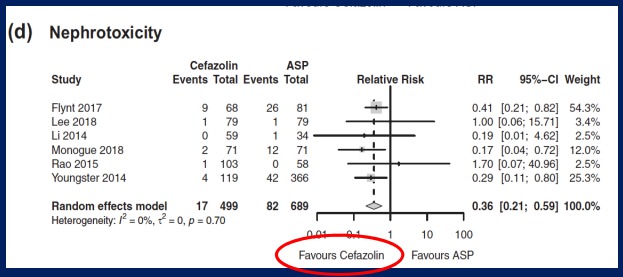
Weis, et al. / Clinical Microbiology and Infection 25 (2019):818e827

Cefazolin vs Anti-staphylococcal Penicillins



Weis, et al. / Clinical Microbiology and Infection 25 (2019):818e827

Cefazolin vs Anti-staphylococcal Penicillins



Weis, et al. / Clinical Microbiology and Infection 25 (2019):818e827

Cefazolin Inoculum Effect (CzIE*) in 3 Hospitals in Argentina

*Beta-lactamase-mediated increase in broth dilution MIC to ≥ 16 µg/ml at high inoculum (5 x 10^7 cfu/ml instead of 5 x 10^5 cfu/ml)

- Anti-staphylococcal penicillins are not available in Argentina
- Cefazolin is the primary beta-lactam used to treat MSSA
- 54.5% prevalence (42/77 patients with SAB)
  - 7-day mortality CIE pos vs CIE neg: 12% vs 6% (p=0.44)
  - 30-day mortality CIE pos vs CIE neg: 40% vs 15% (p=0.03)

Open Forum Infect Dis.018 May 23;5(6):ofy123

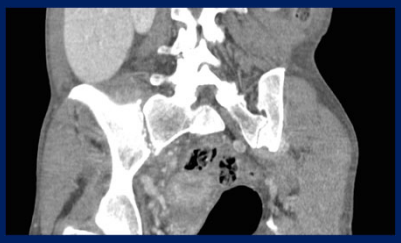
Q6. 36 year old female injection drug user with R hip pain, decreased ROM 2/2 pain; 2/2 blood cultures + for MSSA; CXR, right hip x-ray, CT abdomen and pelvis, MRI, TTE all normal. Treated with empirical vancomycin, blood cultures sterile after 1 day of therapy, now on day 5 of nafcillin. Pain much improved on day 7, but she still uses a cane for ambulation. **Which one of the following antibiotics would you recommend for a 6 week course?**

A. Dalbavancin
B. Ceftriaxone
C. Vancomycin
D. Cefazolin

What about ceftriaxone for MSSA bacteremia?

- Mixed data, low quality studies
- Open Forum Infect Dis. 2018 May 18;5(5):ofy089
  - Single VA medical center
  - 38 cefazolin and 33 with ceftriaxone.
  - Failure rates: 54.5% ceftriaxone versus 28.9% cefazolin; *P* = .029
- Avoid

Two months later….



Aspirate of R SI joint positive for MSSA

Lessons from this Case

- Community-onset is a risk factor for complicated bacteremia
- For the patient with suspected complicated infection, no evident focus, continued symptoms/+ blood cultures
  - Look harder, studies to consider
    - Repeat ECHO
    - MRI (may be false negative in early disease)
    - CT abdomen, pelvis,
    - PET-CT (J Nucl Med. 2018 Dec 14. pii: jnumed.118.221929)
    - Ultrasound to rule out septic thrombophlebitis

Tricky, occult foci of infections

- Spine, psoas muscle
- Fibrous/ligamentous joints: acromioclavicular, manubriosternal, sacroiliac, symphysis pubis
- Deep venous septic thrombosis

Summary: MSSA bacteremia

- Cefazolin is better tolerated than ASPs
- Recommended by AHA as second-line agent for native valve endocarditis
- Overall mortality no worse, may be better with cefazolin compared to ASPs
- Clinical failure rates and recurrences similar
- Anxiety over the inoculum effect, which may adversely impact outcome in a subset of cefazolin-treated patients

Treatment of MRSA Bacteremia

Q7. A patient with complicated MRSA bacteremia on day 9 of therapy with daptomycin q48h develops myalgias with a creatinine kinase of 1250 u/L (upper limit of normal 200). The last positive blood culture was on day 3 of therapy. MICs (μg/ml) of the isolate are as follows: vancomycin 2 (S), daptomycin 0.5 (S), dalbavancin 0.25 (S), telavancin 0.5 (S), ceftaroline 1 (S). **Which one of the following would you recommend?**

A. Ceftaroline
B. Dalbavancin
C. Telavancin
D. Vancomycin
E. Linezolid

First-line choices for MRSA bacteremia

- Vancomycin
  - 30-60 mg/kg/d in 2-3 divided doses
  - Nephrotoxic at higher trough concentrations (15-20 µg/ml)
- Daptomycin
  - Non-inferior to vancomycin
  - Treatment failures due to emergence of resistance on therapy (mprF mutants)
  - Do not use for primary pneumonia
  - Some cross-resistance with VISA

Holland et al: JAMA 312:1330, 2014

FDA-approved antibiotics for MRSA Infections

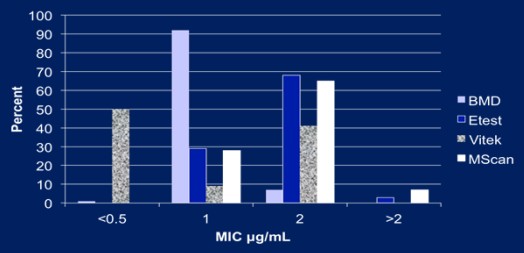
Antibiotic	Indications	Comments
Linezolid	SSTI, HAP, VAP	Serotonin syndrome: avoid use with SSRIs, MAO-Is; bacteriostatic Bone marrow suppression
Telavancin	SSTI, HAP, VAP	Vancomycin derivative Nephrotoxic, black box warning for ClCr ≤ 50 ml/min Artificially prolongs PT, PTT QTc prolongation, teratogenic
Ceftaroline	SSTI, CAP	Rash, usual cephalopsorin reactions

FDA-approved antibiotics for MRSA Infections

Antibiotic	Indications	Comments
Tedizolid	SSTI	May be less toxic than linezolid
Dalbavancin	SSTI	Single dose or 2 doses a week apart Lipoglycopeptide, related to teicoplanin
Oritavancin	SSTI	One time dose Lipoglycopeptide, related to vancomycin May artificially prolong PT, PTT

But what about that vancomycin MIC of 2 µg/ml?

Vancomycin MICs by Method



Int J Antimicro Agent 32:378, 2008

Original Investigation

Association Between Vancomycin Minimum Inhibitory Concentration and Mortality Among Patients With *Staphylococcus aureus* Bloodstream Infections
A Systematic Review and Meta-analysis

Andre C. Kalil, MD, MPH; Trevor C. Van Schooneveld, MD; Paul D. Fey, PhD; Mark E. Rupp, MD

- Meta-analysis, 38 studies, 8291 episodes
- MIC < 1.5 µg/mL (low) versus MIC ≥ 1.5 µg/mL (high)
- Mortality low = 25.8%, high = 26.8%
- Adjusted risk difference = 1.6% (-2.3 to 5.6%), p = 0.43

Kalil, JAMA 312:1552, 2014.

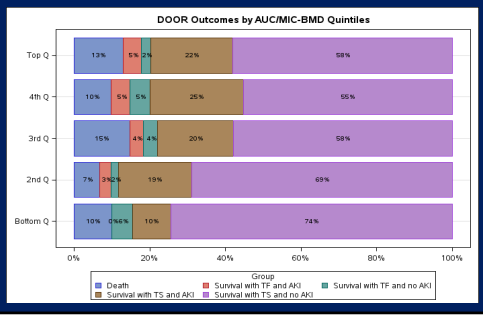
But what about that vancomycin MIC of 2 µg/ml?

- Vancomycin MIC = 1.5 to 2 µg/ml not a reliable predictor of clinical failure and not a reason to alter therapy
- Vancomycin MIC > 2 µg/ml is a reliable predictor of nonsusceptibility and clinical failure and another agent should be used

Vancomycin Dosing: AUC/MIC Correlates Poorly with Outcome

Lodise, et al Clinical Infectious Diseases 2020;70(8):1536–45

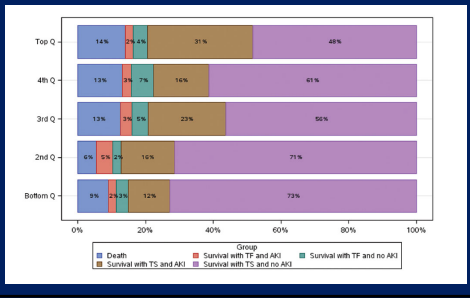
>1019
687-1018
563-686
421-562
< 421



Vancomycin Dosing: Higher AUC Correlates with Worse Outcome

Lodise, et al Clinical Infectious Diseases 2020;70(8):1536–45

>757
621-757
516-621
390-516
< 389



Therapeutic monitoring of vancomycin for serious methicillin-resistant *Staphylococcus aureus* infections: A revised consensus guideline and review by the American Society of Health-System Pharmacists, the Infectious Diseases Society of America, the Pediatric Infectious Diseases Society, and the Society of Infectious Diseases Pharmacists

Am J Health-Syst Pharm. 2020;77:835-864

Highlights of Modern Vancomycin Dosing for MRSA Infections

- Use of troughs no longer recommended
- Target AUC/MIC_{MBD} to 400-600 (assume MIC_{BMD} = 1 µg/ml)
  - Bayesian-derived monitoring, 1-2 samples (Cmax, Cmin)
  - 1st order PK equation with C_{max}, C_{min} at near steady-state
  - Continuous infusion: multiply steady-state concentration x 24
- Consider loading dose for more seriously ill patients
  - Intermittent infusion: 30-35 mg/kg, max 3000 mg (actual body weight), then 15-20 mg/kg q8-12h
  - Continuous infusion: 15-20 mg/kg then 30-60 mg/kg, target steady state of 20-25 µg/ml
- Pediatric doses higher: 60-80 mg/kg/d divided q6-8h

MRSA Decolonization

- Randomized controlled trial of education versus education + decolonization in hospitalized MRSA colonized adults
- Decolonization regimen: 5 days twice monthly of 4% chlorhexidine shower/bath + 0.12% chlorhexidine mouthwash 2x daily + 2% nasal mupirocin 2x daily
- MRSA infection 98/1063 (9.2%, ed) vs 67/1053 (6.3%, decolon) (p=0.015)
- Lower MRSA infection with decolonization: HR 0.70 (95% CI, 0.52-0.96)
- Lower risk of MRSA hospitalization: HR 0.71 (95% CI, 0.51-0.99)
- MRSA infection adherent vs education only: HR 0.56 (95% CI 0.36-0.86)

NEJM 2019;380:638-50

Combination Therapy of S. aureus Bacteremia

Q8. Which one of the following combinations have been shown to improve outcome of patients with S. aureus bacteremia or native valve endocarditis?

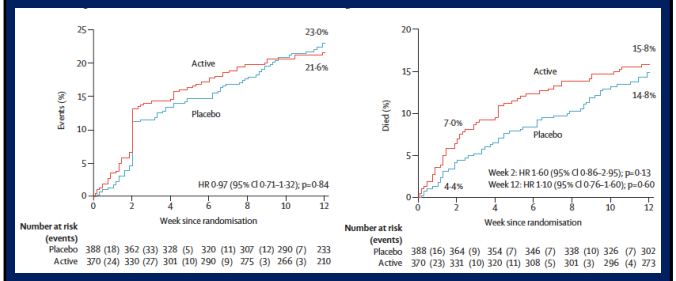
A. Anti-staphylococcal beta-lactam + gentamicin for MSSA
B. Anti-staphylococcal beta-lactam + rifampin for MSSA
C. Vancomycin + a beta-lactam for MRSA or MSSA, pending cultures
D. No combination regimen

Adjunctive rifampicin for *Staphylococcus aureus* bacteraemia (ARREST): a multicentre, randomised, double-blind, placebo-controlled trial

*Guy E Thwaites, Matthew Scarborough, Alexander Szubert, Emmanuel Nsutebu, Robert Tilley, Julia Greig, Sarah A Wyllie, Peter Wilson, Cressida Auckland, Janet Cairns, Denise Ward, Pankaj Lal, Achyut Guleri, Neil Jenkins, Julian Sutton, Martin Wiselka, Gonzalez-Ruiz Armando, Clive Graham, Paul R Chadwick, Gavin Barlow, N Claire Gordon, Bernadette Young, Sarah Meisner, Paul McWhinney, David A Price, David Harvey, Deepa Nayar, Dakshika Jeyaratnam, Tim Planche, Jane Minton, Fleur Hudson, Susan Hopkins, John Williams, M Estee Török, Martin J Llewelyn, Jonathan D Edgeworth, A Sarah Walker, on behalf of the United Kingdom Clinical Infection Research Group (UKCIRG)**

- 758 patients, 388 SOC and 370 SOC + rifampin
  - 40% deep tissue, 30% diabetics, 1y% IVDU, 6% MRSA, Mean of 62h pre-randomization antibiotics
- Primary outcome composite of treatment failure, recurrence, death at 12 weeks

Lancet. 2017 Dec 14. pii: S0140-6736(17)32456-X.
doi: 10.1016/S0140-6736(17)32456-X.



Composite Primary Outcome Death

CAMERA2

JAMA | Original Investigation

Effect of Vancomycin or Daptomycin With vs Without an Antistaphylococcal β-Lactam on Mortality, Bacteremia, Relapse, or Treatment Failure in Patients With MRSA Bacteremia
A Randomized Clinical Trial

Tong, et al. JAMA. 2020;323(6):527-537. doi:10.1001/jama.2020.0103

CAMERA2

- IV vancomycin (n=337) or daptomycin (n=8) (standard therapy) Vs. standard therapy plus 7 days of an anti-staphylococcal β-lactam (flucloxacillin, cloxacillin, or cefazolin [n=27]).
- Composite primary endpoint at 90 days of (1) all-cause mortality, (2) persistent bacteremia at day 5 or beyond, (3) microbiological relapse, or (4) microbiological treatment failure
- Target enrollment 440, 358 enrolled, study terminated by DSMB

CAMERA2

Outcome	Standard Therapy	Combination Therapy	Risk Difference (95% CI)
Primary	68/175 (39%)	59/175 (35%)	−4.2 (−14.3 to 6.0)
90 day mortality	28/174 (16%)	35/170 (21%)	4.5 (−3.7 to 12.7)
+ BC @ day 5	35/172 (20%)	19/166 (11%)	−8.9 (−16.6 to −1.2)
Relapse	18/175 (10%)	14/169 (8%)	-2.0 (−8.1 to 4.1)
Treatment failure	17/175 (10%)	16/170 (9%)	−0.3 (−6.5 to 5.9)
AKI	9/145 (6%)	34/145 (23%)	17.2 (9.3 to 25.2)

Daptomycin + Ceftaroline

Clinical Data on Daptomycin plus Ceftaroline versus Standard of Care Monotherapy in the Treatment of Methicillin-Resistant *Staphylococcus aureus* Bacteremia

Geriak, et al. Antimicrob Agents Chemother. 2019; 63:e02483

Is Daptomycin plus Ceftaroline Associated with Better Clinical Outcomes than Standard of Care Monotherapy for *Staphylococcus aureus* Bacteremia?

Kalil, et al. Antimicrob Agents Chemother. 2019; 63:e00900

Reply to Kalil et al., "Is Daptomycin plus Ceftaroline Associated with Better Clinical Outcomes than Standard of Care Monotherapy for *Staphylococcus aureus* Bacteremia?"

Sakoulas, et al. Antimicrob Agents Chemother. 2019; 63:e01347

Daptomycin + Ceftaroline

Clinical Data on Daptomycin plus Ceftaroline ver… of Care Monotherapy in the Treatment of M… sistant *Staphylococcus aureus* Bacteremia

Geriak, et al. Antimicrob Agents Ch… e83

Is Daptomycin plus Ceftar… ted with Better Clinical Outcomes than Stand… Monotherapy for *Staphylococcus* …eremia?

…icrob Agents Chemother. 2019; 63:e00900

R… et al., "Is Daptomycin plus Ceftaroline …d with Better Clinical Outcomes than Standard of …e Monotherapy for *Staphylococcus aureus* Bacteremia?"

Sakoulas, et al. Antimicrob Agents Chemother. 2019; 63:e01347

Consider for salvage therapy, not first line

Monotherapy versus combination therapy for Staph. aureus bacteremia

- No high quality RCT has ever demonstrated improved outcomes of combination antimicrobial therapy over monotherapy
- Studies suggesting a possible benefit of combination therapy are low quality, retrospective, and based on subjective outcomes not mortality, recurrence, metastatic infections

AHA guidelines for therapy of native valve S. aureus endocarditis

- MSSA
  - Nafcillin (or Oxacillin) 2 gm q4h x 6 weeks
  - Cefazolin 2 gm q8h x 6 weeks, allergic or intolerant to naf
  - No aminoglycoside
- MRSA
  - Vancomycin 30-60 mg/kg/d divided q8-12h to achieve trough of 15-20 µg/ml x 6 weeks
  - Daptomycin 6-10 mg/kg q24h x 6 weeks
  - No aminoglycoside

Circulation. 2015 Oct 13;132(15):1435-86

11

Pharyngitis Syndromes and Group A Strep

Dr. Karen Bloch

11 - Pharyngitis Syndromes and Group A Strep

Speaker: Karen C. Bloch, MD, MPH, FIDSA, FACP

2020 INFECTIOUS DISEASE BOARD REVIEW

Pharyngitis Syndromes Group A Strep

Karen C. Bloch, MD, MPH, FIDSA, FACP
Associate Professor, Division of Infectious Diseases
Vanderbilt University Medical Center

*Special Thanks to Dr. Bennett Lorberl

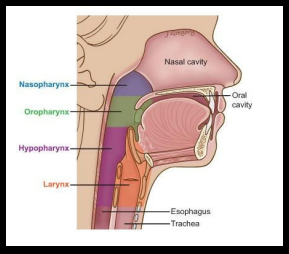
Disclosures of Financial Relationships with Relevant Commercial Interests

- None

Think Like A Realtor

Think Like A Realtor

Pharyngitis



- Small square footage
- Micro-neighborhoods
- Regional differences

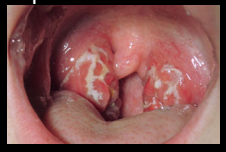
Case 1

38yo healthy female with 1 day of sore throat and fever.

Childhood history of anaphylaxis to penicillin.

Physical exam

- T=102.3
- HEENT-tonsillar purulence
- Neck-Tender bilateral anterior LAN



Labs:

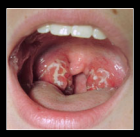
- Rapid antigen diagnostic test negative

Question 1

What is the most appropriate antimicrobial treatment?

A. Cephalexin
B. None
C. Doxycycline
D. Clindamycin
E. Levofloxacin

Group A streptococcus



- AKA *Streptococcus pyogenes*
- 5-15% sore throats in adults.
- Usually self-limited infection (even untreated)
- Viral vs bacterial pharyngitis clinically similar

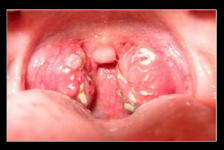
Differentiating Pharyngitis

GAS
- Sudden onset
- Fever
- Onset in winter and early spring
- Lymphadenopathy
- Exposure to close contact with streptococcal pharyngitis

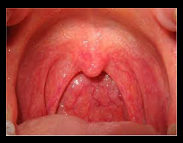
Viral pharyngitis
- The 3 C's
  - Conjunctivitis
  - Coryza
  - Cough
- Hoarseness
- Diarrhea
- Ulcerative stomatitis
- Tonsils red, but rarely enlarged or purulent

Differentiating Pharyngitis

GAS **Viral pharyngitis**



VS



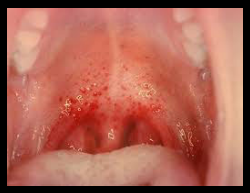
Modified Centor Score

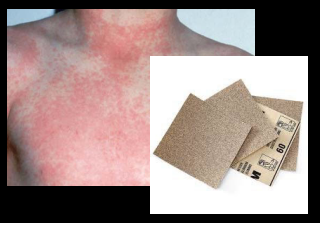
Points	Strep probability	Management
0 or 1	< 10%	No antibiotic or culture
2	11 -17%	Antibiotic if RADT or culture +
3	28 -35%	Antibiotic if RADT or culture +
4 or 5	35-50%	Antibiotic if RADT or culture +

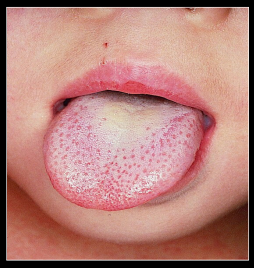
- Centor criteria useful for negative predictive value to exclude streptococcal pharyngitis.
- IDSA guidelines recommend antibiotics only following a positive testing.

Streptococcal Clues

- Palatal petechia
- Scarletina







Strawberry tongue

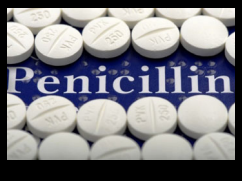
- Group A strep
- Staph toxic shock
- Kawasaki disease

Laboratory Diagnosis

- Adults:
  - RADT screen, if negative, culture optional
- ASO titer or Anti-DNAse B antibodies
  - helpful in diagnosis of rheumatic fever and post-streptococcal glomerulonephritis, but not for strep pharyngitis.

Treatment for GAS Pharyngitis

- First line:
  - Oral Penicillin or amoxicillin x 10 days

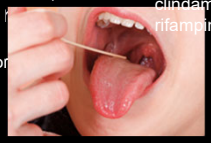


PCN Allergic:

- cephalosporin, clindamycin, macrolides
- Not recommended: tetracyclines, sulfonamides, fluoroquinolones

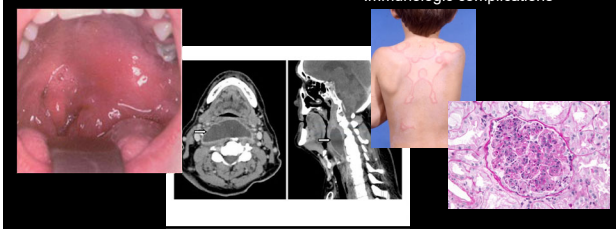
Persistence vs Recurrence

- Asymptomatic carriers (5% adults, ≥20% peds)
- When to screen:
  - Community outbreaks of strep (eg, dorm, barracks)
  - Family or personal h… rheumatic fever
  - To avoid tonsillector…
- Eradication regimens:
  - PCN or amoxicillin monotherapy high rate of failure
  - amoxicillin-clavulanate, clindamycin or PCN plus rifampin (4 days)

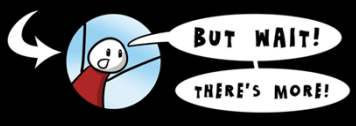


Secondary Complications

- Infectious complications
- Immunologic complications

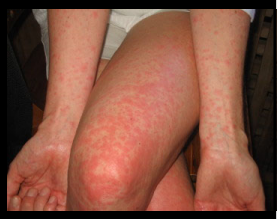


Pharyngitis and….



Pharyngitis & Rash

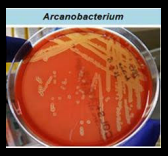
- Young adult with fever, sore throat, tonsillar exudate, scarlet fever-like rash
- Negative RADT and culture.



Arcanobacterium haemolyticum

Arcanobacterium haemolyticum

- Gram positive rod.
- Scarletiniform rash in ~50%.
- Treatment: azithromycin (clinda, PCN).
- Rarely life-threatening sequelae.



Pharyngitis & Rash

- Acute HIV

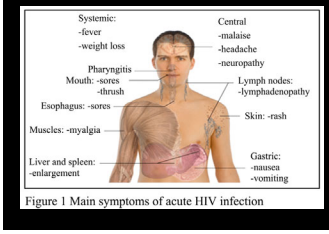
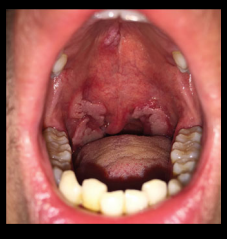


Figure 1 Main symptoms of acute HIV infection

- Secondary syphilis



Pharyngitis after Receptive Oral Intercourse

Neisseria gonorrhoeae	**Herpes simplex virus**
• Highest risk MSM • Most asymptomatic • Nonspecific presentation • Diagnose by nucleic acid amplification test of pharyngeal swab	• HSV 1 or 2 • Usually with acute infection • Nonspecific presentation • Oral or genital ulcers variably present

Pharyngitis & Conjunctivatis

- College freshman with sore throat, fever, and conjunctivitis.
- Roommate and 3 others in her dorm with similar syndrome

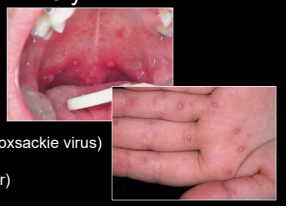
Adenovirus

Epidemics in group living situations—barracks, dorms, camps, etc

Pharyngitis and Vesicles

- 35 yo man with sore throat, low grade fever, and lesions on palms & soles. His 3 yo son is sick with a similar illness.

Hand, Foot, and Mouth disease



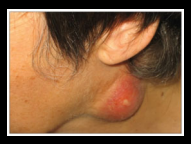
- Caused by enteroviruses (most common Coxsackie virus)
- Overlap with herpangina (oral lesions only)
- More common in kids (often serve as vector)

Case 2

- A 62 yo man presents with 24hr of fever, chills, odynophagia and diarrhea.
- He works on a vineyard in Napa Valley, and last week participated in the grape harvest. He admits to sampling the grape must.

Case 2

- PE:
  - T=102.4, HR=122, BP=97/52
  - Ill-appearing, left tonsil swollen and erythematous
  - Left suppurative lymph node tender to palpation
- WBC=12.3



CMAJ 2014;186:E62

Question 2

What is the most likely cause of this patient's illness?

A. Toxoplasmosis
B. Bartonellosis (Cat Scratch Fever)
C. Tularemia
D. Epstein Barr virus
E. Scrofula (mycobacterial lymphadenitis)

Oropharyngeal Tularemia

- Uncommon in the US
- Typically through ingestion (or rarely inhalation)
  - Inadequately cooked game
  - Contaminated tap water (Turkey)
  - Rodent contamination
- Exudative tonsillitis, ulcers, swollen LAN
- Diagnosis: culture (alert lab), serology
- Treatment: streptomycin, doxycycline

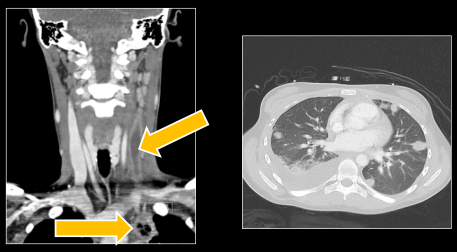
Pharyngitis and Chest Pain

- 20 yo college student with sore throat, chills, GI upset. Despite oral amoxicillin, develops new onset of cough and pleuritic CP.

Lemierre syndrome

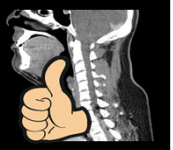
- Septic phlebitis of internal jugular vein
- Often follows Streptococcal pharyngitis or mononucleosis
- Classic cause is *Fusobacterium necrophorum*
- Anaerobic gram-negative rod
- Causes septic pulmonary emboli

Lemierre Syndrome



Extra-Tonsillar Infections: 1

- Epiglottitis
  - Fever, sore throat
  - Hoarseness, drooling, muffled voice, stridor
  - Examine with care!
  - Lateral neck x-ray: Thumb sign
  - *H. influenzae* type B, pneumococcus

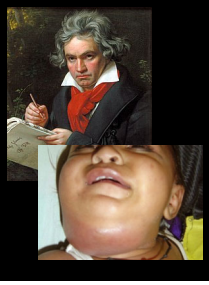


Extra-Tonsillar Infections: 2

- Vincent Angina
  - AKA Trench mouth
  - AKA acute necrotizing ulcerative gingivitis
  - Oropharyngeal pain, bad breath
  - Sloughing of gingiva
  - Mixed anaerobes

Extra-Tonsillar Infections: 3

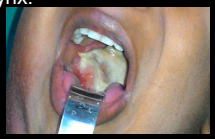
- Ludwig Angina
  - Bilateral cellulitis of floor of the mouth
  - Often starts with infected molar
  - Rapid spread with potential for airway obstruction
  - Fevers, chills, drooling, dysphagia, muffled voice, woody induration of neck
  - Mixed oral organisms (viridans strep, anaerobes)



Case 3

- A 42-year-old, previously healthy woman is seen for a bad "sore throat" that began 4 days earlier while attending her sister's wedding in southern Ukraine.
- She c/o malaise, odynophagia, and low grade fever. Today, she noted a choking sensation, prompting medical evaluation.

- T 100.2F; P 126; BP 118/74.
  HEENT: Submandibular swelling with gray exudate coating posterior pharynx.
  An S3 gallop is heard.



- CBC is normal.
  EKG shows: 1st degree AV nodal block, QT prolongation, and ST-T wave changes.

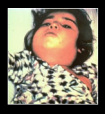
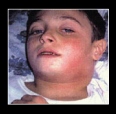
Question 3

The most likely diagnosis is?

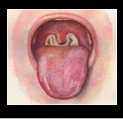
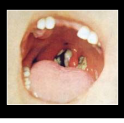
A. Streptococcal pharyngitis
B. Kawasaki disease
C. Vincent angina
D. Diphtheria
E. Lemierre syndrome

Buzz words and Visual Associations

Bull neck:

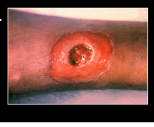




Grey pseudomembrane: extends onto palate or uvula; bleeds when scraped

Other clues

- Location, location, location
  - Almost unheard of in developed countries (vaccination)
  - Large outbreak in former Soviet Union 1990s
  - Still an issue (high mortality) in developing world
- Sore throat and myocarditis (~25%).
- Sore throat and neuropathies (~5%).
- Sore throat and cutaneous ulcer



Noninfectious Mimics

- PFAPA (periodic fever, aphthous stomatitis, pharyngitis, and adenitis)
- Still's disease
- Lymphoma
- Kawasaki disease
- Behçet disease

Karen.bloch@vumc.org

Modified Centor Criteria

- C-"can't" cough +1
- E-exudate +1
- N-neck adenopathy +1
- T-temperature elevation +1
- OR
  - Age less than 15 +1
  - Age >44 -1

12

Photo Opportunity I

Dr. Rajesh Gandhi

2020 INFECTIOUS DISEASE BOARD REVIEW

Photo Opportunity I

Rajesh Gandhi, MD
Director, HIV Clinical Services and Education
Massachusetts General Hospital
Professor of Medicine
Harvard Medical School

*Acknowledgments: Delaney Taylor for assistance with slides

Disclosures of Financial Relationships with Relevant Commercial Interests

- Scientific advisory board: Merck and Company, Inc.

PARTNERS INFECTIOUS DISEASE IMAGES
eMicrobes Digital Library
A Joint Project of the Massachusetts General Hospital Infectious Diseases Division and Microbiology Lab

Cases are from an educational web-site:
www.idimages.org

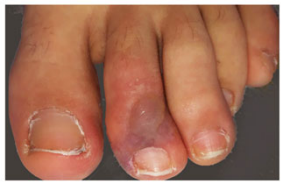
I acknowledge the contributors to the site for their case submissions and images.

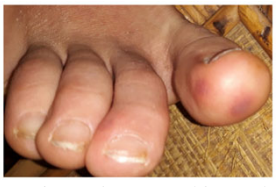
3

Images of Covid-19

Pernio/chilblains-like

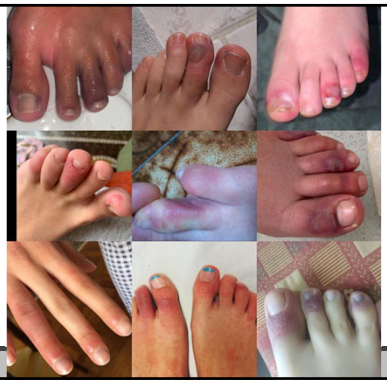
Erythematous to violaceous macules, papules, and and papulonodules, some with pseudovesiculation at the tips of digits and at times including soles of feet.





Slide courtesy of Dr. Daniela Kroshinsky (MGH Dermatology)

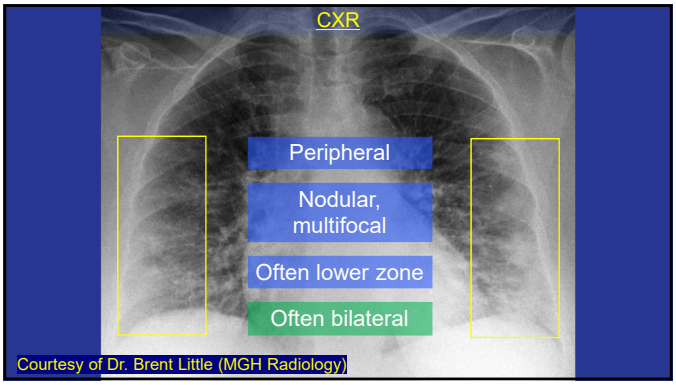
Mazzota F, Troccoli T. Acute acro-ischemia in the child at the time of COVID-19 (Mondays case). https://www.ejpd.com/en/mondayscase.

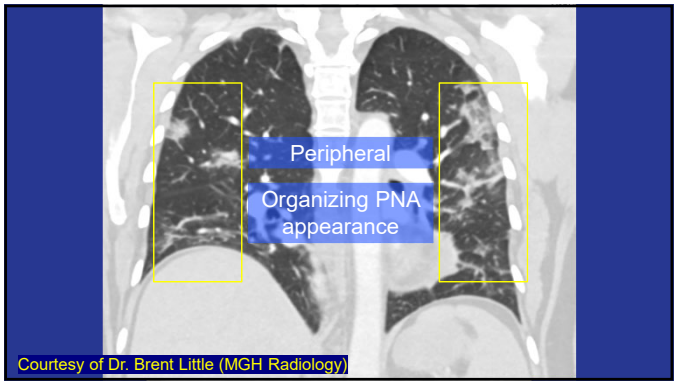


Slide courtesy of
Dr. Daniela Kroshinsky
(MGH Dermatology)

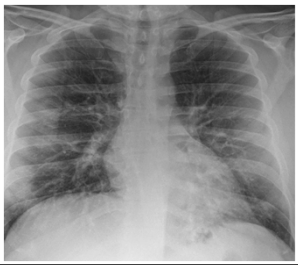
Covid-19: Typical Radiographic Features

- Peripheral, bilateral (multilobar) ground glass opacities with or without consolidation
- Multifocal ground glass opacities of rounded morphology
- Reverse halo sign or other findings of organizing pneumonia



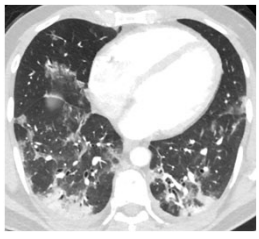


31 M: Bilateral relatively symmetric consolidation and hazy opacities with a lower zone predominance



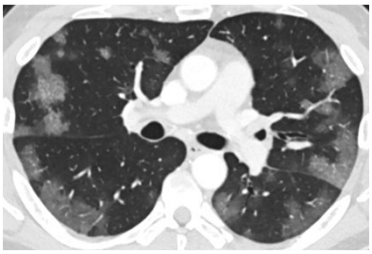
Courtesy of Dr. Brent Little (MGH Radiology)

50 yo M: Bilateral peripheral predominant patchy ground glass opacities and small areas of consolidation.



Courtesy of Dr. Brent Little (MGH Radiology)

50 yo M: bilateral peripheral ground glass opacities, some of which have a round morphology.



Courtesy of Dr. Brent Little (MGH Radiology)

12 – Photo Opportunity I: Photos and Questions to Test Your Board Preparation

Speaker: Rajesh Gandhi, MD

Case 1

A woman in her forties presented with 6 days of fatigue, decreased appetite, fevers and chills. She also had severe headache and myalgias.

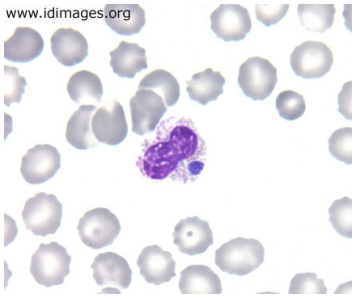
PMH: None.

SH: Patient was single and not sexually active. She denied cigarette, alcohol or illicit drug use. The patient had recently hiked in upper New Hampshire. She denied a history of tick bites. She had a dog but no other animal exposures.

Contributed by Anne Kasmar, M.D.

PE: She appeared well. T 103.5, BP 104/50, HR 122, RR 18, O_2 sat 97% on RA. She had no rash or adenopathy. Remainder of exam was normal.

Studies: WBC 2.3 (51% P, 29% bands, 14% L, 4% atypical lymphocytes); Hct 39%; Platelets 24. Serum chemistries values, including LFTs, were normal. Blood cultures were negative. CXR: normal



Differential Diagnosis

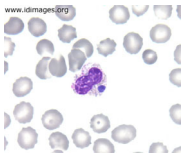
A. Meningococcemia

B. Anaplasmosis

C. Histoplasmosis

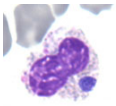
D. Babesiosis

E. "Spotless" Rocky Mountain Spotted Fever (RMSF)



Diagnosis and Follow-up

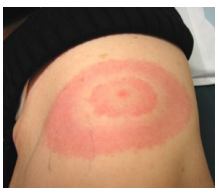
- Peripheral blood smear showed morulae inside white blood cells, consistent with anaplasmosis.



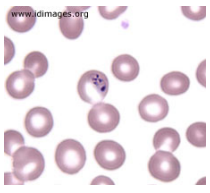
- Diagnosis confirmed with PCR testing.
- She was treated with doxycycline; symptoms completely resolved.

Rule out coinfection with Lyme, Babesia (same vector)

Lyme



Babesia

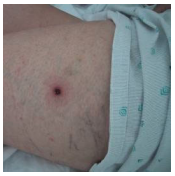


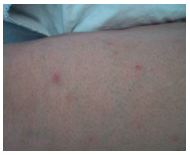
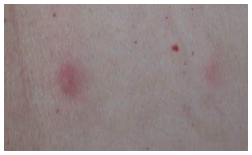
Case 2

- 50 yo F was well until 7 days prior to admission when she noted "bite" on left thigh. Lesion enlarged over several days. Three days later, developed fatigue, arthralgias, myalgias, fever, headache. On day of admission (July), developed generalized rash on extremities, trunk, back.
- Lived in New England. She had seen a mouse in her basement. She had a dog. Denied sexual activity.
- **PE:** appeared well. 100.5 F. No adenopathy. Lesion present on left thigh. Papular erythematous rash on her extremities, back, chest.

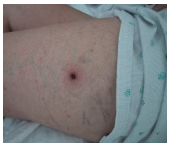
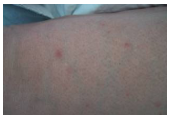
Contributed by Karen Thomas, M.D. and Leena Gandhi, M.D.

A. Varicella
B. Monkeypox
C. Cutaneous anthrax
D. Rickettsialpox
E. Lyme

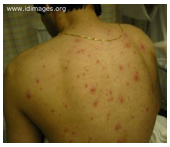
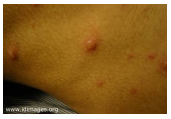


Rickettsialpox

Chickenpox

Case 3

50 yo F developed ulcerated lesion on her left thumb which enlarged over several months despite several courses of antibiotics. She reported no sore throat, fever, chills, dyspnea or cough.

Three months before, she travelled to Ecuador, where she stayed in an ecotourism hotel near a river. No known fresh- or salt-water exposure.

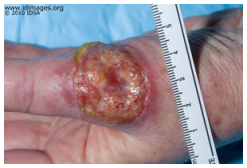
Reported seeing several kinds of insects and receiving several bites. No known animal exposures or tick bites.

Contributed by Rojelio Mejia, MD

Differential Diagnosis

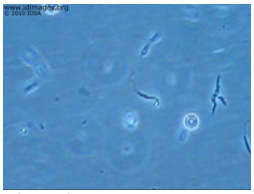
Patient appeared well. T 98.1.
Raised ulcerated lesion on thumb with a violaceous border

A. Cutaneous leishmaniasis
B. Mycobacterium marinum
C. Sporotrichosis
D. Pyoderma gangrenosum
E. Tularemia

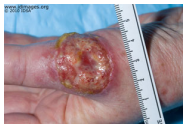


Skin biopsy showed amastigote, with kinetoplast in a vacuole. Culture of tissue from skin biopsy in Schneider's Media revealed promastigotes. PCR of tissue: *Leishmania guyanensis*.

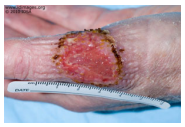

Skin biopsy, H and E stain


Culture of skin biopsy tissue in Schneider's medium

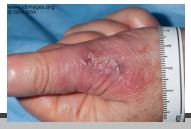
Treated with liposomal amphotericin



One week after treatment

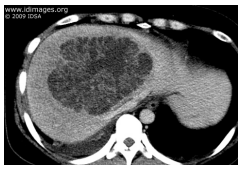


Follow-up at 3 months



Case 4

- A woman from China in her 40s developed fever, epigastric pain, and nausea. One week later, she was brought to ED with confusion and fever.
- T 101°F. Right upper quadrant abdominal tenderness.
- Abdomen CT: 10 cm hypoattenuated liver lesion



Contributed by Diana I. Mercado MD, Dong H. Lee MD, Todd I. Braun, MD

Is this abscess most likely due to:

A. Entamoeba histolytica
B. E. coli
C. Streptococcus milleri
D. Actinomyces
E. Klebsiella pneumoniae

Culture from liver aspirate

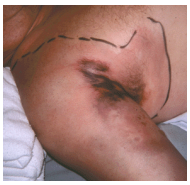
Case 5

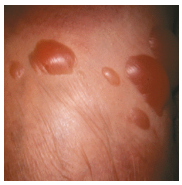
- 60 yo M presented to ED with a few hours of severe pain in right upper extremity. There was no history of trauma. Exam was normal with no obvious skin changes. He was discharged home.
- Over the next few hours, he developed progressive swelling of right upper extremity.
- Exam: right upper extremity was diffusely swollen with a deep-red discoloration; several bullae.
- Studies: WBC 8,900 (47% polys, 38% bands). X-ray: air in soft tissues.

Contributed by Steve Calderwood, M.D.

Does this patient most likely have:

A. Vibrio vulnificus
B. Group A streptococcal necrotizing fasciitis
C. Mixed aerobic/anaerobic necrotizing fasciitis
D. Clostridial gas gangrene
E. Bullous pemphigoid





Case 6

30 yo woman with HIV (CD4 cell count 20, not on therapy) presented with gradual onset of word-finding difficulties, expressive aphasia and right upper extremity weakness over 4 weeks.

She lived in New England. No recent travel or known insect bites. Not sexually active.

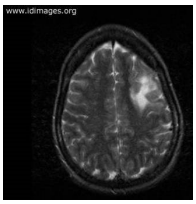
On exam, she was afebrile. She had oral thrush. She had difficulty naming objects and right-sided weakness.

Studies: WBC count of 2.2 (44% P, 45% L)

Contributed by Wendy Yeh, M.D.

Her clinical syndrome is most likely caused by:

A. An arbovirus
B. A polyomavirus
C. A herpes virus
D. A spirochete
E. A dematiaceous fungus

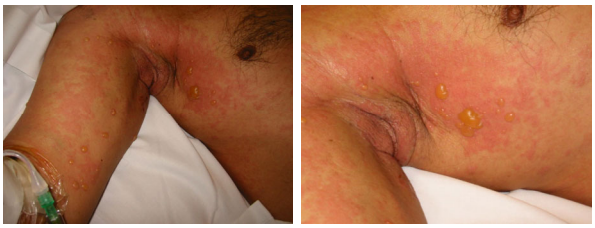


MRI: Abnormal T2 signal involving white matter, left fronto-parietal region. No enhancement, edema, mass effect

Case 7

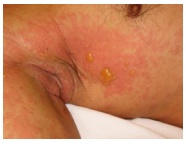
- 55 yo M was admitted with nephrolithiasis and *E. coli* urosepsis. Course was complicated by ARDS, requiring prolonged ventilatory support and tracheostomy. On hospital day 21, he developed methicillin resistant *Staph aureus* pneumonia. On hospital day 28, he developed fever and rash.
- PMH: hypertension, atrial fibrillation
- Medications: vancomycin, nifedipine, coumadin.
- Exam: T 103.2. Skin: erythematous areas in axillae, back, left thigh. On this erythematous base, there were tight bullae, which expressed yellow, serous, non-purulent fluid when opened. Exam otherwise normal.
- Studies: WBC 15.7 (84% P, 9% L, 3% M, 3% E), and hematocrit 28.6%. Cultures of the bullous fluid were negative.

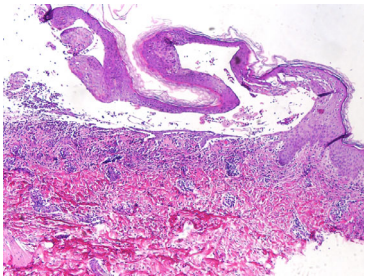
Contributor: John Beigel, M.D.



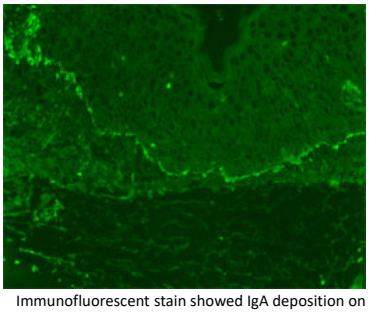
Differential Diagnosis

A. Dermatitis herpetiformis
B. Bullous pemphigoid
C. Linear IgA bullous disease from vancomycin
D. Herpes zoster
E. Staphylococcal scalded skin syndrome





H & E stain of skin bx showed neutrophilic infiltrate at the dermal-epidermal junction and a sub-epidermal bulla

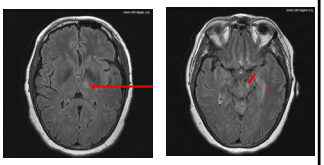


Immunofluorescent stain showed IgA deposition on the basement membrane at the dermal-epidermal junction

Treatment/ Follow up: Vancomycin was discontinued, and the bullae gradually resolved after one week.

Case 8

- Woman in her 50s presented with fatigue, confusion, word-finding difficulties and fever for 3 days
- Lived in Midwestern US
- Avid outdoors person, frequently in wooded areas; husband recalls pulling a tick off her trunk recently
- T 101.3. Somnolent woman, oriented only to self
- CSF: WBC 146 (9% N, 56% L, 35% M); RBC 14; Glc 70; Pro 109

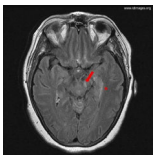


MRI: T2 hyperintensity left thalamus and substantia nigra; leptomeningeal enhancement

Contributed by Joy Chen, M.D. and Virk Abinash, M.D.

Differential Diagnosis

A. Neisseria meningitides meningitis
B. Herpes simplex virus encephalitis
C. Lyme meningoencephalitis
D. Powassan meningoencephalitis
E. Lymphocytic choriomeningitis



Diagnostic Procedures & Results

- CSF gram stain, fungal smear, bacterial and fungal cultures were negative
- CSF PCR tests for HSV, WNV, VZV, CMV negative
- CSF positive for immunoglobulin M against Powassan virus by ELISA. Confirmed at CDC

Case 9

19 yo M presented with 2 wks of painful swelling in his left groin. He reported fevers to 101 with night sweats, fatigue and malaise.

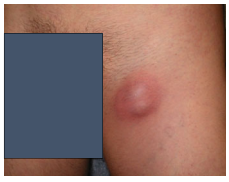
Denied urinary complaints, penile discharge or ulcers, change in bowel habits, abdominal pain or trauma to his legs.

Lived in Northeast US. No travel. Two female sexual partners, one of whom recently immigrated from Mexico. Lived with mother and grandmother, who had a cat and dog. Worked in food services. Denied seeing mice or rats.

Differential Diagnosis

T: 98.6 F. Tender lymph node inferior to inguinal ligament. WBC: 9.6; Urinalysis: negative

A. Lymphogranuloma venereum (LGV)
B. Chancroid buboe
C. Bubonic plague
D. Cat-scratch disease (CSD)
E. Incarcerated hernia



Contributed by Stephen Walsh, M.D.

12 – Photo Opportunity I: Photos and Questions to Test Your Board Preparation

Speaker: Rajesh Gandhi, MD

13

Management of AIDS-Related Opportunistic Infections I

Dr. Henry Masur

13 – Management of AIDS-Related Opportunistic Infections I

Speaker: Henry Masur, MD

2020 INFECTIOUS DISEASE BOARD REVIEW

Management of AIDS-Related Opportunistic Infections I

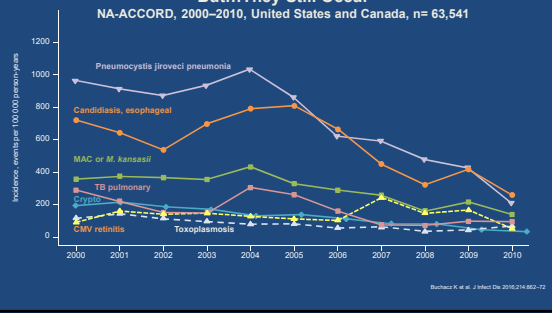
Henry Masur, MD, FIDSA, MACP
Clinical Professor of Medicine
The George Washington University

Disclosures of Financial Relationships with Relevant Commercial Interests

- None

Opportunistic Infections Among HIV Infected Persons Are Declining But…They Still Occur

NA-ACCORD, 2000–2010, United States and Canada, n= 63,541



Buchacz K, et al. J Infect Dis 2016;214:862–72

Question #1

- **An asymptomatic patient with a new diagnosis of HIV (CD4 = 10 cells/uL and HIV Viral Load 300,000 copies/uL is started on antiretroviral therapy (dolutegravir plus tenofovir alafenamide/emtricitabine)**
- **His labs are unremarkable as is his chest xray**
- **His serum toxoplasma IgG is positive**
- **He asks whether you want to add prophylaxis for pneumocystis pneumonia but warns you that twice when he has taken sulfonamides he has developed hives and laryngeal edema**

What would you recommend regarding PCP and Toxo prophylaxis?

A. No chemoprophylaxis: his viral load should fall quickly, and his CD4 will rise quickly in response to this first exposure to antiretroviral therapy
B. Trimethoprim sulfamethoxazole plus solu-medrol dose pak
C. Dapsone
D. Aerosol pentamidine plus pyrimethamine
E. Atovaquone

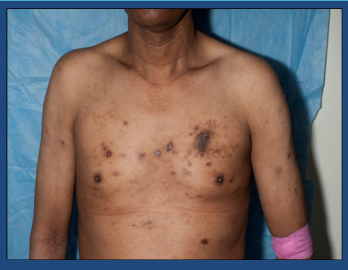
Question #2

The patient whose photo is shown is HIV positive (CD4=10 cells/uL, VL=2 mil copies) and has noted these lesions developing on his trunk, face and extremities over the past 8 months.

He has had low grade fevers for several months.

For your differential diagnosis, what besides Kaposi sarcoma would be the most likely cause of these lesions and their associated fever?

Question #2



13 – Management of AIDS-Related Opportunistic Infections I

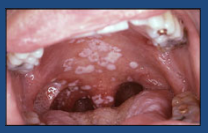
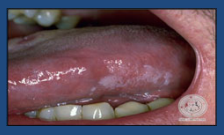
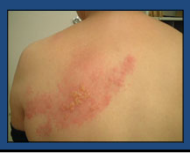
Speaker: Henry Masur, MD

Question #2

The most likely cause of these skin lesions, if they are not Kaposi sarcoma, is:

A. HHV-6
B. CMV
C. Cryptococcus neoformans
D. Bartonella
E. Rhodococcus

Clinical Indicators of Immunosuppression

Cardinal AIDS-Defining Illnesses

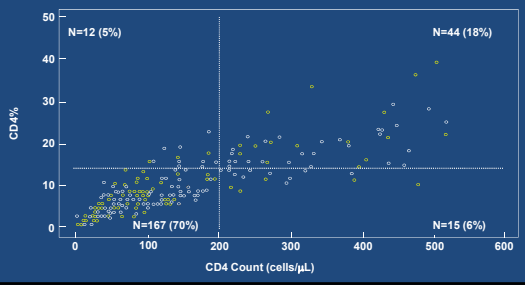
- **Pneumocystis pneumonia**
- **Toxoplasma encephalitis**
- **CMV Retinitis**
- **Disseminated Mycobacterium avium complex/Tuberculosis**
- **Chronic cryptosporidiosis/microsporidiosis**
- **Kaposi Sarcoma**

Susceptibility to Opportunistic Infections Patients with HIV

- **CD4 Count**
  - Current Count is most important
  - Prior Nadir count is much less important
- **Viral Load**
  - Independent risk factor for OIs

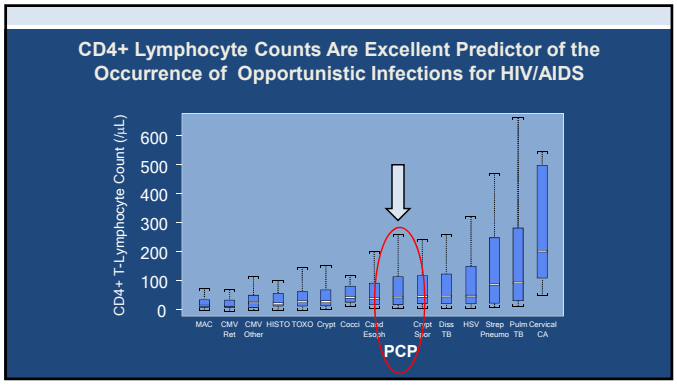
At What CD4 Counts Do Opportunistic Infections Occur?

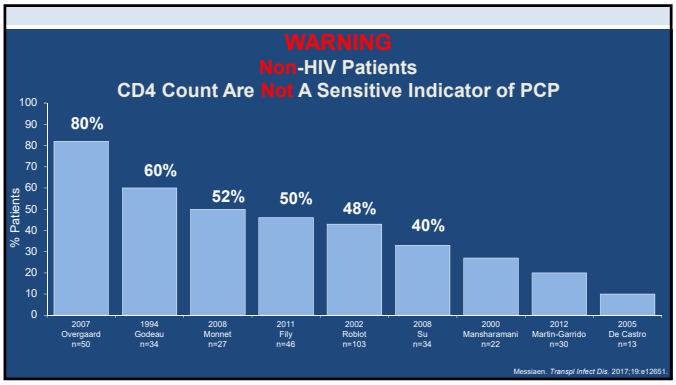
Scatterplot of CD4 Number vs CD4 Percent Within 6 Months of HIV-Associated PCP



13 – Management of AIDS-Related Opportunistic Infections I

Speaker: Henry Masur, MD





What is the Most Effective Intervention to Prevent Opportunistic Infections and Neoplams Regardless of CD4 Count and Viral Load?

What is the Most Effective Intervention to Prevent Opportunistic Infections and Neoplams Regardless of CD4 Count and Viral Load?

Antiretroviral Therapy

When to Start ART Following Opportunistic Infection

When to Start ART Following Opportunistic Infection

- **Most OIs**
  - **Within 2 weeks of diagnosis**

13 – Management of AIDS-Related Opportunistic Infections I

Speaker: Henry Masur, MD

When to Start ART Following Opportunistic Infection

- **Tuberculosis : 2-8 weeks**
  - CD4<50-within 2 weeks of diagnosis
  - CD4>50-within 8-~~12~~ weeks of diagnosis
- **Cryptococcal Meningitis:4-6 weeks after start of Ampho**
  - Sooner if mild and if CD4<50
  - Later (up to 10 weeks) if severe (CSF sterility reduces risk of IRIS)
- **"Untreatable" OIs, ie PML, Cryptosporidiosis**
  - Start immediately

Primary and Secondary OI Prophylaxis

- **Primary Prophylaxis**
  - PCP (CD4 <200, ~~oral candida, prior AIDS Defining~~)
  - Toxo (CD4 <100, positive anti Toxo IgG)
  - Cocci (CD4<250, positive cocci IgM or IgG
  - ~~MAC (CD4 < 50)~~ ----NIH/CDC/IDSA guideline has eliminated this
  - *
- **Secondary Prophylaxis /Chronic Suppression**
  - PCP
  - Toxo
  - MAC
  - CMV
  - Cryptococcus
  - Histoplasma
  - Coccidio

*Some experts would give Histo primary prophylaxis with itraconazole in high risk situations if CD4<150

Discontinue Prophylaxis/Chronic Maintenance

Board might consider this a "look up"

Primary Prophylaxis	CD4 Count Due to ART
– PCP or Toxo	>200 x 3 months
– PCP	(>100 and VL<50)

Secondary Prophylaxis/Chronic Maintenance

– PCP	>200 x 3 months
– Toxo	>200 x 6 months*
– Crypt	>200 x 6 months*
– MAC	>100 x 6 months*+ 12 m Rx
– CMV	>100 x 3-6 months*

*"Adequate response of primary disease"-see guidelines for details

Primary Coccidiomycosis Prophylaxis 2020 OI Guideline

Testing

- **Once or twice yearly testing for seronegative patients**
- **No prophylaxis if seronegative**

Primary Prophylaxis

- **Within the endemic area**
  - New positive IgM or IgG serology
  - CD4 count is <250 cells (BIII)
  - No Active Disease
- **Regimen**
  - Fluconazole 400mg qd until CD4>250 and fully suppressed viral load

www.aidsinfo.nih.gov

NIH CDC IDSA Guidelines for the Prevention and Treatment of Opportunistic Infections in Adults and Adolescents with HIV

Recommendations May Vary from the Advisory Committee on Immunization Practices

VACCINE	All persons	Where varies by age				Where varies by CD4 cell count (cells/mm³)	
		13-26 years	27-49 years	50-64 years	≥ 65 years	< 200	≥ 200
Hepatitis A	2-3 doses (varies by formulation)						
Hepatitis B	2-3 doses (varies by formulation)						
Human papillomavirus (HPV)		3 doses	3 doses				
Influenza	1 dose annually						
Measles, mumps, rubella (MMR)						Contraindicated	2 doses if born after 1956 or nonimmune
Meningococcal A,C,W,Y conjugate (MenACWY)	2 doses, booster every 5 years						
Meningococcal B (MenB)	2-3 doses (varies by formulation)						
Pneumococcal conjugate (PCV13)	1 dose						
Pneumococcal polysaccharide (PPSV23)		2 doses five years apart			1 dose		
Tetanus, diphtheria, pertussis (Tdap/Td)	Tdap once then Td or Tdap booster every 10 years						
Varicella (VAR)						Contraindicated	2 doses
Zoster recombinant (RZV) (preferred)				2 doses			

Recommended for all adults and adolescents with HIV who meet the age requirement or lack documentation of vaccination or evidence of past infection

Recommended for adults and adolescents with HIV with another risk factor (medical, occupational, or other indication) or in select circumstances

Contraindicated

HBV Recommendation

- **Who to vaccinate**
  - All HIV+ who are HBs Ab negative
- **What Vaccine to Use**
  - Consider HAV/HBV combination (3-4 doses) (0,1,6 months +/1 2 month)
  - Either of the two recombinant vaccines is recommended-3 doses
  - **Adjuvant vaccine (Heplisav)** is more immunogenic but no firm recommendation for use in HIV-2 doses (months 0,1)
    - (Is Adjuvant associated with more cardiovascular events?)
- **Assure that serum ab level remains >10 IU/ml for patients with HIV**
  - Assess Ab 1-2 month after series completed and then annually
  - Booster for those still at risk if antibody <10IU

13 – Management of AIDS-Related Opportunistic Infections I

Speaker: Henry Masur, MD

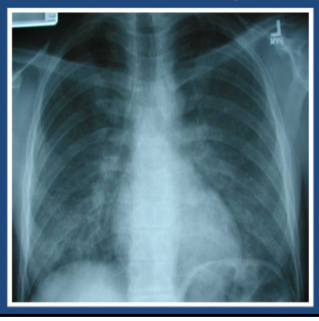
HBV Vaccination for HIV Infected Persons
Special Problems That Are Likely Untestable

- **What to do about Isolated HBc pos (HBs neg)**
  - Not testable
  - Give one dose: if titer rises to >100 IU, stop; if not >100 IU, complete 4 dose series
- **Initial Regimen Failures (Titers <10 IU)**
  - Give one booster
  - Give another 3 dose series
  - Give double dose 3-4 like dialysis patients
  - Give adjuvant vaccine
  - Wait for CD4 to rise due to ART

What Should You Know About "Newer" Vaccines?

- **Heplisav-B**
  - Hepatitis B vaccine, recombinant, adjuvanted (Dynavax)
  - Likely safe to use in HIV infected persons
  - Insufficient data in HIV for most guidelines to recommend as preferred
- **Shingrix**
  - Recombinant Vaccine with adjuvant (A501B)
    - Preferred over Zostavax (zoster vaccine live) for non HIV infected persons over 50 years
  - Split Decision for PLWH Recommendation
    - Insufficient data for ACIP guideline recommendation for HIV infected persons
    - "Preferred" in IDSA/CDC/NIH HIV guideline

HIV Associated Pulmonary Disease



Etiology of HIV Associated Pulmonary Disorders

Common	Uncommon	Rare
• Pneumococcus	• Aspergillus	• CMV
• Hemophilus	• Histo/Cocci	• MAC
• Pneumocystis	• Staphylococci	• HSV
• Tuberculosis	• Toxoplasma	
• "Atypicals/viral"	• Lymphoma	
	• Kaposi sarcoma	

Respiratory Disease in Patients with HIV
Do Not Focus Only on OIs!

- **Non-Infectious**
  - **Congestive Heart Failure** **(Age, cocaine, pulm hypertension)**
  - **Pulmonary emboli** **(Increased risk)**
  - **Drug toxicity** **(Abacavir, Lactic acidosis, dapsone)**
  - **Neoplastic** **(KS, Lymphoma, Lung CA)**

Respiratory Disease in Patients with HIV
Do Not Focus Only on OIs!

- **Non-Infectious**
  - **Congest Heart Failure** **(Age, cocaine, pulm hypert)**
  - **Pulmonary emboli** **(Increased risk)**
  - **Drug toxicity** **(Abacavir, Lactic acidosis, dapsone)**
  - **Neoplastic** **(Kaposi sarcoma, Lymphoma, Lung CA)**
- **Non-Opportunistic Infections**
  - **Community acquired** **(Influenza and MRSA)**
  - **Aspiration** **(Opioid related, nosocomial)**
  - **Septic Emboli** **(IV catheters, endocarditis)**

13 – Management of AIDS-Related Opportunistic Infections I

Speaker: Henry Masur, MD

Approach to Diagnosis and Therapy of Pneumonia in Patients with HIV Infection

Parameter	Example
Rapidity of onset	> 3 days: PCP, TB <3 days: bacteria
Temperature	Afebrile: neoplasm
Character of sputum	Purulent: bacteria Scant: PCP, TB, virus
Physical Exam	Normal in PCP; Consolidation in Bacterial
X-ray	Pattern: Suggestive, but not definite

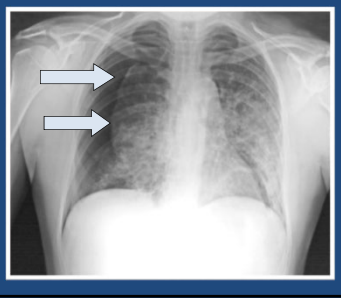
Pneumococcal Disease in Persons with HIV Infection

- CD4<200
  - Severity/Extrapulmonary Complications Enhanced
- CD4>350
  - Frequency: Enhanced
  - Severity: No difference
- Comorbidities Predisposing to Pneumococci Over-Represented in HIV
  - Opioid Use Disorder, Etoh, Tobacco, Lack of Immunization
  - COPD, CHF, Obesity, MRSA colonization, Liver Disease

Question #3

- A 28 year old male with HIV (CD4 count = 10 cells) presents to the ER 4 weeks of malaise and mild cough, and now has bilateral interstitial infiltrates and a right sided pneumothorax.
- The patient lives in Chicago, works in an office and has never left the Midwest and no unusual exposures.
- The most likely INFECTIOUS cause of this pneumothorax is:

HIV Patient with Shortness of Breath



Question #3

A 28 year old male with HIV (CD4 count = 10 cells) presents to the ER 4 weeks of malaise and mild cough, and now has bilateral interstitial infiltrates and a right sided pneumothorax.

The patient lives in Chicago, works in an office and has never left the Midwest and no unusual exposures.

The most likely INFECTIOUS cause of this pneumothorax is:

A. Cryptococcosis
B. Blastomycosis
C. PCP
D. CMV
E. Aspergillosis

Pneumocystis Jirovecii (Formerly *P. carinii*)

- Taxonomy
  - Fungus (no longer Protozoan)
- Epidemiology
  - Environmental source unknown
- Life Cycle
  - Unknown
- Transmission
  - Respiratory

13 – Management of AIDS-Related Opportunistic Infections I

Speaker: Henry Masur, MD

Host Susceptibility to PCP

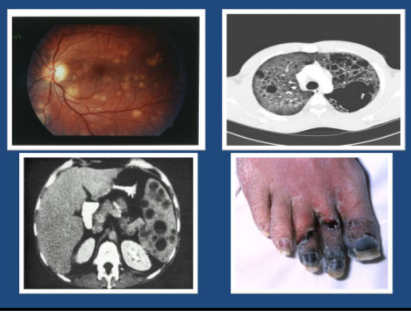
- CD4 < 200 cells/μL --(90% of cases)
- CD4% <14

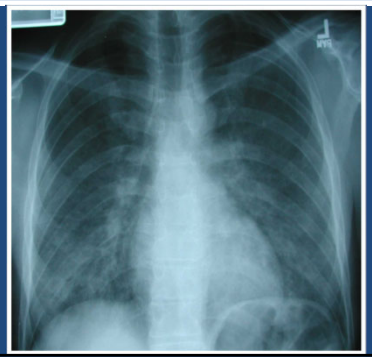
Clinical Features of Pneumocystis Pneumonia, (n=168)

Symptom	% of Patients
Dyspnea	91%
Fever	66%
Cough	47%
Productive	7%
Non-productive	40%
Chest Pain	7%
Signs	
Cyanosis	39%
Rales	33%

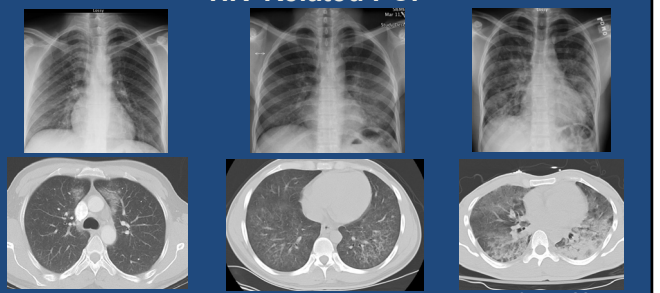
Walzer, Ann Intern Med 1974

Uncommon Manifestations of PCP





HIV Related PCP



Asymptomatic
Incidental Finding

Fever, Wt. Loss, No SOB
Pulse Ox. 99%, to 89% w/Exercise

2 Weeks of Fever, SOB Room
Air PAO_2=67 mm Hg

Radiologic Patterns Associated with Documented Pneumocystis Pneumonia

- **Most Frequent**
  - Diffuse symmetric interstitial infiltrates progressing to diffuse alveolar process
    - butterfly pattern radiating from hilum

13 – Management of AIDS-Related Opportunistic Infections I

Speaker: Henry Masur, MD

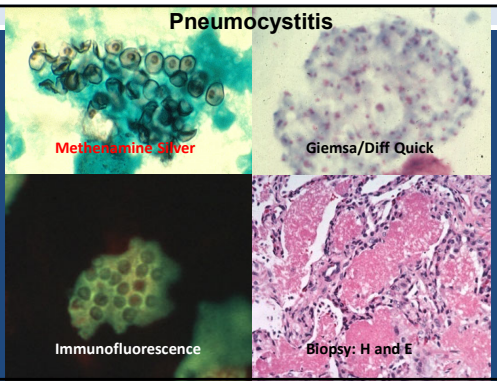
Radiologic Patterns Associated with Documented Pneumocystis Pneumonia

- **Other Patterns Recognized**
  - (Other concomitant infectious or neoplastic disease processes?)
  - Lobar infiltrates
  - Upper lobe infiltrates
  - Pneumothorax
  - Solitary nodules
  - Cavitating lesions
  - Infiltrates with effusions
  - Asymmetric or unilateral processes
  - Normal chest x-ray

Diagnosis of Pneumocystis Pneumonia

Specimen Acquisition		Organism Detection
	1957	
Open lung biopsy		Methenamine silver
Transbronchial biopsy		Immunofluorescence
Bronchoalveolar lavage		Giemsa / Diff Quik
Induced sputum		PCR
	2020	

Pneumocystitis



PCR
For Diagnosis of Pneumocystis in Bronchoalveolar Lavage

- **Highly sensitive in BAL**
  - Not useful in blood/serum/plasma
- **High biologic specificity**
  - Positive result might be infection or disease
  - Cycle number (copy number)helpful but not definitive

PCR
For Diagnosis of Pneumocystis in Bronchoalveolar Lavage

- **High**
  - No
- **High**
  - Po
  - Cy

Negative BAL PCR rules out PCP

Positive BAL PCR *might* be PCP
- **Colonization vs Disease**

Is There A Serologic Test for PCP?
No!

- **Serum Antibody or PCR Test**
  - Not useful…yet
- **LDH**
  - Sensitivity depends on severity
  - Non-specific
- **Beta Glucan**
  - Sensitive but not specific
  - Maybe useful for
    - Heightened suspcicion of PCP if BAL or sputum not feasible
    - Following response to Rx

13 – Management of AIDS-Related Opportunistic Infections I

Speaker: Henry Masur, MD

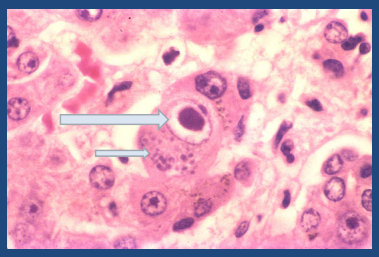
Question #4

- **A 45 year old woman with HIV (CD4 = 50 cells/uL, HIV viral load = 500,000 copies/uL) presents with fever, shortness of breath, room air P02 =80mm Hg) and diffuse bilateral infiltrates and is started on TMP-SMX. The bronchoalveolar lavage is positive for pneumocystis by direct fluorescent antibody test.**
- **The cytology lab reports several CMV inclusion bodies in the BAL.**

The best course of action in addition to considering antiretroviral therapy would be:

A. To add ganciclovir to the TMP-SMX regimen
B. To add prednisone to the TMP-SMX regimen
C. To add ganciclovir plus prednisone to the TMP-SMX regimen
D. To add ganciclovir plus IVIG to the regimen
E. To add nothing, ie continue TMP-SMX alone

CMV Cytology



Eosinophilic Intranuclear Inclusion and Coarse Basophilic Cytoplasmic Inclusions

CMV Almost Never Causes Pneumonia In HIV Infected Pts

Question #5

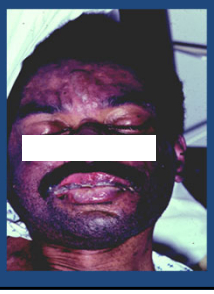
A 23 year old male with HIV Related PCP (CD4=25 cells/uL) was started on IV trimethoprim-sulfamethoxazole for PCP.

He is on no other meds

On day 7 of therapy, he developed fever, myalgias and on day 8 bullous skin lesions diffusely, most notably on his face, and developed substantial mucositis and a new fever to 39 C with pain over the blistered areas. His palms and soles were spared

Which of the following would be the most effective intervention:

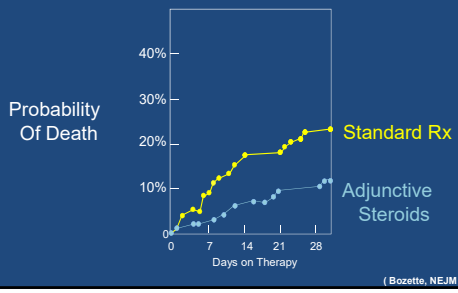
1) Add IV Acyclovir and swab lesions for HSV PCR
2) Add vancomycin for scalded skin syndrome
3) Switch TMP-SMX to IV Clindamycin plus oral Primaquine
4) Add IV Clindamycin to IV TMP-SMX
5) Add Prednisone to IV TMP-SMX



Therapy for Pneumocystis Pneumonia

- **Specific Therapy**
  - **First Choice**
    - **Trimethoprim-Sulfamethoxazole**
  - **Alternatives**
    - **Parenteral Pentamidine**
    - **Atovaquone**
    - **Clindamycin-Primaquine**
- **Adjunctive Corticosteroid Therapy**

Likelihood of Death in Patients with Moderate-Severe PCP Receiving Corticosteroids (n=251)



(Bozette, NEJM 5/90)

How to Manage Patients Who Are Failing TMP-SMX

- **Average Time to Clinical Improvement**
  - 4-8 Days
- **Radiologic Improvement**
  - Lags clinical improvement

13 – Management of AIDS-Related Opportunistic Infections I

Speaker: Henry Masur, MD

Reasons to Deteriorate During Treatment for PCP

- **Fluid overload**
  - Iatrogenic, cardiogenic, renal failure (Sulfa or Pentamidine related)
- **Anemia**
- **Methemoglobinemia**
  - Dapsone, primaquine
- **Pneumothorax**
- **Unrecognized concurrent infection**
- **Immune Reconstitution Syndrome (IRIS)**

Reasons to Deteriorate During Treatment for PCP

- **Fluid overloa**
  - Iatrogenic, ca entamidine related)
- **Anemia**
- **Methemoglob**
  - Dapsone, prim
- **Pneumothora**
- **Unrecognize**
- **Immune Rec**

Patients Failing TMP-SMX

- **Whether to Switch**
- **When to Switch**
- **What to Switch To**
- **How to Manage Steroid Dosing**

Question #6

A patient with HIV infection newly diagnosed (CD4=10, VL= 200,000 copies/uL) was started on the following medications: efavirenz, emtricitabine, tenofovir, dapsone, clarithromycin. Fluconazole was added when oral thrush was noted.

Ten days later the patient returns with headache, shortness of breath, a normal chest CT, and ABG which shows pH 7.40, pO2=96mmHg, pCO2 =39mm Hg, O2 Sat 79%.

The most likely cause of this patient's syndrome is:

A. Pneumocystis pneumonia
B. Pulmonary Kaposi sarcoma
C. Fluconazole interaction with another drug
D. Dapsone
E. Clarithromycin

Question #7

A patient with HIV infection presents with PCP (room air pO_2=84mHg).

He has a history of a severe exfoliative rash to TMP-SMX.

Which of the following therapies would you recommend:

A. **TMP-SMX plus prednisone**
B. **Dapsone plus trimethoprim**
C. **Aerosolized pentamidine**
D. **Intravenous pentamidine**
E. **Clindamycin-pyrimethamine**

Can *Pneumocystis Jiroveci* Become Resistant to TMP-SMX?

Question-Non ARS

A 50-year-old male with HIV and PCP is receiving pentamidine 4 mg/kg IV over 1 hr qd.

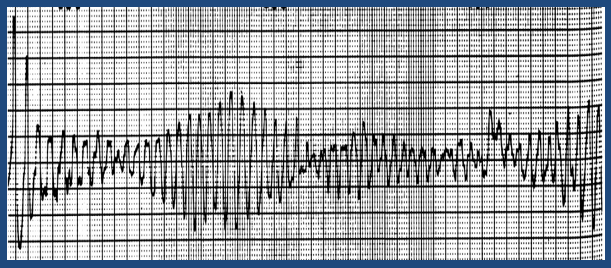
On the ninth day of therapy, while awaiting transportation home, he has a syncopal episode.

What is this rhythm?

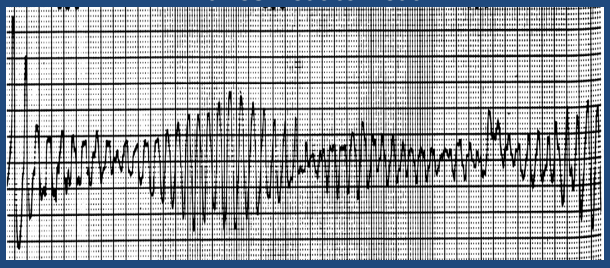
13 – Management of AIDS-Related Opportunistic Infections I

Speaker: Henry Masur, MD

What is this rhythm?

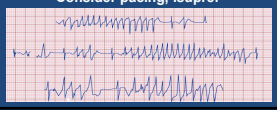


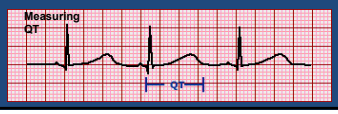
Polymorphic Ventricular Tachycardia Varies Beat to Beat



Prolonged QT

- **Prolonged QT predisposes to Torsades**
  - **Worry: >0.5 sec (500ms)**
  - **Corrected QT interval (QTc) is calculated by formula**
- **Therapy for Torsades**
  - **Fix underlying cause, stop offending drug(s)**
  - **If Pulseless: Defibrillate, epinephrine bolus, Magnesium**
    - **Magnesium sulfate 2g bolus**
    - **Consider pacing, isuprel**





Causes of Prolonged QT

Electrolytes

Hypo: magnesemia, kalemia, calcemia

Antibiotics

- Pentamidine
- Chloroquine/Hydroxychlor
- Clarithromycin
- Atazanavir
- Quinolones
- Quinidine
- Azoles

Other Drugs

- Tricyclic antidepressants
- Disopyramide (Norpace)
- Amiodarone
- Sotalol
- Thioridazine
- Procainamide
- Haloperidol

Question #8

A 50-year-old male with HIV and PCP is receiving pentamidine 4 mg/kg IV over 1 hr qd.

On the ninth day of therapy, while awaiting transportation home, he has a syncopal episode.

An EKG done by the code team is normal.

What Non cardiac toxicity of pentamidine would be most likely

A. Hyponatremia
B. Seizure
C. Hypoglycemia
D. Hypertensive crisis and stroke
E. Pulmonary embolus

Toxicities of TMP-SMX and Pyrimethamine-Sulfadiazine

Drug	Toxicities
TMP-SMX	↓WBC, ↓plat, ↑LFT, ↑Creat, ↑Amylase, rash, fever, pruritus, "Sepsis" Hyperkalemia (TMP) Cross reactivity: dapsone (± 50%) Role of Folinic Acid - questionable
Pyrimethamine-Sulfadiazine	Similar to TMP-SMX Folinic acid necessary (not folate)

13 – Management of AIDS-Related Opportunistic Infections I

Speaker: Henry Masur, MD

Toxicity and Other Considerations Regarding Antipneumocystis Therapy

Drug	Issues
Pentamidine - IV	Hypotension-rate related ↑Creatinine, ↑Amylase, ↓WBC ↑ early and then↓Glucose: Associated with↑Creatinine may occur days-wks post therapy Torsade de Pointes
Atovaquone	Absorption if low fat diet Rash, N + V, diarrhea, LFT

Other Conditions Where PCP Is Common

- **Prednisone >=20mg qd x > 4 weeks**
- **Cytoxan**
- **Purine Analogs**
  - Azathioprine - Mercaptopurine
  - Pentostatin -Fludarabine
- **Various Biologics**
  - Rituximab
  - Alemtuzumab (Campath) for at least 2 months post therapy or until CD4>200
  - TNF Inhibitors
  - Acute lymphocytic leukemia during acute and maintenance therapy
  - Allogeneic stem cell transplant recipients, at least 6 months
  - Graft vs host disease
  - Solid organ transplant recipients, at least 6 months and during acute rejection rx
  - Idelalisib, a phosphatidylinositol 3-kinase inhibitor
  - Probably: Ibrutinab, TNF Inhibitors
  - Concomitant temozolomide and radiotherapy, until recovery of lymphopenia

Thank You!

2020 INFECTIOUS DISEASE BOARD REVIEW

GW | Office of Continuing Education in the Health Professions

25th Annual

COMPREHENSIVE REVIEW *for* INFECTIOUS DISEASE BOARD PREPARATION

DAY 2

COURSE DIRECTORS:
John E. Bennett, MD
Henry Masur, MD

COURSE CO-DIRECTORS:
Paul Auwaerter, MD
David N. Gilbert, MD
Roy M. Gulick, MD, MPH
Andrew Pavia, MD
Richard J. Whitley, MD

www.IDBoardReview.com

SUNDAY, AUGUST 23, 2020

#	START	END	PRESENTATION	SPEAKER(S)
14	9:45 AM	10:15 AM	**Daily Question Preview 2**	*John Bennett, MD (Moderator)*
15	10:15 AM	10:45 AM	**Sexually Transmitted Infections: Genital Ulcers Diseases (GUD)**	*Khalil Ghanem, MD*
16	10:45 AM	11:15 AM	**Herpes Viruses in Immunocompetent and Immunosuppressed Patients; CMV, EBV, HHV 6, HHV 8**	*John Gnann, MD*
	11:15 AM	11:30 AM	***BREAK***	
17	11:30 AM	12:30 PM	**Sexually Transmitted Infections: Other Diseases and Syndromes**	*Khalil Ghanem, MD*
18	12:30 PM	1:30 PM	**Herpes Viruses: HSV and VZV in Immuno-competent and Immunocompromised Hosts**	*Richard Whitley, MD*
	1:30 PM	1:45 PM	***BREAK***	
19	1:45 PM	2:30 PM	**Board Review Session 2**	*Drs. Whitley (Moderator), Dhanireddy, Dorman, Ghanem, Thomas, and Tunkel*
20	2:30 PM	3:15 PM	**Encephalitis including West Nile and Rabies**	*Allan Tunkel, MD*
21	3:15 PM	4:15 PM	**Immunizations: Domestic, Travel, and Occupational**	*Shireesha Dhanireddy, MD*
	4:15 PM	4:30 PM	***BREAK***	
22	4:30 PM	5:15 PM	**Acute Hepatitis**	*David Thomas, MD*
23	5:15 PM	5:45 PM	**Viral and Bacterial Meningitis**	*Allan Tunkel, MD*
24	5:45 PM	6:45 PM	**Chronic Hepatitis**	*David Thomas, MD*
25	6:45 PM	7:15 PM	**Brain Abscess, Cavernous Sinus Thrombosis, and Subdural and Epidural Empyema**	*Allan Tunkel, MD*

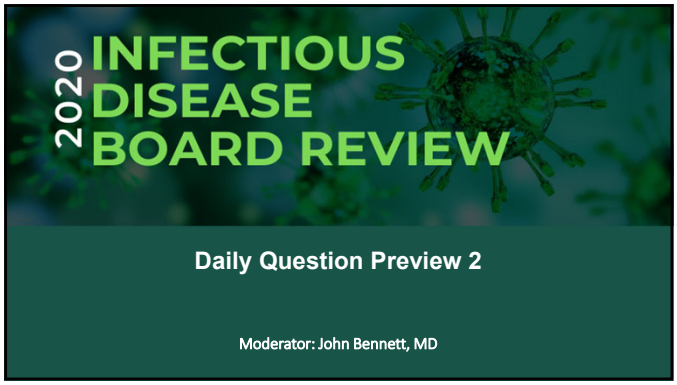
14

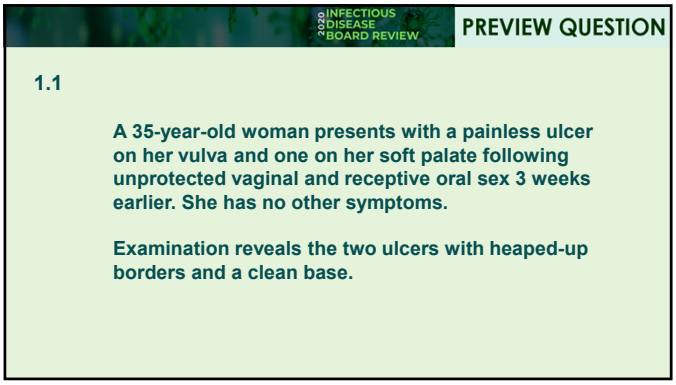
Daily Question Preview *2*

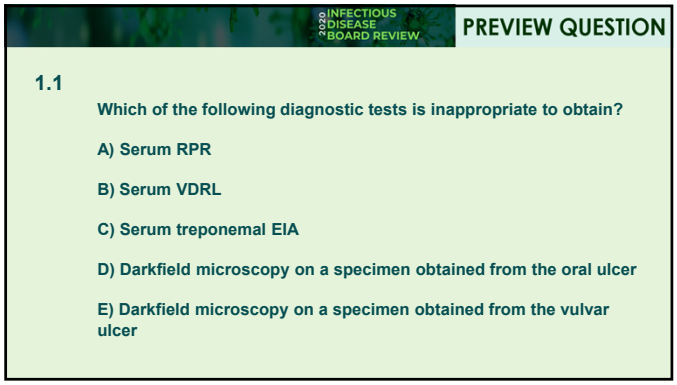
Dr. John Bennett (Moderator)

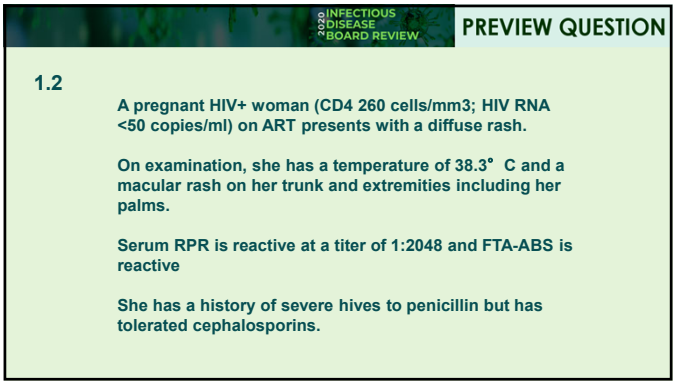
14 – Daily Question Review 2

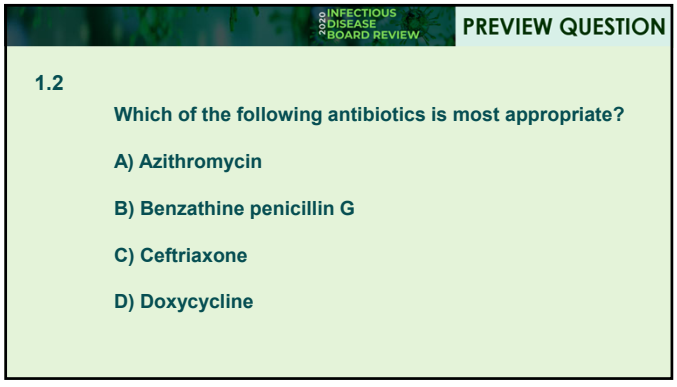
John Bennett, MD (Moderator)

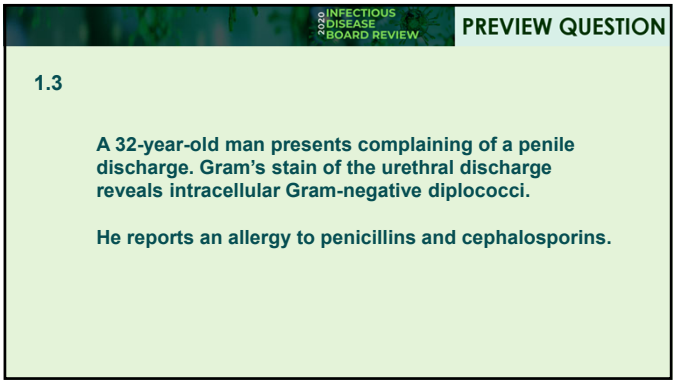












14 – Daily Question Review 2

John Bennett, MD (Moderator)

PREVIEW QUESTION

1.3

Which of the following regimens does the CDC recommend as the most appropriate therapy?

A) Azithromycin

B) Azithromycin plus ceftriaxone

C) Azithromycin plus gentamicin

D) Ciprofloxacin

E) Spectinomycin

PREVIEW QUESTION

1.4

A 22-year-old woman presents complaining of a vaginal discharge.

Her examination is remarkable for a gray homogenous discharge. A vaginal swab is obtained which reveals a pH>6.0, motile trichomonads, and the presence of 3 Amsel's criteria.

PREVIEW QUESTION

1.5

Which of the following is the most appropriate antimicrobial regimen for her and her partner?

	Patient	Partner
A	Metronidazole 2g X1	None
B	Metronidazole 2g X1	Metronidazole 2g X1
C	Metronidazole 1 week	None
D	Metronidazole 1 week	Metronidazole 2g X1
E	Metronidazole 1 week	Metronidazole 1 week

PREVIEW QUESTION

1.6

A 36-year-old man is on a hiking trip in northern California and is bitten on his lower leg by a skunk.

Upon presentation, he is afebrile and has several puncture wounds on his right lower extremity.

You irrigate with wounds with soap and povidone iodine, and administer a tetanus booster.

He has never been vaccinated against rabies.

PREVIEW QUESTION

1.6

In addition to administration of rabies vaccine, what is the most appropriate management?

A) Rabies immune globulin at the bite sites

B) Rabies immune globulin in the deltoid muscle

C) Rabies immune globulin in the buttocks

D) Rabies immune globulin intraperitoneally

E) Nothing further is indicated

PREVIEW QUESTION

1.7

A 22-year-old woman with no significant past medical or psychiatric history develops headache and low-grade fever followed by confusion and hallucinations.

On presentation, she is afebrile and disoriented; she has evidence of abnormal movements of her mouth and face.

CSF analysis reveals a WBC count of 20/mm3, with normal glucose and protein.

Brain MRI is normal.

14 – Daily Question Review 2

John Bennett, MD (Moderator)

PREVIEW QUESTION

1.7

EEG reveals diffuse slowing

CSF Gram stain and cultures, and PCR for HSV are negative

A diagnosis of autoimmune encephalitis is considered and appropriate studies sent

CSF returns positive for antibodies to the NR1 subunit of the N-methyl-D-aspartate receptor

Corticosteroids and IV immune globulin are initiated

PREVIEW QUESTION

1.7

Which of the following studies should now be performed?

A) CT scan of the chest

B) CT scan of the abdomen

C) Carotid ultrasound

D) Renal ultrasound

E) Transvaginal ultrasound

PREVIEW QUESTION

1.8

A 22-year-old man with h/o egg allergy and no prior influenza vaccine presents for routine visit. He states he has had hives after eating eggs. No h/o anaphylaxis.

Which of the following is recommended?

A) Defer vaccination and refer to an allergist for testing

B) Vaccinate with any inactivated influenza vaccine without monitoring

C) Vaccinate and monitor for 30 minutes after receiving any inactivated influenza vaccine

D) Vaccinate with only live attenuated influenza vaccine

PREVIEW QUESTION

1.9

A 24-year-old healthy male presents for routine clinic visit. He is not on any medications. He smokes cigarettes. He is sexually active with both men and women and uses condoms consistently.

Which of the following is correct regarding HPV vaccine?

A) He should receive 2 doses of HPV-9 spaced 6 months apart

B) He should receive 3 doses of HPV-9 at 0, 1, and 6 months

C) He does not need HPV vaccine as he is already sexually active

D) HPV vaccination is only recommended in males through age 21

PREVIEW QUESTION

1.10

A 62-year-old woman with a self-reported history of shingles 10 years ago and type II diabetes presents to clinic. She received the live-attenuated zoster vaccine (ZVL) 2 years ago.

What do you recommend regarding the zoster vaccine?

A) Vaccine not indicated given her history of zoster

B) Vaccine not indicated as she has received ZVL

C) Check VZV titer to confirm history. If negative, proceed with vaccination

D) Recommend recombinant zoster vaccine

PREVIEW QUESTION

1.11

A 42-year-old female has malaise and RUQ pain; she just returned from 6 month stay at an IDP camp in north Uganda.

She endorses tick and other 'bug' bites and swam in the Nile. 1st HAV vaccine 2 days before departure. Prior HBV vaccine series.

Exam shows no fever, vitals are normal. RUQ tender. Mild icteric. ALT 1245 IU/ml; TB 3.2 mg/dl; WBC 3.2k nl differential.

14 – Daily Question Review 2

John Bennett, MD (Moderator)

INFECTIOUS DISEASE BOARD REVIEW 2020

PREVIEW QUESTION

1.11

Which test result is most likely positive?

A) Ebola PCR

B) IgM anti-HEV

C) IgM anti-HAV

D) Schistosomiasis "liver" antigen

E) 16S RNA for Rickettsial organism

INFECTIOUS DISEASE BOARD REVIEW 2020

PREVIEW QUESTION

1.12

24-year-old 33 wks gestation with nausea and vomiting and RUQ pain.

Taking acetaminophen 1gm q 4-6; has dog and bird; recent visit to mom in NC.

T 37.2; BP 158/110;2/6 SEM; RUQ tender; no rash. Plt 103K; Hct 26; WBC 6.6 10%L; PMN 82%; G 85; creat 0.6; ALT 225; AST 559; TB 1.4; CRP 15.8; PT WNL; fibrinogen NL.

INFECTIOUS DISEASE BOARD REVIEW 2020

PREVIEW QUESTION

1.12

What is the best diagnosis?

A) HELLP

B) Acute fatty liver of pregnancy

C) HAV infection

D) HSV infection

E) HEV

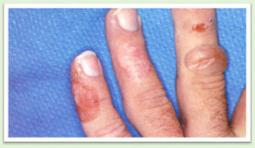
INFECTIOUS DISEASE BOARD REVIEW 2020

PREVIEW QUESTION

1.13

A 44-year-old, anti-HCV and HCV RNA positive man feels bad after a recent alcohol binge.

He has a chronic rash on arms that is worse and elevated ALT and AST.



INFECTIOUS DISEASE BOARD REVIEW 2020

PREVIEW QUESTION

1.13

The most likely dx is:

A) Cirrhosis due to HCV and alcohol

B) Vibrio vulnificus

C) Porphyria cutanea tarda

D) Essential mixed cryoglobulinemia

E) Yersinia infection

INFECTIOUS DISEASE BOARD REVIEW 2020

PREVIEW QUESTION

1.14

A 60-year-old man with chronic kidney disease immigrated from Brazil to the US and underwent a cadaveric renal transplant.

Prior to transplant, he had episodes of recurrent epigastric pain. At the time, his WBC was 6,500/mm3 with 15% eosinophils.

After transplant, he received immunosuppressive therapy

14 – Daily Question Review 2

John Bennett, MD (Moderator)

PREVIEW QUESTION

1.14

Presented 1 month later with headache, meningismus and altered mental status, and a temperature of T 39oC

Lumbar puncture had WBC 2500/mm3 (98% neutrophils), glucose 20 mg/dL, and protein 450 mg/dL

Placed on empiric antimicrobial therapy with vancomycin, ampicillin, and ceftriaxone
Cultures of blood and CSF grew Escherichia coli

PREVIEW QUESTION

1.15

Which of the following diagnostic tests would most likely establish the pathogenesis of E. coli meningitis in this patient?

A) MRI of the head and sinuses

B) Right upper quadrant ultrasound

C) Serial stool examinations

D) Cisternography

E) Colonoscopy

PREVIEW QUESTION

1.16

A 38-year-old woman presents with a 2-day history of fever, headache and stiff neck; similar episodes have occurred every 3-4 months over several years, with spontaneous abatement after 4-5 days

She is sexually active only with her husband of 8 years, and has 2 children at home (ages 2 and 5 years)

On exam, T 99.8oF and other vital signs are normal; she has evidence of meningismus, but is alert and oriented and with no focal findings

Laboratory studies are normal
CSF analysis reveals a WBC of 70/mm3 (100% lymphs), glucose of 60 mg/dL, and protein of 100 mg/dL; Gram stain negative

PREVIEW QUESTION

1.16

Which of the following is the most likely etiology of this patient's meningitis?

A) Coxsackie A virus

B) Coxsackie B virus

C) Human immunodeficiency virus

D) Herpes simplex virus type 2

E) Human herpesvirus 6

PREVIEW QUESTION

1.17

A 24-year-old female who presented with pain and swelling on the right side of her jaw that had been progressing over the last several weeks.

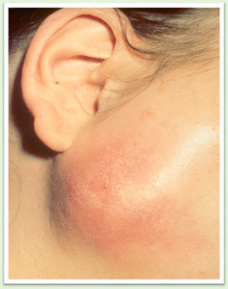
She was unable to open her mouth. She denied fever or headache, and had no past hospitalizations or illnesses.
The patient had not been to the dentist within 10 years.

T 99.8oF, P 88, RR 14, BP 110/80

Exam revealed swelling and erythema along her right mandible

PREVIEW QUESTION

1.17

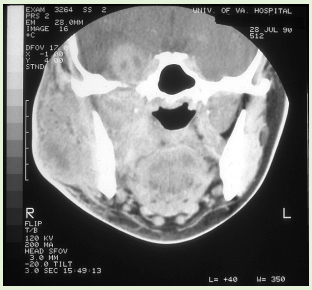


14 – Daily Question Review 2

John Bennett, MD (Moderator)

INFECTIOUS DISEASE BOARD REVIEW 2020 — PREVIEW QUESTION

1.17



INFECTIOUS DISEASE BOARD REVIEW 2020 — PREVIEW QUESTION

1.17

Which of the following empiric antimicrobial regimens should be initiated?

A) Ceftriaxone + metronidazole

B) Vancomycin + cefepime

C) Trimethoprim-sulfamethoxazole

D) Voriconazole

E) Liposomal amphotericin B

INFECTIOUS DISEASE BOARD REVIEW 2020 — PREVIEW QUESTION

1.18

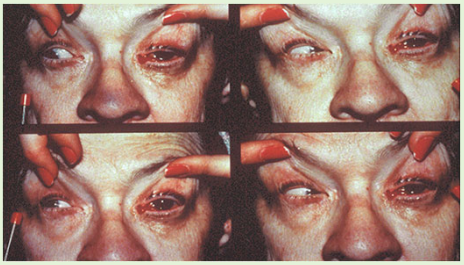
A 79-year-old female is transferred from a nursing home for failure to thrive as a result of decreased oral intake. A nasogastric tube is placed via the left nares for enteral hyperalimentation

One week into her hospital course, the patient develops fever to 101.5o F, and left periorbital edema and chemosis

CT scan of the head without contrast reveals opacification of the sphenoid sinus

INFECTIOUS DISEASE BOARD REVIEW 2020 — PREVIEW QUESTION

1.18



INFECTIOUS DISEASE BOARD REVIEW 2020 — PREVIEW QUESTION

1.18

Which of the following studies should be performed to establish the diagnosis?

A) CT scan of the head and sinuses with contrast

B) MR imaging with MR venography

C) Cerebral angiography

D) Positron emission tomography of the head

E) Lumbar puncture

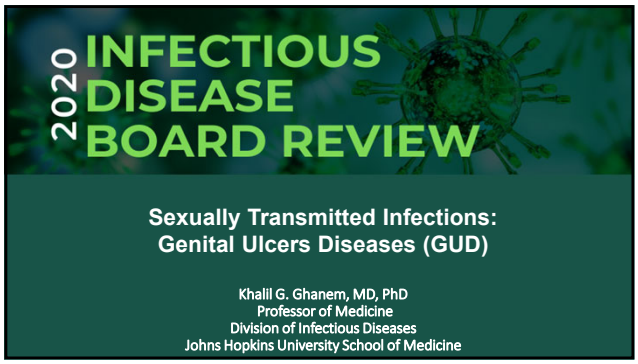
15

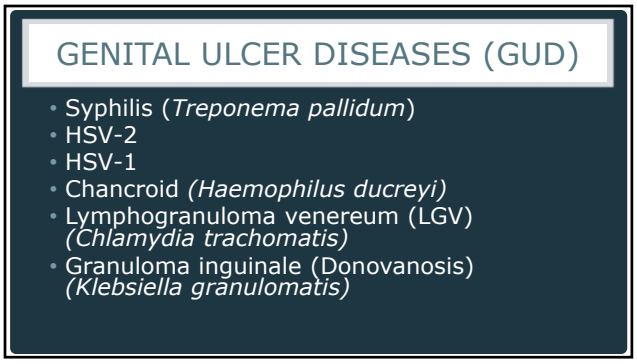
Sexually Transmitted Infections: Genital Ulcers Diseases (GUD)

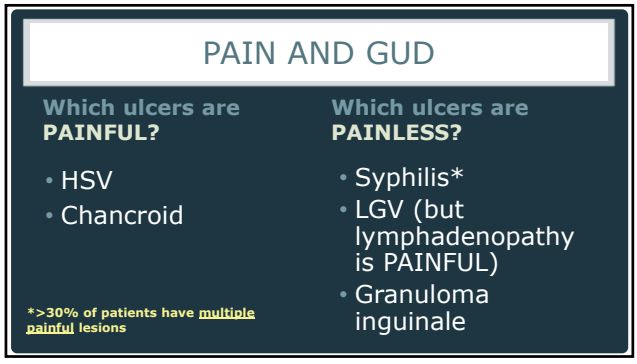
Dr. Khalil G. Ghanem

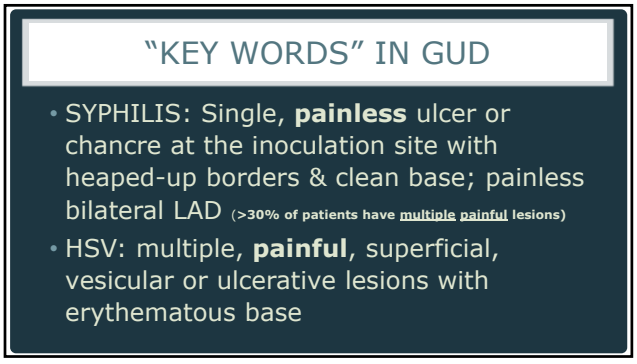
15 – Sexually Transmitted Infections: Genital Ulcers Diseases (GUD)

Speaker: Khalil Ghanem, MD









"KEY WORDS" IN GUD CONTINUED

- CHANCROID: painful, indurated, 'ragged' genital ulcers & tender **suppurative inguinal adenopathy** (50%); **kissing lesions** on thigh
- GI: **Painless**, progressive (destructive), **"serpiginous"** ulcerative lesions, without regional lymphadenopathy; beefy red with white border & highly vascular
- LGV: short-lived **painless** genital ulcer accompanied by **painful suppurative inguinal lymphadenopathy; "groove sign"**

GUD: CONCEPTS TO KNOW

- Organisms that cause disease
- Geographic distribution for less common agents
- Diagnostic approach(es)
- Therapeutic approach(es)

QUESTION #1

A 35-year-old woman presents with a painless ulcer on her vulva and one on her soft palate following unprotected vaginal and receptive oral sex 3 weeks earlier. She has no other symptoms.

Examination reveals the two ulcers with heaped-up borders and a clean base.

QUESTION #1

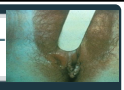
Which of the following diagnostic tests is **inappropriate** to obtain?

A. Serum RPR
B. Serum VDRL
C. Serum treponemal EIA
D. Darkfield microscopy on a specimen obtained from the oral ulcer
E. Darkfield microscopy on a specimen obtained from the vulvar ulcer

SYPHILIS: TAKE-HOME POINTS

- Neurological and ocular manifestations may occur during any stage of syphilis
- Both treponemal and non-treponemal tests may be nonreactive in primary syphilis but they are almost ALWAYS reactive in secondary and early latent syphilis (remember prozone reaction for non-treponemal test in secondary syphilis)
- Treponemal tests are almost always reactive in late syphilis (once positive always positive) irrespective

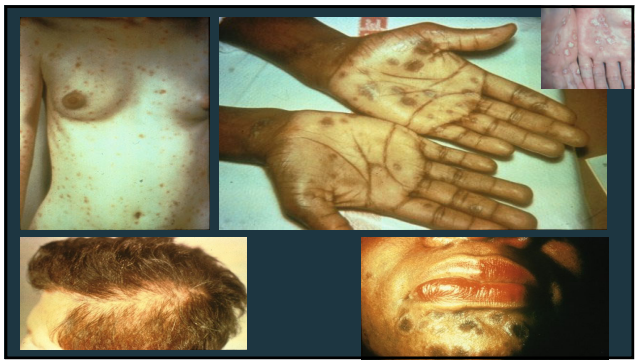
EARLY SYPHILIS: CLINICAL MANIFESTATIONS



- Incubation ~3 weeks
- Primary: chancre; LAD; resolves 3-6 wks
- Secondary: **Systemic symptoms**: low-grade fever, malaise, sore throat, adenopathy
  - RASH: evanescent, copper-colored, macular (dry) rash; followed by a red papular eruption (involving palms and soles); mucosal lesions (gray plaques or ulcers) ; condyloma lata- wart-like lesions that develop in moist areas
  - Other manifestations: uveitis, patchy alopecia, hepatitis (mild elevation of aminotransferases with disproportionately high alkaline phosphatase), gastritis, periostitis, glomerulonephritis

15 – Sexually Transmitted Infections: Genital Ulcers Diseases (GUD)

Speaker: Khalil Ghanem, MD



NEUROLOGICAL MANIFESTATIONS OF SYPHILIS

- **Can occur during any stage of infection**
- Can be either asymptomatic or symptomatic
- **Symptomatic Early Neurosyphilis**
  - Occurs within the **first year** after infection
  - **Mainly among HIV+ persons**
  - **Presents as meningitis** (headache; photophobia; cranial nerve abnormalities; ocular symptoms)
- Symptomatic Late Neurosyphilis (tertiary syphilis)
  - Usually occurs ~10 years AFTER primary infection
  - Divided into 2 categories:
    - Meningovascular
    - Parenchymatous

LATE NEUROSYPHILIS (TERTIARY)

Meningovascular

- Endarteritis of the small blood vessels of the meninges, brain, and spinal cord.
- Typical clinical manifestations include **strokes (middle cerebral artery distribution is classic)** and seizures

Parenchymatous

- Due to actual destruction of nerve cells
- **Tabes Dorsalis**: shooting pains, ataxia, cranial nerve abnormalities; optic atrophy
- **General Paresis**: dementia, psychosis, slurring speech; Argyll Robertson pupil

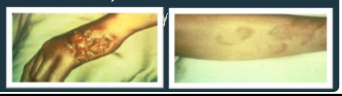
OTHER TERTIARY MANIFESTATIONS

Cardiovascular

- 15-30 years after latency
- Men 3X> women
- Aortic aneurysm; aortic insufficiency; coronary artery stenosis; myocarditis

Late benign syphilis

- 'Gummas'
- Granulomatous process involving skin, cartilage, bone (less commonly in viscera, mucosa, eyes, brain)



SYPHILIS: EYES AND EARS

Eyes

- Ocular manifestation may occur during any stage and may involve any portion of the eye
  - Uveitis & neuroretinitis: mainly secondary stage
  - Interstitial keratitis: occurs in both congenital (typically at age 5-20; 80% bilateral) and acquired (both early and late infections)
  - **CSF examination normal in ~30% of cases of ocular syphilis**

Ears

- Sensorineural hearing loss w/vestibular complaints (sudden or fluctuating hearing loss, ringing or vertigo)
  - Congenital (early and late)
  - Acquired (secondary and late stages)
  - **CSF examination is normal in >90% of cases of otic syphilis**

SYPHILIS SEROLOGICAL TESTING

Nontreponemal tests

- RPR (serum) or VDRL (serum or CSF)
- May be used as screening test (traditional algorithm)
- False+: endemic treponematoses, old age, pregnancy, autoimmune disease (APS), viral infections
- Reactive result must be confirmed with treponemal test
- False negative: PROZONE effect
- Four-fold (i.e. 2-dilution) decline after treatment = CURE (irrespective of the end-titer)

Treponemal tests

- MHA-TP, TPPA, FTA-Abs, EIAs, CIA
- Detect IgG +/- IgM antibodies against treponemal antigens
- Usually used as confirmatory test if nontreponemal test reactive
- Once reactive, always reactive
- False + may occur with endemic treponemal infections (e.g. yaws, pinta, bejel)or with Lyme disease

SEROLOGICAL TESTING: DIFFERENT ALGORITHM

+EIA/ –RPR / –FTA Abs

- False positive EIA
  - See previous slide

+EIA/ –RPR / +FTA Abs

- The patient had syphilis in the past and was adequately treated
- The patient had syphilis in the past but was **not** adequately treated
- The patient has early syphilis and the EIA became positive before the RPR did (this is rare)
- Prozone reaction in secondary syphilis

SYPHILIS: DIAGNOSTICS

- Darkfield microscopy for **genital** ulcers of primary syphilis; **sensitivity of serology in primary syphilis only~70%**
- **Sensitivity of serology for secondary or early latent syphilis ~100%**
- Over time, non-treponemal serological titers decline and may become nonreactive even in the absence of therapy while treponemal titers remain reactive for life*

SYPHILIS: DIAGNOSTICS CONTINUED

- No single test can be used to diagnose neurosyphilis
  - 50% of neurosyphilis cases may have negative CSF VDRL; it is highly specific, but **insensitive**
  - CSF treponemal tests are very sensitive but NOT specific (i.e. high false+)
    - May be used to **rule out** neurosyphilis
  - ~30% of persons with LATE neurosyphilis may have nonreactive SERUM nontreponemal test

SYPHILIS THERAPY

- Early stages (primary, secondary, early latent)
  - 2.4 MU of long-acting benzathine penicillin or doxycycline 100mg PO BID X 14 days
- Late latent/unknown duration
  - 2.4 MU of long acting benzathine penicillin G IM X3 (over 2 weeks) [7.2 MU total] or doxycycline 100mg po BID X 4 weeks

SYPHILIS THERAPY CONTINUED

- Neurosyphilis/Ocular syphilis
  - Aqueous penicillin 18 to 24 MU IV X 10-14 days
  - Procaine penicillin 2.4 MU IM qd + probenecid 500 mg po QID X 10-14 days
  - Ceftriaxone 1-2g IV/IM X 10-14 days (2nd line regimen)
- Jarisch-Herxheimer: within 6 hours (up to 24 hours) after therapy of (usually) early syphilis; antipyretics only; **may induce early labor**

QUESTION #2

A pregnant HIV+ woman (CD4 260 cells/mm^3; HIV RNA <50 copies/ml) on ART presents with a diffuse rash.

On examination, she has a temperature of 38.3°C and a macular rash on her trunk and extremities including her palms.

Serum RPR is reactive at a titer of 1:2048 and FTA-ABS is reactive

She has a history of severe hives to penicillin but has tolerated cephalosporins.

15 – Sexually Transmitted Infections: Genital Ulcers Diseases (GUD)

Speaker: Khalil Ghanem, MD

QUESTION #2

Which of the following antibiotics is most appropriate?

A. Azithromycin
B. Benzathine penicillin G
C. Ceftriaxone
D. Doxycycline

SYPHILIS & HIV

- Clinical manifestations similar but timeline may be compressed
  - HIV+ patients more susceptible to early neurosyphilis
- Testing and therapy similar to HIV-uninfected
- Serological failure is more likely among HIV+
- Serological response may be slower among HIV+
- Follow-up is more frequent (every 3 months)

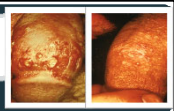
SYPHILIS & PREGNANCY

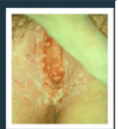
- Screen all women at 1st prenatal visit
- Screen all high risk women and those women living in high-prevalence areas twice in the 3rd trimester: at 28-32 weeks and again at the time of delivery
- Screen all women who deliver a stillborn infant after 20 weeks' gestation
- **Pregnant penicillin-allergic women with syphilis need to be desensitized to penicillin and treated with a penicillin-based regimen. There are NO OTHER OPTIONS (not even ceftriaxone)**

HSV TAKE-HOME MESSAGES

- Both HSV-1 (particularly among young women and MSM)and 2 cause genital infections
- Most people are unaware that they are infected
- Asymptomatic shedding is the most common reason for transmission
- Condoms and antiviral suppressive therapy decrease risk of male to female transmission by 30% and 55% over time, respectively (condoms less effective from female to male)
- Currently, no formal screening recommendations
- C-section ONLY in women who have active lesions at the time of delivery

HSV





- Both HSV-1 and HSV-2 cause genital disease
- HSV-1 is now becoming a more frequent cause of genital disease (especially in young women and MSM)
- In general, HSV-1 recurrences are less severe and less frequent and asymptomatic shedding is less frequent
- Prior infection with HSV-1 may attenuate severity of HSV-2 infection
- Classical presentation of multiple, painful, superficial, vesicular or ulcerative lesions with erythematous base may be absent

HSV: DIAGNOSTICS

Patient presents with genital ulcer

- Tzanck smear (40% sensitive)
- **Culture (sensitivity 30-80%)**
- Antigen detection (~70% sensitive)
- **PCR (FDA cleared, >90% sensitive)**

Asymptomatic Patient

- Use **Glycoprotein G-based type-specific assays** (gG1 & gG2)
- If gG2 is reactive, patient has genital herpes*
- If gG1 is reactive, patient either has oral herpes or genital herpes**
- **Positive predictive value is low in low prevalence settings**
- Serologic testing NOT routinely recommended for screening
- **Never** obtain IgM or try to interpret IgM results!

*** Assay has low specificity depending on cutoff**
**** Assay has low sensitivity**

HSV: PREGNANCY

- Risk of vertical transmission if mom acquires FIRST episode (i.e. primary infection) of herpes at time of delivery= up to 80%
- Risk of vertical transmission if mom has RECURRENT episode of herpes at time of delivery <1%
- C-sections are recommended ONLY IF ACTIVE LESIONS OR PRODROMAL SYMPTOMS (i.e. vulvar pain/burning) PRESENT AT DELIVERY
  - ACOG: "For women with a primary or nonprimary first-episode genital HSV infection during the 3rd trimester of pregnancy, cesarean delivery MAY BE OFFERED due to the possibility of prolonged shedding". ACOG Practice Bulletin #220, May 2020
- Efficacy data on routine acyclovir use during 3rd trimester of pregnancy to prevent HSV vertical transmission are lacking.
  - ACOG: Women with a clinical history of genital herpes should be offered suppressive viral therapy at or beyond 36 weeks of gestation ACOG Practice Bulletin #220, May 2020 & Cochrane Systematic Review 2008: https://doi.org/10.1002/14651858.CD004946.pub2

QUESTION #3

A 32 year-old man presents with a single, non-painful, clean-based penile ulcer that developed 3 days earlier

He was in India for 2 weeks 5 months ago

His physical examination is otherwise unremarkable

Serum RPR is negative

QUESTION #3

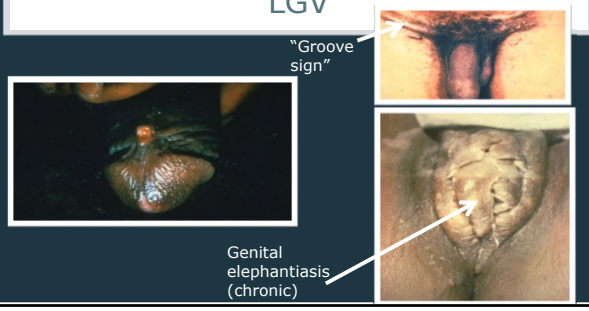
What is the <u>most appropriate</u> next step?

A. Obtain a tissue biopsy to evaluate for *Klebsiella granulomatis*
B. Obtain a serum FTA-Abs
C. Perform darkfield microscopy on a swab from the ulcer
D. No further testing; treat with doxycycline for two weeks
E. Serum glycoprotein G-based testing

CHLAMYDIA TRACHOMATIS L1-L3: LGV

- Classical manifestation is a short-lived **painless** genital ulcer accompanied by **painful** inguinal lymphadenopathy
- Outbreaks in US and Western Europe associated with **proctitis** particularly among MSM**********
  - Rectal pain, tenesmus, rectal bleeding/discharge
  - May be mistaken for inflammatory bowel disease histologically (early syphilitic proctitis may also be mistaken for IBD on histology)

LGV



LGV DIAGNOSIS & THERAPY

- **Routine NAATs** do not distinguish between serotypes D-K and L1-L3 (LGV). **Multiplex PCR** can be performed for specific serotypes. Serology may support the clinical diagnosis but is not a definitive diagnostic test; four-fold rise of IgM and IgG antibody is diagnostic of active infection. A single IgM antibody >1:64 or single IgG >1:256 are considered positive for invasive disease (standardized for genital infections).
- Therapy: **doxycycline 100mg PO BID X 3* weeks** or azithromycin 1g PO q week X 3 weeks

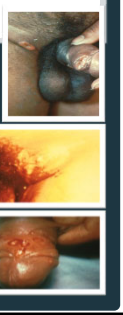
*Experts feel that in mild LGV proctitis, 1 week of doxycycline or 2g of azithromycin is sufficient

15 – Sexually Transmitted Infections: Genital Ulcers Diseases (GUD)

Speaker: Khalil Ghanem, MD

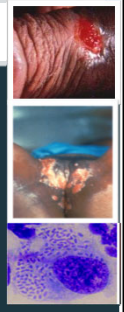
CHANCROID

- *Haemophilus ducreyi*
  - Endemic in parts of the southern US/ Rates have gone down
  - Increased risk with HIV infection and commercial sex work
- Symptoms: painful, indurated, 'ragged' genital ulcers & tender suppurative inguinal adenopathy (50%); kissing lesions on thigh; 10% of patients co-infected with syphilis or HSV; bacterial superinfection not uncommon
- Dx: culture (80% sensitive) [antigen detection and PCR not widely available]
- Rx: Azithromycin 1g PO X1 OR Ceftriaxone 250mg IM X1 (erythromycin and ciprofloxacin may also be used)
- Treat all partners in preceding 60 days



GRANULOMA INGUINALE OR DONOVANOSIS

- *Klebsiella granulomatis (Calymmatobacterium granulomatis)*
- Not endemic in US; common in SE Asia (India), & Southern Africa (recently eradicated in Australia)
- Painless, progressive (destructive), "serpiginous" ulcerative lesions, without regional LAD (pseudobuboes occasionally); beefy red with white border & highly vascular
- Dx: tissue biopsy (no culture test; PCR not FDA cleared); demonstrating the organisms in macrophages, called **Donovan bodies**, using **Wright-Giemsa** stain (NOT Gram's stain)
- Rx: Doxycycline 100mg PO BID X 3 weeks (or until resolution) OR azithromycin 1g PO q week X3 (can also use trimethoprim/sulfa, and ciprofloxacin) +/- aminoglycoside if slow to improve



GUD	Pain	Characteristics	Diagnosis	Treatment
HSV 1 & 2	Painful	Multiple, superficial, vesicular/ulcerative, erythematous base	-NAATs -Culture (sensitivity ~70%) -Serology	-Acyclovir etc. -Foscarnet -Cidofovir
Syphilis (T. pallidum)	Painless	Single, well circumscribed, heaped-up borders, clean base	- Serology - PCR	-Penicillin -Doxycycline
Chancroid (H. ducreyi)	Painful	Indurated, tender suppurative inguinal LAD (50%); kissing lesions on thigh	- Culture - PCR	-Azithromycin -Ceftriaxone -Erythromycin -Ciprofloxacin
LGV (C. trachomatis)	Painless	short-lived ulcer, painful suppurative LAD, "groove sign" PROCTITIS	- NAATs - Serology - Culture (rarely)	-Doxycycline -Azithromycin
Granuloma Inguinale (Klebsiella granulomatis)	Painless	Progressive "serpiginous" without LAD; beefy red with white border & highly vascular	- Biopsy	-Doxycycline -Azithromycin -Bactrim -Ciprofloxacin -Aminoglycosides

16

Herpes Viruses in Immunocompetent and Immunosuppressed Patients; CMV, EBV, HHV 6, HHV 8

John Gnann, MD

2020 INFECTIOUS DISEASE BOARD REVIEW

Herpesviruses in Immunocompetent and Immunosuppressed Patients: CMV, EBV, HHV-6, HHV-8

John W. Gnann Jr., MD
Medical University of South Carolina

Disclosures of Financial Relationships with Relevant Commercial Interests

Consultant – GlaxoSmithKline

DSMB Member – BioCryst

Human Herpesviruses

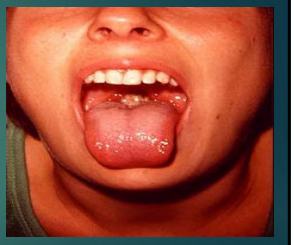
3

1. Herpes simplex virus type I (HSV-1)
2. Herpes simplex virus type 2 (HSV-2)
3. Varicella-zoster virus (VZV)
4. Epstein-Barr virus (EBV)
5. Cytomegalovirus (CMV)
6. Human herpesvirus type 6 (HHV-6)
7. Human herpesvirus type 7 (HHV-7)
8. Human herpesvirus type 8 (HHV-8)
   - Kaposi sarcoma-associated herpesvirus (KSHV)

"Mononucleosis Syndrome"

4

- Clinical Features:
  - Fever
  - Malaise
  - myalgias, arthralgias
  - Pharyngitis
  - Lymphadenopathy
  - Hepatomegaly / splenomegaly
- Laboratory Findings:
  - Lymphocytosis (>50%; >4500/mm^3)
  - Atypical lymphocytes (>10%)
  - Abnormal LFTs



Acute Mononucleosis Syndrome in Adults

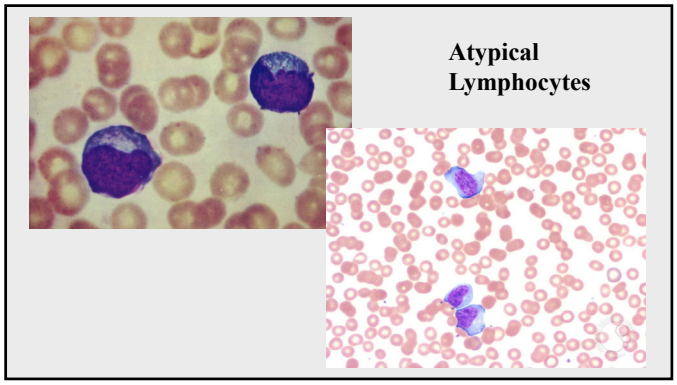
5

- Associated etiologic agents:
  - Epstein-Barr virus (~80% of cases)
  - Cytomegalovirus
  - Human immunodeficiency virus (acute HIV infection)
  - Toxoplasmosis
  - Uncommon - Rubella, HSV, HHV-6, HHV-7, Adenovirus, Mycoplasma, Mumps, others

Atypical Lymphocytes

6

- Large pleomorphic, non-malignant peripheral blood lymphocytes
- CD8+ cytotoxic T cells activated by exposure to viruses (e.g., CMV, EBV, HIV, etc.) or other antigens (e.g., toxo)
- Downey types 1-3
- General features:
  - Low nuclear / cytoplasmic ratio
  - Indented or lobulated nuclei with nucleoli
  - Cytoplasm often basophilic; can be "sky blue"
  - Cytoplasmic vacuoles and granules



Differential Features of Acute Mononucleosis Syndrome

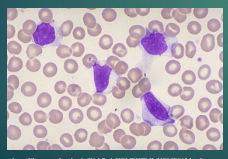
8

	EBV	CMV	Toxo	HIV
Fever	++++	++++	++	++++
Myalgias / Arthralgias	++	+++	+	+++
Lymphadenopathy	++++	+	++++	+++
Sore throat	++++	++	+	+++
Exudative pharyngitis	++++	+	0	0
Headache	+++	++	+	++
Rash	+	+	+	+++
Splenomegaly	+++	++	+	++
Hepatomegaly	+	++	+	0
Atypical lymphocytes	++++	+++	+	++
Elevated LFTs	++++	+++	0	+

Question #1

9

A previously healthy 24 year old man presents complaining of the acute onset of fever and myalgias. He is married and has an 18 month old child. On exam, he has no adenopathy, pharyngeal exudate or rash. His AST and ALT are 2.5X normal. Peripheral smear is below:



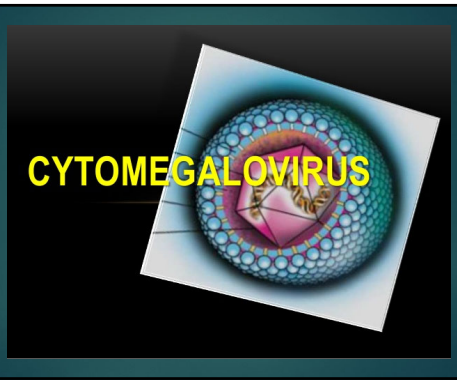
The likeliest pathogen is:

A. CMV
B. EBV
C. HIV
D. HHV-6
E. HHV-7

Question #1 - Answer

10

- The correct answer is A – CMV
- The image demonstrates atypical lymphocytes.
- All of these viruses can cause a mononucleosis-like syndrome. Compared with EBV, CMV tends to cause less pharyngitis and less lymphadenopathy. The presence of a young child in the household is a strong epidemiologic clue for CMV.



11

Pathogenesis of CMV Infection (1)

12

- Beta herpesvirus
- Infection transmitted via:
  - body fluids (urine, semen, cervical secretions, saliva, breast milk)
  - transplanted tissue (blood, organs)
- Primary infection is usually asymptomatic (<10% report symptoms)
- Viral replication in WBCs, epithelial cells (kidney, salivary glands, etc.)
- T cell immune responses control infection, but do not prevent establishment of latency

Pathogenesis of CMV Infection (2) — 13

- Following primary infection, prolonged viremia (weeks) and viruria (months) persist despite humoral and cellular immune responses. Important factor in transmission.
- Lifelong latent viral infection
  - Latency is primarily in mononuclear cells
  - Reactivation disease (symptomatic) is rare in immunocompetent host
  - CMV can reactivate with immunosuppression later in life, causing disease
- Re-infection with novel exogenous CMV strains has been documented; clinical significance uncertain.
- No vaccine available

Epidemiology of CMV Infection — 14

- Age-specific peaks in incidence:
  - Children:
    - 10-15% infected before age 5
    - 30-40% infected by age 12 years
  - Young adults at onset of sexual activity
- Seroprevalence of CMV correlates inversely with socioeconomic development. In the developing world, CMV seroprevalence approaches 100%.
- U.S. seroprevalence (age 6-49 years) varies with demographics:
  - Non-Hispanic whites – 40%
  - Non-Hispanic blacks – 71%
  - Latin-Americans – 77%

CMV Routes of Transmission — 15

- Children
  - Congenital - most common virus transmitted *in utero*
  - Perinatal - intra-partum or post-partum; breast feeding
  - Horizontal transmission - e.g., daycare (chronic asymptomatic viral shedding in urine; stable on fomites for 1-6 hours)
- Adults
  - Sexual - heterosexual, male homosexual
  - Horizontal - child-to-parent; child-to-daycare worker (low risk among health care providers)
- Nosocomial
  - Blood transfusion – reduced with serologic screening and routine use of WBC-depleted pRBCs
  - Banked breast milk
  - Organ transplantation

CMV: Three Main Clinical Syndromes — 16

1. Congenital infection
   - Primary maternal CMV infection - 30-40% risk
   - Reactivation maternal CMV infection - 0.9-1.5% risk
2. Mononucleosis syndrome
   - Primary CMV infection causing "heterophile-negative mononucleosis."
3. Invasive visceral organ disease
   - Usually in immunocompromised patients
     - CMV colitis has been described in otherwise immunocompetent adults receiving corticosteroid therapy
   - Primary infection or re-activation of latent CMV

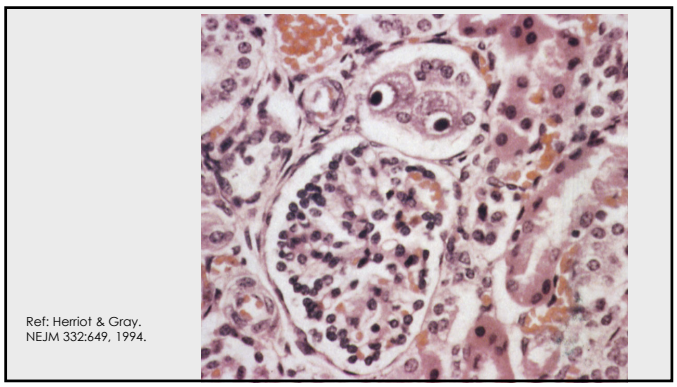
CMV Mononucleosis Syndrome — 17

- CMV causes ~20% of mono syndrome cases in adults
- Presentation: fever, myalgias, atypical lymphocytosis.
  - High fever ("typhoidal"). Pharyngitis and lymphadenopathy (13-17%) less common than with EBV IM (80%).
  - Rash in up to 30% (variety of appearances)
  - However, may be clinically indistinguishable from mono syndrome caused by other pathogens
  - Complications: colitis, hepatitis, encephalitis, GBS, anterior uveitis
- Symptoms may persist ≥ 8 weeks
- Diagnosis: IgG seroconversion or CMV blood PCR
- Antiviral therapy not indicated (except for severe complications)

Laboratory Diagnosis of CMV (1) – — 18

How to distinguish CMV infection (common) from CMV disease (uncommon)?

- Molecular diagnostics
  - Quantitative PCR - Detection of CMV DNA in blood, other fluids, tissues
    - Lower sensitivity of blood PCR for CMV pneumonitis, retinitis, or GI disease
  - Antigen detection in blood neutrophils (pp65 antigen)
    - Less sensitive than PCR; not useful in neutropenia
    - Largely replaced by PCR
- Histopathology of biopsied tissue
  - Presence of basophilic intranuclear inclusion bodies surrounded by a clear halo – "owl's eye" cells. Low sensitivity.
    - Cytology, e.g., BAL
  - CMV-specific immunohistochemical stains
  - In situ hybridization of tissue – research tool



Laboratory Diagnosis of CMV (2) –
How to distinguish CMV infection (common) from CMV disease (uncommon)?

20

- Serology
  - To diagnose acute infection, detect IgM or document IgG seroconversion
    - High rate of false-positives with CMV IgM
  - IgG very useful to establish D/R sero-status in transplantation
- Viral culture
  - Specimens: PBMCs, BAL, biopsy, etc.
  - Tissue culture: slow; cytopathic effect in 3-21 days (shell vial technique is faster); expensive; sensitivity is not optimal
  - Positive CMV culture (except for blood) is highly specific for *infection*, not for *disease*
    - Positive culture from a distant site is non-specific (e.g., recovering CMV from urine does not diagnose CMV pneumonia)
  - No longer routinely used

Human Herpesvirus Type 6

21

- Beta herpesvirus, discovered in 1986
- Two subgroups:
  - HHV-6A – uncommon pathogen
  - HHV-6B – very common pathogen, frequent infections in healthy children, etiology of roseola (exanthem subitem)
- Replicates and establishes latency in mononuclear cells, esp. activated T-lymphocytes
- Can integrate into human germline cells; chromosomally inherited
- Primary infection common in first year of life, >60% infected by 12 months. Seroprevalence >80% by age 5 yr.
  - Common cause of febrile illness 6-18 mo. infants
- Transmission by saliva; incubation period ~9 days (5-15 days)
- No vaccine available

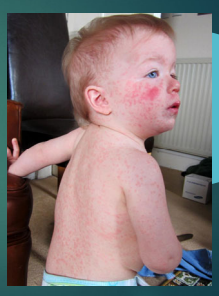
Human Herpesvirus Type 6

22

- Associated diseases:
  - Exanthem subitum (roseola infantum, sixth disease)
    - children <4 y.o.; usually benign disease
    - high fever for 5 days (febrile seizures), followed by a rash
  - Primary infection in adults (rare) - Mono syndrome
  - Reactivation disease in transplant patients, esp. encephalitis and pneumonitis. Syndromes not well defined
  - Mesial temporal lobe epilepsy
- Diagnosis
  - IgG seroconversion
  - PCR from target organ tissue or cell-free plasma. Problem of distinguishing latent infection (very common) from active disease.
- Therapy
  - Supportive care
  - Antivirals? Anecdotal reports of GCV benefit (esp. encephalitis in immunocompromised patients), but no controlled data. Efficacy unproven.

Exanthem subitum (roseola, sixth disease)

23

Epstein-Barr Virus

24

EBV Infection: Pathogenesis

25

- Gamma herpesvirus; HHV-4
- Infectious virus intermittently shed from oropharyngeal epithelial cells.
- Transmission by saliva ("kissing disease")
- Long incubation period – 4 to 8 weeks
- Usual site of latency is peripheral blood mononuclear cells, esp. B lymphocytes. EBV is capable of transforming B lymphocytes, resulting in malignancy.
- EBV reactivation not usually assoc. with symptomatic disease.

Epstein-Barr Virus: Epidemiology

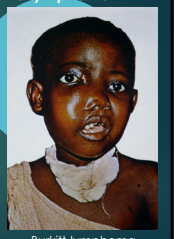
26

- Asymptomatic infection in early childhood
- Adolescent seroprevalence:
  - Developing countries >90%
  - Developed countries 40-50%
- Primary infection in adolescents or adults results in symptomatic dz (infectious mononucleosis) in 50% of cases
- IM in US - 45 cases/100,000 population/year
- Occasionally transmitted by transfusion or transplantation

Epstein-Barr Virus Diseases

27

- Infectious mononucleosis (IM)
  - Variants with severe, prolonged IM symptoms, progression to lymphoma
    - Chronic active EBV (rare, more common in Asia and SA)
    - X-linked lymphoproliferative disease; XMEN syndrome
- EBV-associated malignancies, including:
  - Burkitt lymphoma (Africa). Malaria as a co-factor.
  - Nasopharyngeal carcinoma (southern China).
  - Malignancies in HIV+ persons. NHL (usually B cell); leiomyosarcomas (children)
  - Post-transplant lymphoproliferative diseases (PTLD)
  - T cell lymphoma
  - Hodgkin lymphoma
- Oral hairy leukoplakia (in HIV)



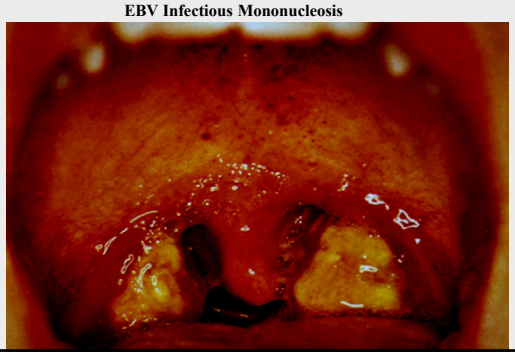
Burkitt lymphoma in an African child

Infectious Mononucleosis

28

- Etiology - 1° Epstein-Barr virus infection
- Transmission - saliva (EBV shed >6 mo. after IM)
- Clinical – prodrome of fever, malaise, HA.
  - Pharyngitis with tonsillar exudate
  - Symmetrical cervical adenopathy, posterior > anterior
  - Acute symptoms persist 1-2 weeks, fatigue can last for months
  - Rash with ampicillin
- Lab - lymphocytosis with atypical lymphocytes
- Diagnosis - serologic. Non-specific heterophile Ab ("monospot"); specific Ab (VCA, EBNA)
- Therapy - supportive, no antiviral therapy
- Prevention - no vaccine

Exudative Pharyngitis in a Patient with EBV Infectious Mononucleosis



Clinical Findings in EBV Infectious Mononucleosis

30

Symptoms	%	Signs	%
Sore throat	82%	Lymphadenopathy	100%
Malaise	57%	Fever	98%
Headache	51%	Pharyngitis	85%
Anorexia	21%	Splenomegaly	52%
Myalgias	20%	Hepatomegaly	12%
Chills	15%	Palatal petechiae	11%
Nausea	12%	Rash	10%
Abdominal pain	9%	Jaundice	9%

Complications of EBV Infectious Mononucleosis

31

- Splenic rupture. 1 to 2 events/1000 cases, male > female
- Airway obstruction 2° to massive adenopathy
- Hepatitis, including acute liver failure
- Neurologic syndromes: encephalitis, myelitis, G-B syndrome, CN palsies, optic neuritis, etc.
- Heme syndromes: cytopenias, TTP-HUS, DIC
- Hemophagocytic lymphohistiocytosis (HLH)
- Pneumonitis
- Prolonged fatigue/malaise (>6 mo. in 13%)

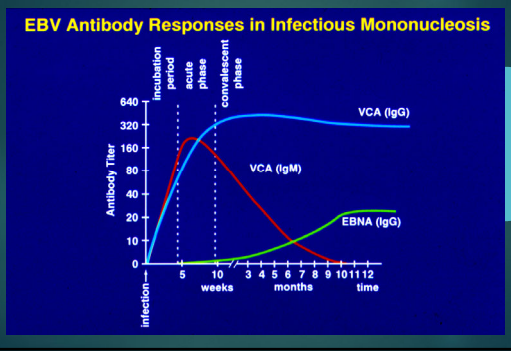
Laboratory Findings in EBV Infectious Mononucleosis

32

- CBC shows lymphocytosis
  - WBC = 12,000 - 18,000/mm^3, 60-70% mononuclear
  - Atypical lymphocytes = 30% (range 10-90%)
- Elevated liver function tests
  - AST, ALT (90%), alkaline phosphatase (60%), bilirubin (45%, but jaundice in <10%)
- Positive heterophile antibodies ("monospot")
  - Non-specific IgM against animal RBCs
  - Positive in 90% of cases, disappear within 1 year
- EBV-specific antibodies. Acute infection defined by:
  - Positive viral capsid antigen (VCA) IgG and IgM
  - Negative EBV nuclear antigen (EBNA) IgG
- PCR - not necessary for routine IM, may be useful in transplant patients

EBV Antibody Responses in Infectious Mononucleosis

33



Management of EBV Infectious Mononucleosis

34

- Supportive care
- Corticosteroids only for life-threatening manifestations (e.g., liver failure, hemolytic anemia, airway obstruction)
- Avoid contact sports for a minimum of 4 weeks
- Antiviral therapy: acyclovir, ganciclovir, valGCV?
  - *In vitro* activity demonstrated during lytic phase of EBV replication; no activity on latent phase of EBV
  - *Not* indicated for IM; no benefit in clinical trials
  - Anecdotal reports of benefit from ACV in EBV-induced HLH

Question #2

35

An 18-year-old woman presents to your office with signs and symptoms consistent with acute infectious mononucleosis. However, her heterophile antibody test (Monospot) is negative. In addition to other tests, you order EBV-specific serology.

Which EBV-specific antibody profile would confirm a diagnosis of acute infectious mononucleosis?

A. VCA IgM positive, VCA IgG positive, EBNA IgG positive
B. VCA IgM positive, VCA IgG positive, EBNA IgG negative
C. VCA IgM negative, VCA IgG positive, EBNA IgG positive
D. VCA IgM positive, VCA IgG negative, EBNA IgG positive
E. VCA IgM negative, VCA IgG negative, EBNA IgG negative

Question #2 - Answer

36

The correct answer is B - VCA IgM positive, VCA IgG positive, EBNA IgG negative.

Antibodies directed against the viral capsid antigen (VCA), both IgM and IgG, are usually detectable at the time of symptom onset. VCA IgG persists for life, while VCA IgM disappears after about a year. Epstein-Barr nuclear antigen (EBNA) IgG does not appear for several weeks after symptom onset and also persists for life.

Human Herpesvirus Type 8

37

- Kaposi sarcoma-associated herpesvirus (KSHV)
- Gamma herpesvirus, discovered 1995
- Partial sequence homology with EBV
- KS previously known to be endemic in Africa, Mediterranean regions
- HHV-8 seroprevalence in the US:
  - Blood donor populations: 1-5%
  - MSM: 8-25%
  - HIV-positive MSM: 30-77%
  - HIV-positive with KS: 90%
- Route of transmission unknown – Sexual, saliva? Transmission via SOT documented (rare).
- 1° infection usually asymptomatic. Febrile rash syndrome described.

HHV-8 Associated Diseases

38

- Kaposi sarcoma. 4 types:
  - Classic. Leg lesions in elderly men of Mediterranean or Ashkenazi Jewish origin
  - Endemic. Sub-Saharan Africa, not assoc. with immune deficiency
  - Transplant-associated. Usually (but not always) donor-derived
  - Epidemic (AIDS-related)
- Primary effusion lymphoma (body cavity-based lymphoma)
  - Non-Hodgkin B-cell lymphoma, usually in HIV+. Involves pleural, pericardial, or peritoneal spaces
- Castleman's disease. Seen in HIV positive and negative patients
  - Unicentric or Multicentric; hyaline vascular or plasma cell variants – all HHV-8 related. Fever, hepatomegaly, splenomegaly, massive lymphadenopathy
- KSHV Inflammatory Cytokine Syndrome (KICS) in HIV+.
  - Fever, elevated IL-6 & IL-10, high HHV-8 VL. High mortality rate.

39

Thank you for your attention!

JOHN GNANN, MD
GNANN@MUSC.EDU

CMV Reactivation in Critically Ill Patients

- Multiple studies have demonstrated CMV reactivation in 25-30% of immunocompetent patients requiring ICU care.
- Clinical significance uncertain
  - Some studies have shown positive association between CMV reactivation and duration of ICU stay, duration of ventilator support, and mortality. Association not supported by other studies.
  - One study of CMV antiviral prophylaxis in this setting failed to show benefit.

Chronic Active EBV Infection

- Persistent IM sx; rare; maybe more common in Asian and SA populations
- Diagnosis: Persistent IM sx (fever, lymphadenopathy, H-Smegaly) with EBV viremia, cytopenias, transaminitis, hypogammaglobulinemia, clonal proliferation of lymphocyte population (B, T, or NK)
- Therapy: Steroids, ganciclovir, proteasome inhibitors (e.g., bortezomib, ixazomib, etc.)
- Prognosis: Poor 2° to lymphocytic infiltration of tissues, HLH, liver failure, coronary artery aneurysms
- Note: Not to be confused with the unsubstantiated link between "chronic EBV" and myalgic encephalomyelitis/ CFS

EBV-Associated Lymphoproliferative Disorders

- X-linked lymphoproliferative disease
  - XMEN syndrome (with magnesium deficiency)
- Post-transplant lymphoproliferative disease (PTLD)
- Hemophagocytic lymphohistiocytosis (HLH)
- Lymphomatoid granulomatosis
- Miscellaneous: Oral hairy leukoplakia (usually in HIV+)

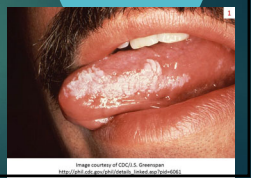


Image courtesy of CDC/J.S. Greenspan
http://phil.cdc.gov/phil/details_linked.asp?pid=6061

EBV-Associated Malignancies

- B cell NHL, esp. in HIV+
- Burkitt lymphoma. Most common childhood malignancy in Africa. Usually jaw. Malaria as a co-factor
- Nasopharyngeal carcinoma. Among most common cancers in southern China. Incidence 55 cases/100,000 population/yr.
- Nasal angiocentric lymphoma. Rare NK cell lymphoma. Described mostly in Asia, SA
- T cell lymphoma. May follow acute EBV infection
- Hodgkin Disease. Complex epidemiologic association, varying with geography and EBV sub-type
- Leiomyosarcoma, esp. in HIV+ children

Human Herpesvirus Type 7

45

- Beta herpesvirus, discovered in 1990, closely related to HHV-6
- Tropism for CD4+ T-lymphocytes
- High frequency of asymptomatic infection during childhood (50% by age 3). Over 95% of adults are seropositive. Route of transmission unclear.
- Infection diagnosed by seroconversion
- Disease associations are not well-defined:
  - Likely causes a pediatric febrile rash illness similar to roseola; febrile seizures?
  - other dermatologic dz (pityriasis rosea, lichen planus)?
  - possible pathogen in organ transplant patients

Management of HHV-8 Disease

Diagnosis

1. PCR (blood)
   - Limited for diagnosis of KS by frequent low copy number positivity due to latent virus in at-risk populations
   - Has diagnostic and prognostic value for HHV-8 associated lymphoproliferative diseases
2. Serology
   - Moderate sensitivity and specificity
   - Positive result indicates infection, not necessarily disease

Antiviral Therapy

- GCV, CDV, FOS, NFV have *in vitro* activity against HHV-8
- Therapy may reduce HHV-8 shedding in saliva, but no impact on blood VL.
- No evidence for clinical benefit after malignant transformation
- In HIV+, dramatic response of HHV-8 disease to effective ART

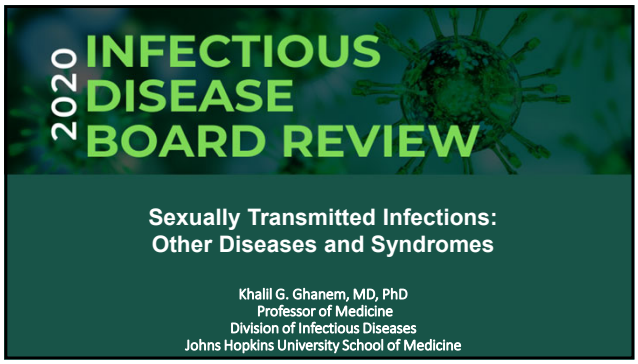
17

Sexually Transmitted Infections: Other Diseases and Syndromes

Dr. Khalil G. Ghanem

17 – Sexually Transmitted Infections: Other Diseases and Syndromes

Speaker: Khalil Ghanem, MD



Please note: all photos are freely available from the following website unless otherwise noted: http://www.cdc.gov/std/training/clinicalslides/slides-dl.htm

OTHER STI SYNDROMES

- Urethritis/Cervicitis/Vaginitis
- Proctitis
- PID
- Epididymitis
- HPV
- Ectoparasites

URETHRITIS/CERVICITIS/VAGINITIS

- *Neisseria gonorrhoeae*
- *Chlamydia trachomatis*
- *Mycoplasma genitalium*
- *Trichomonas vaginalis*
- Bacterial vaginosis

QUESTION#1

A 32 year old man presents complaining of a penile discharge. Gram's stain of the urethral discharge reveals intracellular Gram-negative diplococci. He reports an allergy to penicillins and cephalosporins. Which of the following regimens does the CDC recommend as the most appropriate therapy?

A. Azithromycin
B. Azithromycin plus ceftriaxone
C. Azithromycin plus gentamicin
D. Ciprofloxacin
E. Spectinomycin

QUESTION#2

Annual screening of which of the following STIs should be performed in HIV-infected but not in HIV-uninfected women?

A. Bacterial vaginosis
B. Chlamydia trachomatis
C. Neisseria gonorrhoeae
D. Herpes simplex virus
E. Trichomonas vaginalis

CHLAMYDIA TRACHOMATIS: TAKE-HOME POINTS

- Annual screening of all sexually active women aged ≤25 years is recommended for serotypes D-K, as is screening of older women with risk factors (e.g. new or multiple sex partners)
- High rate of reinfection for D-K
- Rectal LGV (L1-L3) has made a resurgence***
- Longer duration of therapy for L1-L3 serotypes **if symptomatic*****
- Association with reactive arthritis (Reiter's); prompt treatment reduces risk of reactive arthritis

CHLAMYDIA TRACHOMATIS

- Serological classification
  - A,B, Ba, C (Trachoma)
  - D-K (Genitourinary and ocular infections)
  - L1-L3 (Lymphogranuloma venereum)

CHLAMYDIA TRACHOMATIS D-K

MEN	WOMEN
• Asymptomatic	• Asymptomatic
• Urethritis	• Cervicitis
• Epididymitis (70% of cases in young men)	• Urethritis
• Proctitis	• **Pelvic inflammatory disease**
• Conjunctivitis	• Bartholinitis
• Pharyngitis (rare)	• Proctitis
• **Reactive arthritis (urethritis, conjunctivitis, arthritis, skin lesions)**	• Conjunctivitis
	• **Reactive arthritis**

CHLAMYDIA: DIAGNOSTICS

- Detection of WBCs on Gram's stain is not sensitive
- Cell culture (sensitivity 70%), direct immunofluorescence, non-amplified molecular tests (sensitivity ~85%), and NAATs (gold standard; sensitivity >95%; specificity >99%)
- FDA cleared for the detection of *C. trachomatis* on endocervical and urethral swab specimens, urine, vaginal swab specimens, throat and rectal swabs
- **Routine NAATs do NOT distinguish between D-K and L1-L3 serotypes. Multiplex tests do. The latter are not commercially available**

CHLAMYDIA TRACHOMATIS TREATMENT

- Duration of therapy depends on serotype:
  - D-K serotypes: Azithromycin 1g PO X1 OR **doxycycline 100mg PO BID X 7d**
  - L1-L3 serotypes (if symptomatic): **Doxycycline 100 mg PO BID X3 weeks** (preferred) OR Azithromycin 1g PO q week X 3 weeks
- Use of azithromycin is safe in pregnancy
- Test-of-cure (repeat testing 3–4 weeks after completing therapy) is **not** routinely recommended
- Screen all women treated for chlamydia infection 3 months later (REINFECTION rates are high)

AZITHROMYCIN VS. DOXYCYCLINE

- **Urogenital** *C. trachomatis*
  - A metaanalysis of 23 RCTs: pooled efficacy difference in favor of doxycycline of 1.5% to 2.6% CID 2014; 59(2):193-205
  - Recent RCT in correctional facility: azithromycin=97% vs. doxycycline=100% (noninferiority of azithromycin was **not** established) NEJM 2015; 373;26:2513-2521
- **Rectal** *C. trachomatis*
  - A metaanalysis of 8 observational trials: pooled efficacy difference in favor of doxycycline of 19.9%

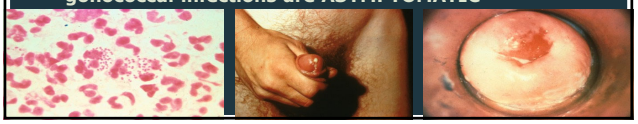
JAC 2015; doi:10.1093/jac/dku574

GONORRHEA: TAKE-HOME POINTS

- Drug resistance: dual therapy (ceftriaxone + azithromycin) is now the rule; NO FLUOROQUINOLONES
  - Macrolide resistance increasing!
- Pharyngeal gonorrhea: ceftriaxone and azithromycin have excellent efficacy; cefixime only 90% effective and spectinomycin only 70% effective
- Disseminated gonococcal infection: patients may NOT have symptoms of urethritis
- Gonococcal conjunctivitis: 1g of ceftriaxone (not 250mg) plus azithromycin

NEISSERIA GONORRHOEAE

- Clinical presentation similar to that seen with *C. trachomatis*.
  - no association with Reiter's
  - responsible for 30% of cases of epididymitis in young men
  - **MOST cases (>90%) of pharyngeal and rectal gonococcal infections are ASYMPTOMATIC**



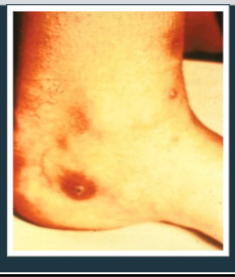
SCREENING FOR GONORRHEA

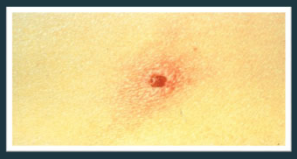
- HIV-infected men and women
- Sexually active MSM (**at all sites of exposure**)
- Individuals with new or multiple sexual partners
- Sexually active women <25
- Sexually active individuals living in areas of high *N. gonorrhoeae* prevalence
- Individuals with a history of other sexually transmitted infections
- Women ≤35 and men ≤30 in correctional facilities at intake

DISSEMINATED GONOCOCCAL INFECTION (DGI)

- DGI frequently results in petechial or pustular acral skin lesions (< 12 lesions), asymmetrical arthralgia, tenosynovitis, or (monoarticular) septic arthritis
- The infection is occasionally complicated by perihepatitis and rarely by endocarditis or meningitis.
- Strains of *N. gonorrhoeae* that cause DGI may cause minimal genital inflammation
- Risk factor for DGI: terminal complement deficiency (acquired form often seen in SLE)
- Differential diagnosis: meningococcemia, RMSF, dengue, staphylococcal endocarditis, Reiter's
- Treatment: Ceftriaxone IM/IV PLUS a single dose of azithromycin

DGI





GONORRHEA DIAGNOSTICS

- A negative Gram's stain should NOT be considered sufficient for ruling out infection in **asymptomatic** men. In addition, Gram's stain of endocervical specimens, pharyngeal, or rectal specimens are not sufficiently sensitive or specific to detect infection
- Sensitivity of culture ~80-90% from endocervical or urethral specimens in symptomatic persons; <50% from throat/rectum
- NAATs offer the widest range of testing specimen types because they are FDA-cleared for use with endocervical swabs, **vaginal swabs**, male urethral swabs, and female and **male urine**
- NAATs are now FDA-cleared for specimens obtained from the rectum and pharynx; they are the 'tests of choice' for these sites

GONORRHEA THERAPY

- **Fluoroquinolones not recommended for the treatment of gonorrhea in the U.S.**
- The only first-line option is **ceftriaxone** (250mg IM x1) PLUS 1g PO azithromycin X1* (even if Chlamydia ruled out).
- High-level resistance to azithromycin emerging in the US
  - 4.6% of isolates in the US in 2018 had elevated MICs to azithromycin

***The use of azithromycin is likely to be abandoned in the next year; the dose of ceftriaxone MAY increase to 500mg IM**

GONORRHEA THERAPY (CONT.)

- **Second-line agents:**
  - **Cefixime (400mg PO X1) PLUS azithromycin**
  - **Gentamicin IM+ 2g azithromycin OR Gemifloxacin+ 2g azithromycin in persons with a cephalosporin allergy**
  - Azithromycin 2g PO X1 is **no longer recommended**
  - Cefixime is only 90% effective at eradicating pharyngeal infection
  - Emerging resistance to cephalosporins (particularly oral)
  - Gentamicin may have lower efficacy for pharyngeal infections (~80%) Ross JDC, et al. *Lancet* 2019
  - If any second-line regimen is used to treat pharyngeal infection, must do a test of cure within 2 weeks
  - Spectinomycin: Previous second-line agent; no longer available in the US; ~70% effective for pharyngeal infections

GONORRHEA THERAPY CONTINUED

- **DGI**: Ceftriaxone 1g IM or IV PLUS one dose of azithromycin until clinically better (can also use cefotaxime and ceftizoxime); then, can complete 7 day course of therapy with a PO cephalosporin (following antibiotic susceptibility testing)
- **Gonococcal conjunctivitis**: Ceftriaxone 1g IM X1 + azithromycin

EXTRAGENITAL GONORRHEA AND CHLAMYDIA

- 90% are asymptomatic
- NAATs, now FDA cleared, are the preferred (and most sensitive)diagnostic modality
- CDC recommends screening for both GC and CT in the rectum but screening for only GC in the throat
- Sexually active MSM should be screened at all sites of exposure
  - The majority of GC cases in MSM would be missed if genital-only testing were performed
- No formal screening guidelines for women

NON-GONOCOCCAL URETHRITIS (NGU)

- Gram stain of urethral secretions demonstrating ≥2 WBC per oil immersion field or positive leukocyte esterase test on first-void urine or microscopic examination of sediment from a spun first-void urine demonstrating ≥10 WBC per high power field
- More common etiologies:
  - *Chlamydia trachomatis* (25% cases)
  - *Mycoplasma genitalium* (30% of cases)
  - *Trichomonas vaginalis* (10-25% of cases)
  - *Ureaplasma urealyticum* (controversial)
  - HSV
- Less common etiologies: anaeobes; enterobacteriaceae, Haemophilus, *Staphylococcus saprophyticus*, adenovirus
- NGU treatment: Azithromycin 1g PO x1 OR **doxycycline 100mg PO BID X 7d***

NON-GONOCOCCAL URETHRITIS (NGU) CONTINUED

- If a person with NGU fails to respond to therapy, think of 4 possibilities: (1) Reinfection (2) *M. genitalium* that did not respond to above therapy (see next slide) (3) *T. vaginalis*- rare in MSM (treat with metronidazole) or (4) HSV

MYCOPLASMA GENITALIUM

- Moderate to strong association with non-gonococcal urethritis (NGU) [up to 30% of cases] and up to 35% of cases of persistent urethritis
- Moderate association with cervicitis and PID; weaker association with infertility
- DRUG RESISTANCE
- FDA-cleared diagnostic test now available

M. GENITALIUM THERAPY

- Treatment with Azithromycin 1g PO X1 (success rate <50%) superior to doxycycline 100mg PO BID X 7days (success rate ~30%). Clin Infect Dis. 2015;61:1389–99
  - A longer course of azithromycin (an initial 500-mg dose followed by 250 mg daily for 4 days) ?better than single dose regimen
- **Moxifloxacin 400mg POX 7-14 days** if azithromycin fails PLoS One. 2008;3(11):e3618
  - Emerging resistance to fluoroquinolones (13.6% moxifloxacin resistance in a recent study) Emerg Infect Dis. 2017;23(5):809-812
- Pristinamycin was highly effective in treating macrolide- and quinolone-resistant strains Clin Infect Dis. 2015 ;60(8):1228-36

QUESTION #3

A 22 year old woman presents complaining of a vaginal discharge.

Her examination is remarkable for a gray homogenous discharge. A vaginal swab is obtained which reveals a pH>6.0, motile trichomonads, and the presence of 3 Amsel's criteria.

QUESTION #3

Which of the following is the most appropriate antimicrobial regimen for her and her partner?

	Patient	Partner
A	Metronidazole 2g X1	None
B	Metronidazole 2g X1	Metronidazole 2g X1
C	Metronidazole 1 week	None
D	Metronidazole 1 week	Metronidazole 2g X1
E	Metronidazole 1 week	Metronidazole 1 week

TRICHOMONAS VAGINALIS

- May be asymptomatic in both men and women; causes vaginitis and NGU
- Diagnosis: culture and PCR; wet mount is not sensitive
- Vaginal pH usually >4.0
- Therapy: metronidazole 2g PO X1 OR **tinidazole** 2g PO X1 OR metronidazole 500mg PO BID X 7 days [do NOT use topical gel formulations]
  - Recent clinical trial in HIV- women: 7 days of metronidazole superior to 2g single dose (but guidelines have not yet changed) Kissinger et al. Lancet Inf Dis 2019
- **Preferred Rx for HIV+ women: 7 days of metronidazole**
- Resistance: ~5% of strains have low-level resistance to metronidazole; <1% have high level resistance (see next slide)
- Partners in the preceding 60 days must be treated
- No need to screen asymptomatic pregnant women for trichomonas; **screen all HIV+ women annually**

TRICHOMONAS & NITROIMIDAZOLES

- **Tinidazole** has a longer serum half-life and achieves higher tissue concentrations than metronidazole; MICs to tinidazole lower than to metronidazole
- If patient fails Rx with metronidazole 2g PO X1 & reinfection is excluded:
  - Option 1: Tinidazole 2 g PO X1
  - Option 2: Metronidazole 500mg PO BID X 7d
- If patients fails either option 1 or 2 above:
  - Option 3: Metronidazole 2g PO QD X 5d
  - Option 4: Tinidazole 2g PO QD X 5d

BACTERIAL VAGINOSIS

- Complex polymicrobial infection; causes vaginitis (thin, white, discharge with 'fishy' odor) and cervicitis; may increase risk of PID
- May be sexually-associated but not a STD; partners do NOT need to be treated
- Dx: Nugent's score preferred in research settings; Amsel's clinical criteria performed in clinical settings:(1) discharge (2)pH>4.5 (3) clue cells (4) amine odor with KOH (whiff test)

BACTERIAL VAGINOSIS

- Rx: Metronidazole 500mg PO BID X 7days OR Clindamycin 300mg PO TID X 7 days OR topical metronidazole gel or clindamycin cream
  - *L crispatus* supplements after topical metronidazole resulted in a 34% reduction in recurrence at 3m Cohen NEJM 2020
- **Do NOT use metronidazole 2g PO X1**
- **BV during pregnancy:** associated with preterm labor, PROM, post-partum endometritis
- Treat all **symptomatic** cases of BV during pregnancy; **screen asymptomatic pregnant women for BV ONLY if high risk for pre-term delivery (e.g. history of premature delivery)**

PELVIC INFLAMMATORY DISEASE (PID)

- Diagnostic criteria- only ONE of the following:
  - Cervical motion tenderness
  - Uterine tenderness
  - Adnexal tenderness
- Hospitalize
  - Pregnant
  - Tubo-ovarian abscess
  - Appendicitis cannot be excluded
  - Did not respond to PO antibiotics
  - Patient has nausea and vomiting, or high fevers/severe illness
  - Unreliable follow-up if treated as outpatient
- MOST patients with PID can be treated as outpatients (including first-episode PID and HIV positive women who do not meet above criteria)

PELVIC INFLAMMATORY DISEASE (PID)

- **THERAPY**
  - **Ceftriaxone** 250 mg IM in a single dose **PLUS Doxycycline** 100 mg orally twice a day for 14 days **WITH OR WITHOUT Metronidazole** 500 mg orally twice a day for 14 days
  - **Cefotetan** 2 g IV every 12 hours **OR Cefoxitin** 2 g IV every 6 hours **PLUS Doxycycline** 100 mg orally or IV every 12 hours
- Additional recommended regimens can be found at:

  http://www.cdc.gov/std/tg2015/pid.htm
- All patients treated with PO regimens should improve within 3 days otherwise, admit for parenteral antibiotics
- Treat all sex partners in preceding 60 days

FITZHUGH-CURTIS SYNDROME

- Perihepatitis: RUQ pain or pleuritic pain; usually NO LFT abnormalities (or very mild)
- Complicates ~10% of PID cases
- Pathophysiology: ?Direct extension of pathogens vs. immunological mechanism
- Rx: NSAIDs (+ treat PID)

EPIDIDYMITIS

- In young men:
  - *C. trachomatis* (70%)
  - *N. gonorrhoeae* (30%)
- In older men: *E. coli* causes majority of cases
- Therapy:
  - **Ceftriaxone 250mg IM X1 + Doxycycline 100mg PO BID X 10 days**
  - For acute epididymitis most likely caused by sexually-transmitted chlamydia and gonorrhea and enteric organisms (men who practice insertive anal sex): Ceftriaxone IM X1 + levofloxacin X 10 days
  - For acute epididymitis most likely caused by enteric organisms: Levofloxacin 500mg PO X10 days

QUESTION #4

A 30 year old HIV+ man presents with severe pain on defecation and bloody anal discharge. He had unprotected anal sex one week ago. He experiences pain with DRE. There are no visible anal ulcers but a bloody mucoid anal discharge is noted. No diagnostic tests are available.

Which of the following empiric antibiotic regimens is most appropriate?

A. Ceftriaxone 250mg IM + Azithromycin 1g PO X1
B. Ceftriaxone 250mg IM + Doxycycline 100mg PO BID X 7d
C. Ceftriaxone 250mg IM + Azithromycin 1g PO weekly X 3wks
D. Ceftriaxone 250mg IM + Doxycycline 100mg PO BID X 21d
E. Ceftriaxone 250mg IM + Doxycycline 100mg PO BID X 7d + oral valacyclovir

PROCTITIS/ PROCTOCOLITIS

COMMON

- *Neisseria gonorrhoeae*
- *Chlamydia trachomatis* D-K
- *Chlamydia trachomatis* L1-L3 (LGV)
- *T. pallidum*
- HSV (severe especially among HIV+)

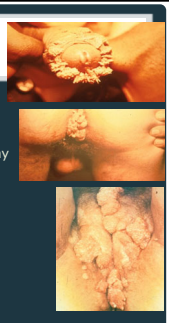
OTHER CAUSES

- Campylobacter
- Shigella
- Entamoeba
- CMV
- *Giardia lamblia** (mainly enteritis; especially among MSM)

PROCTITIS THERAPY

- **Ceftriaxone 250mg IM X1 + Doxycycline 100mg PO BID X 7 days**
- Treat for LGV: Bloody discharge, perianal ulcers, or mucosal ulcers among MSM with acute proctitis and either a positive rectal chlamydia NAAT or HIV infection
- Treat for HSV: Painful perianal ulcers or mucosal ulcers are detected on anoscopy
- Azithromycin may be less effective than doxycycline when treating proctitis due to *C. trachomatis*.

HPV



- >30 types cause genital infections
- High risk (e.g. 16, 18) and low-risk (e.g. 6 &11)
- 16 & 18 cause ~70% of cervical cancers in addition to significant proportion of vulvar, vaginal, anal, and upper airway cancers
- Low-risk types can cause genital warts and low-grade dysplasia (CIN I)
- Low-risk types cause recurrent respiratory papillomatosis
- Single biggest risk factor for dysplasia is PERSISTENCE of infection
- Risk factors for persistence: older age; immunosuppression; smoking; concurrent infection with multiple types

GENITAL WARTS

- 90% of warts caused by HPV 6 & 11; concomitant infection with types 16, 18, 31, 33, and 35 increases risk of HSIL
- Genital warts may develop months or years after infection
- Up to 60% of warts will recur within 3 months after therapy. Many will clear spontaneously after 12 months
- Available therapies do not completely eradicate infectivity
- Hypopigmentation or hyperpigmentation can occur with ablative modalities (cryotherapy and electrocautery) and with immune modulating therapies (imiquimod).
- No c-section in pregnant women with visible warts
  - C-section only if the warts are obstructing the birth canal or if vaginal delivery may lead to increased risk of bleeding

HPV VACCINES

- **Nonavalent (6, 11, 16, 18, 31, 33, 45, 52, 58)**; 2-3 doses given over 6-12 months (2 doses induce good immunity if age<=14 years)
- Consists of VIRUS-LIKE PARTICLES (**noninfectious**; NO DNA)
- Efficacy: >97% against CIN 2/3, vulvar, and vaginal lesions; >98% against genital warts*
- Recommended for routine use in 9 to 26 year old women (even those who have a history of abnormal Pap smears); routine use in boys ages 11-12 years, catch-up for males ages 13-21, and permissive use of the vaccine in men ages 22-26; vaccine FDA cleared for women up to age of 45 (but ACIP has not recommended it in women age>26)

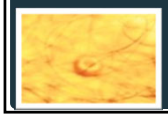
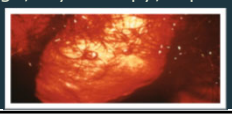
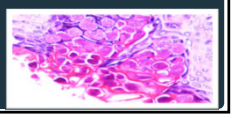
*FDA approved a supplemental biologics licensure application in 6/2020: prevention of oropharyngeal and other head and neck cancers caused by HPV types targeted by the vaccine

HPV VACCINES (CON'T.)

- Do not give during pregnancy; no need to restart schedule for patients who don't follow-up on time: JUST PICK UP WHERE YOU LEFT OFF
- Continue routine Pap smears on all women who get the vaccine
- Side effects: vasovagal response; local reactions
- Not a therapeutic vaccine

MOLLUSCUM CONTAGIOSUM

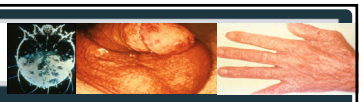
- Poxvirus
- 1 to 5mm lesions; painless papules; CENTRAL UMBILICATION
- Not necessarily sexually transmitted
- Molluscum bodies: intracytoplasmic inclusions
- Rx: curettage; cryotherapy; topical cidofovir

PEDICULOSIS PUBIS

- Pediculosis pubis= pubic lice= crabs (*Pthirus pubis*)
  - Nits confined to upper shaft=old infection (no need for retreatment)
  - Maculae ceruleae (blue gray macules)
  - Permethrin 1% cream OR Pyrethrins with piperonyl butoxide (topical)
  - Resistance increasing; consider malathion 0.5% lotion or Ivermectin in case of treatment failure
  - Do NOT use Lindane; toxicities include seizures and aplastic anemia
  - Treat sex partners within previous 30 days


SCABIES



- *Sarcoptes scabei*
- Severe pruritus; especially at night or after bathing; burrows; the diagnosis is usually a clinical one
  - Permethrin cream 5% (wash off after 8 hours) OR
  - Ivermectin 200 mcg/kg PO day 1 and 14
  - Only use Lindane as an alternative
- **Crusted scabies** or 'Norwegian scabies'
  - **Mainly occurs in immunodeficient patients (HIV)**
  - **May NOT cause pruritus or burrows**
  - Contagious and aggressive
  - **Ivermectin 250mcg/kg on days 1, 15, and 29**
- Rash and pruritus of scabies may persist for up to 2 weeks after successful therapy***

Arch Dermatol. 2007;143(5):626

THE END

18

Herpes Viruses: HSV and VZV in Immunocompetent and Immunosuppressed Patients

Dr. Richard Whitley

2020 INFECTIOUS DISEASE BOARD REVIEW

Herpes Viruses: HSV and VZV in Immunocompetent and Immunosuppressed Patients

Richard J. Whitley, MD
Co-Director, Pediatric Infectious Diseases
Children's Hospital of Alabama
Loeb Eminent Scholar Chair in Pediatrics
Distinguished Professor of Pediatrics
Professor of Microbiology, Medicine, and Neurosurgery
The University of Alabama at Birmingham

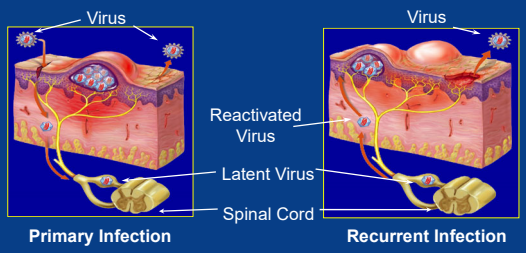
Disclosures of Financial Relationships with Relevant Commercial Interests

- Member of the Board of Directors and the Health Policy Advisory Board: Gilead
- Chairperson: NIAID HIV and COVID-19 Vaccine and 'Dried Blood Spot' DSMBs
- Chairperson: Merck Letermovir and DSMB

Herpes Viruses: The Family

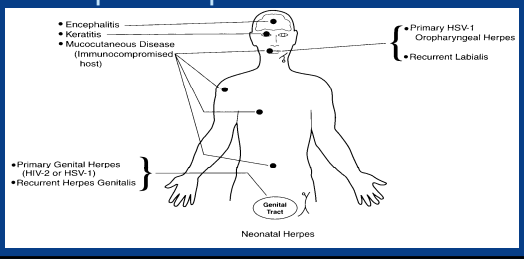
- Herpes simplex virus, type 1 (HSV-1)
- Herpes simplex virus, type 2 (HSV-2)
- Varicella zoster virus (VZV)
- Cytomegalovirus (CMV)
- Epstein Barr virus (EBV)
- Human herpesvirus 6 (HHV 6 A and B)
- Human herpesvirus 7 (HHV 7)
- Human herpesvirus 8 (HHV 8)

Viral Latency and Reactivation

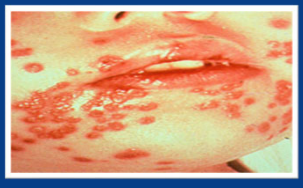


Netter FH. ©2001 by Icon Learning Systems.

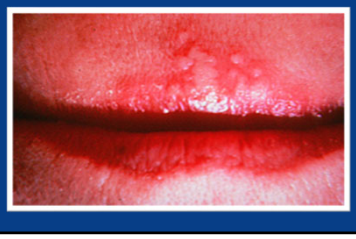
Clinical Manifestations of Herpes Simplex Virus Infections



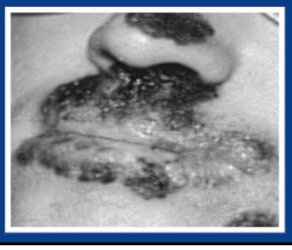
Primary Herpes Simplex Virus Infection: Cutaneous Lesions



Herpes Simplex Labialis

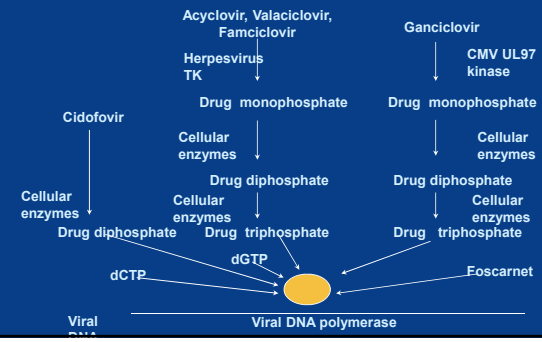


Immunocompromised Host



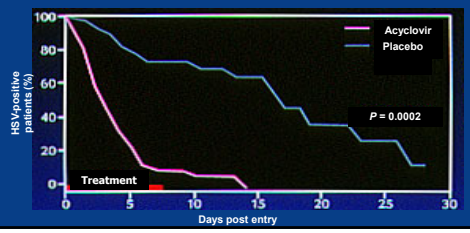
Most Widely Used Systemic Anti-HSV and VZV Drugs

- Acyclovir (ACV, Zovirax)
- Famciclovir (FCV, Famvir)
- Valacyclovir (VACV, Valtrex)
- Foscarnet (PFA, Foscavir)
- Ganciclovir (GCV, Cytovene)
- Val-Ganciclovir (Valcyte)
- Others:
  - Cidofovir



Intravenous Acyclovir for Herpes Simplex Virus Infections in Immunocompromised Hosts

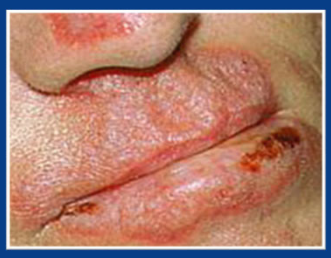
Time to cessation of viral shedding with acyclovir



Acyclovir Prophylaxis for HSV Infection in BMT Patients

Acyclovir (250 mg iv/m2 /tid) or placebo for 18 days beginning 3 days before transplant

Group	Number of Patients	Number of HSV Infections	P
Acyclovir	10	0	~0.003
Placebo	10	7	



Question #1

A 30 year old heart transplant has received acyclovir for the past 0 days with recurrent cutaneous HSV infection. The lesions are now progressive in spite of high-dose intravenous therapy. The most likely cause for disease progression is a deficiency or alteration of:

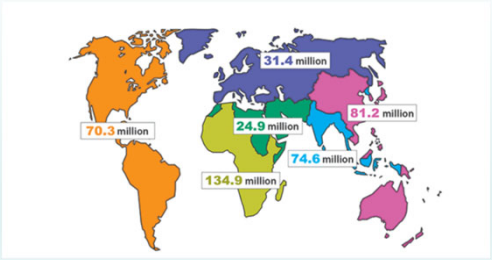
A. Ribonucleotide reductase
B. Reverse transcriptase
C. Protease
D. Thymidine kinase
E. DNA polymerase

Question #1b

Which is the best treatment choice for this patient?

A. Give high-dose of intravenous acyclovir
B. Give intravenous ganciclovir
C. Give oral famciclovir
D. Give oral ganciclovir
E. Give intravenous foscarnet

Global Prevalence of HSV-2 Infection



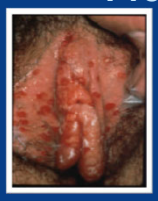
Total estimated number of people (in millions) infected with HSV-2 in 2012 by WHO region, gender and age range.
Source: WHO, as published in PLOS ONE (21 Jan 2015)

Acyclovir Therapy of Genital Herpes

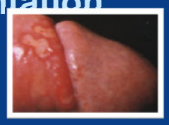
Summary of clinical benefit for treatment of:

- Primary
- Recurrent
- Suppressive

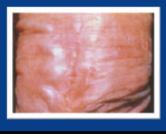
Spectrum of HSV Clinical Presentation



First infection

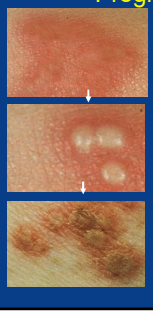


Classical recurrence



Atypical recurrence

Progression of Lesions



Early Redness/Swelling

Thin-Walled Fluid-Filled Vesicles and Pustules

Early Healing of Vesicles, Erosions, or Ulcers

Clinical Spectrum of HSV-2

HSV-2 Seroprevalence

Mertz GJ. *Infect Dis Clin North Am.* 1993;7:825-839.

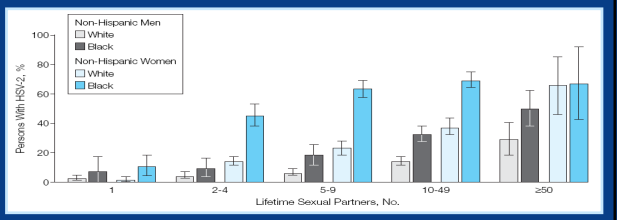
Changes in Weighted Herpes Simplex Virus 2 Seroprevalance Age 14 to 49 years

NHANES

	1988-1994		1999-2004		
	Sample Size	HSV-2 Seroprevalence (95% CI)	Sample Size	HSV-2 Seroprevalence (95% CI)	Change (95% CI)
Overall	9165	21.0	11,508	17.0	-19.0
Age Group					
14-19	1787	5.8	4650	1.6	-72.4
20-29	2750	17.2	2412	10.6	-38.4
30-39	2557	27.8	2251	22.1	-20.5
40-49	2061	26.3	2195	26.4	0

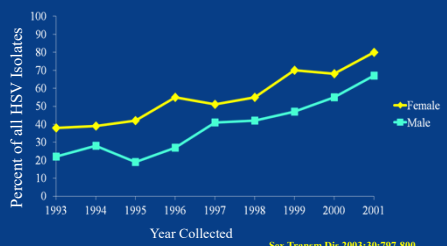
JAMA, August 23/30, 2006 Vol 296 No 8 pg 968

Age-Adjusted Herpes Simplex Virus Type 2 Seroprevalence According to the Lifetime Number of Sex Partners by Race/Ethnicity and Sex on NHANES in 1999-2004



JAMA, August 23/30, 2006 Vol 296 No 8 pg 967

HSV-1 Genital Isolates Among U.S. College Students



Sex Transm Dis 2003;30:797-800

Genital Herpes: Transmission

Men — Asymptomatic Recurrence ⇄ Women

Transmission — Symptomatic Recurrence → 30%

70%

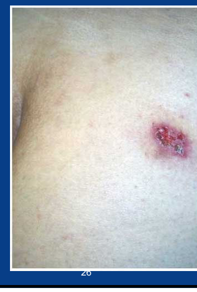
Corey L. *Sex Transm Dis.* 1994;21(S38-S44.
Mertz GJ, et al. *Ann Intern Med.* 1992;116:197-202.

Genital Herpes: Viral Shedding

- Duration is longer in primary than in recurrent episodes
- Higher rates in
  - People with frequent outbreaks
  - First year after acquisition
  - Primary: 12 days
  - Recurrent: 2-3 days
- Oral antiviral suppressive therapy shortens the duration of, but does not eliminate, viral shedding

Genital Herpes – A Clinician's Guide to Diagnosis and Treatment. American Medical Association. 2001:1-20.
Whitley RJ, et al. *Clin Infect Dis.* 1998;26:541-555.

Herpes Presenting as Ulceration



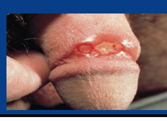
- The patient had been to her doctor 3 times over the past 8 months with this pruritic and mildly painful rash on her right buttock. She had been told that it was an irritation from riding a bicycle.
- What is the key to the diagnosis?
  - A. the fact that lesions recurred
  - B. site of involvement is not unusual
  - C. trauma can induce reactivation

26

Photo courtesy of Jeffrey Gilbert, MD.

Question #2

An 18 year old man presents with a history of malaise, low-grade fevers, and new-onset painful genital lesions seen in the picture below. He had unprotected sexual intercourse with a female partner 2 weeks earlier. Neither he nor his partner has traveled outside the United States.



Which of the following diagnostic tests is most likely to yield the specific diagnosis?

A. Serum RPR
B. Serum FTA-Abs
C. Darkfield microscopy
D. Glycoprotein-G 1 serum antibodies
E. PCR on lesion swab

Oral Antiviral Therapies

- Famciclovir [Famvir®]

500 mg 250 mg 125 mg

- Valaciclovir [Valtrex®]

1 g 500 mg

800 mg 600 mg 200 mg

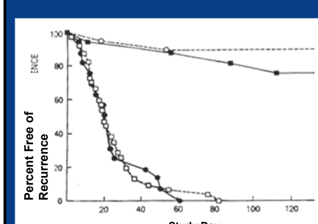
- Acyclovir [Zovirax®]

Valtrex® and Zovirax® are registered trademarks of GlaxoSmithKline

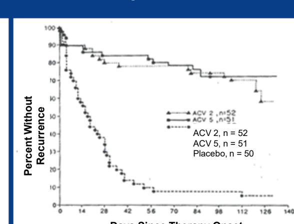
Impact of Acyclovir Therapy on Primary Genital HSV Infection

	Treatment Group (Days)			
	Acyclovir	Placebo	RR	P
Virus Shedding	2.8	16.8	6.82	0.0002
Pain	8.9	13.1	2.00	0.01
Scabbing	9.3	13.5	2.21	0.004
Healing	13.7	20.1	1.83	0.04

Effect of Acyclovir Prophylaxis on Recurrent Genital Herpes



Straus, et al. *NEJM*, 1984



Douglas, et al, *NEJM*, 1984

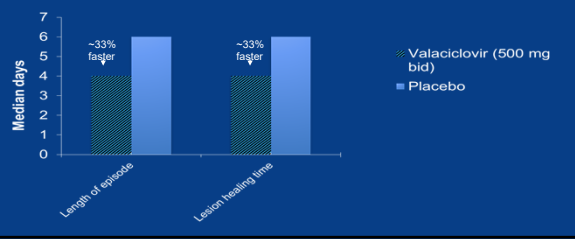
Second Generation Anti-Herpetic Medications

- Valacyclovir (prodrug of acyclovir)
- Famciclovir (prodrug of penciclovir)

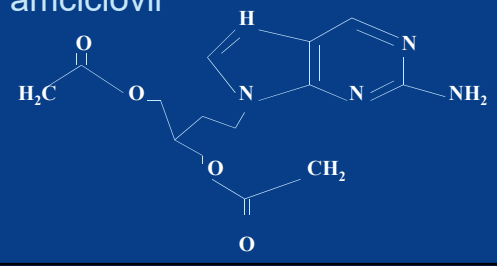
Acyclovir/Valacyclovir Kinetics

DRUG	DOSE	PHARMACOKINETICS	
		C_{max} (μg/mL)	Daily AUC (μg/mL•h)
VALTREX	1 g 3x/d	5.0	47
Oral ZOVIRAX	800 mg 5x/d	1.6	24
IV ZOVIRAX	5 mg/kg 3x/d	9.8	54
	10 mg/kg 3x/d	20.7	107

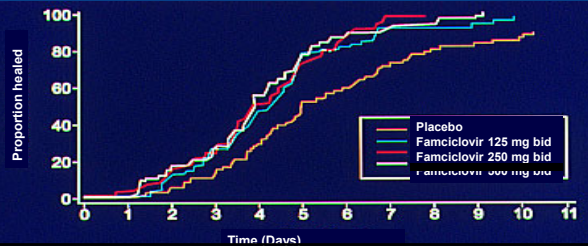
Therapy of Recurrent Genital Herpes: Duration of Disease



Famciclovir



Famciclovir Therapy of Recurrent Genital Herpes



Shorter and Shorter Therapy

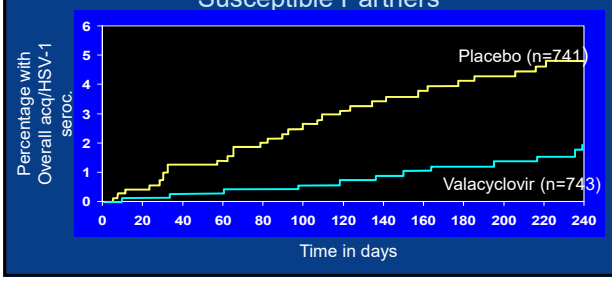
- Genital Herpes
  - Valacyclovir: three days
  - Famciclovir: one day
- Labial Herpes
  - Valacyclovir: two days
  - Famciclovir: one day

Prevention of Person to Person Transmission

Valacyclovir Prevention of HSV Transmission to Susceptible Partners

Susceptible Partner	Val-ACV N = 743	Placebo N = 741	Total
No. acquired HSV-2	14	28	42
No. acquired HSV-1	0	4	4
No. developed clinical HSV-2	4	17	21

Time to Acquisition of HSV-1 or HSV-2 in Susceptible Partners



Genital Herpes: CDC STD Guidelines

Recommended Treatment For Initial Episode

Acyclovir	400 mg orally three times a day for 7–10 days
ORAcyclovir	200 mg orally five times a day for 7–10 days
ORValacyclovir	1 g orally twice a day for 7–10 days
ORFamciclovir	250 mg orally three times a day for 7–10 days

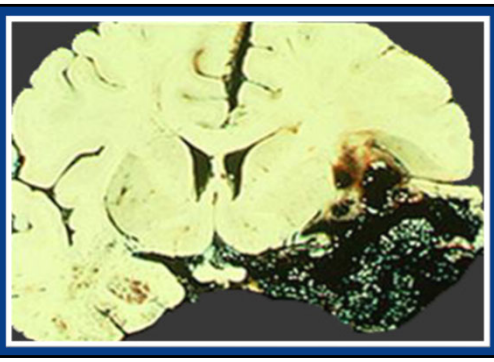
*Treatment can be extended if healing is incomplete after 10 days of therapy.

Recommended Treatment for Recurrent Episodes

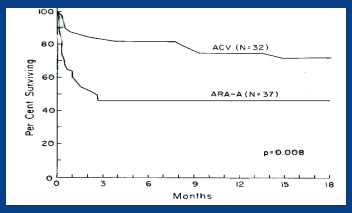
Acyclovir	400 mg orally three times a day for 5 days
OR Acyclovir	800 mg orally twice a day for 5 days
OR Acyclovir	800 mg orally three times a day for 2 days
OR Valacyclovir	500 mg orally twice a day for 3 days
OR Valacyclovir	1 g orally once a day for 5 days
OR Famciclovir	125 mg orally twice daily for 5 days
OR Famciclovir	1 gram orally twice daily for 1 day
ORFamciclovir	500 mg once, followed by 250 mg twice daily for 2 days

Suppressive Therapy for Recurrent Genital HSV: CDC Guidelines

Acyclovir	400 mg orally twice a day
OR Valacyclovir	500 mg orally once a day
OR Valacyclovir	1 g orally once a day
OR Famiciclovir	250 mg orally twice a day



Herpes Simplex Encephalitis Survival



Vidarabine (ARA-A) vs Acyclovir (ACV); P=0.008

HSE Morbidity

Percent Patients
Patient Normal / Mild Impairment

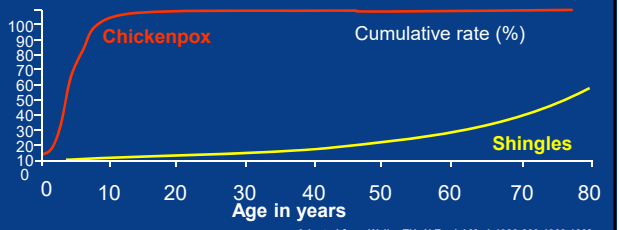
Age	Glasgow Coma Scale	
	≤6	>6
<30	0	60
>30	0	36

Sensitivity and Specificity of PCR

	Biopsy Positive	Biopsy Negative
PCR Positive	53	3
PCR Negative	1	44

Sensitivity 98%
Specificity 94%
Positive Predictive Value 95%
Negative Predictive Value 98%

Varicella Zoster Virus Infection



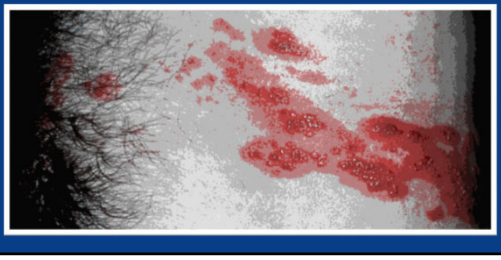
Adapted from Weller TH. *N Engl J Med.* 1983;309:1362-1368

CHICKEN POX: Is Therapy of Value

Treatment of Chicken Pox: Adults (>18 Years) < 24 Hour Duration

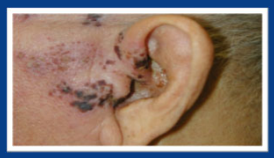
	Acyclovir (n=38)	Placebo (n= 38)	*P*
Time to maximum number of skin lesions (days)	1.5	2.1	0.002
Days of new lesion information	2.7	3.3	0.03
Time to onset of cutaneous healing (days)	2.6	3.3	<0.001
Time to 100% crusting (days)	5.6	7.4	0.001
Maximum number of lesions	268	500	0.04

Thoracic Herpes Zoster



Questions

1. What is the most likely diagnosis?
2. How would you prove the etiology?



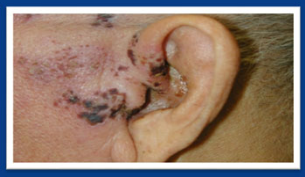
Answer

- Clinically this is herpes zoster
- The lesion shown is Tzank prep positive on skin scraping. The sensitivity of this test is only ~60% and, therefore, is not recommended
- Immunofluorescence is positive for VZV, having a sensitivity of ~80%.
- Preferably, PCR can be performed even when lesions are scabbed and has the highest sensitivity.

Question #3

What complication would you be most concerned about?

A. Facial paralysis
B. Keratitis
C. Encephalitis
D. Optic neuritis
E. Oculomotor palsies



http://www.itfnoroloji.org/kranyalnoropatiler/Kranyalnoropatiler.html

Question #4 Stem

The patient has only the observed finding in the picture.

- **What is your most likely diagnosis?**
- **What is the name of this sign?**

www.medscape.com

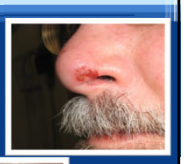
Question #4

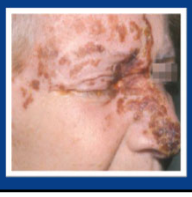
What complication is it most likely to be associated with this illness?

A. Deafness
B. Vertigo
C. Optic neuritis
D. Keratitis
E. Stroke

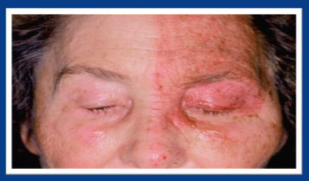
Hutchison's Sign

Zoster Involving nasociliary branch, Cranial Nerve VII which inervates the tip of the nose and the cornea





Zoster Ophthalmicus



NATURAL HISTORY OF ZOSTER IN THE NORMAL HOST

- **Acute neuritis may precede rash by 48 - 72 hours**
- **Maculopapular eruption, followed by clusters of vesicles**
- **Unilateral dermatomal distribution**

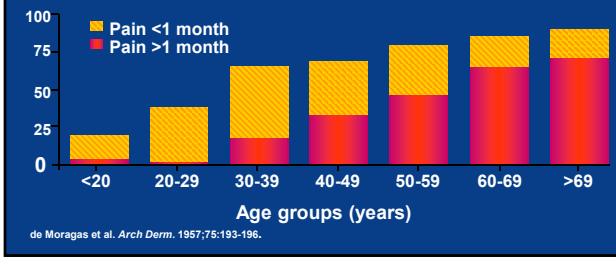
NATURAL HISTORY OF ZOSTER IN THE NORMAL HOST

- **Events of healing:**
  - **Cessation of new vesicle formation: 3 - 5 days**
  - **Total pustulation: 4 - 6 days**
  - **Total scabbing: 7 - 10 days**
  - **Complete healing 2 - 4 weeks**
- **Cutaneous dissemination can occur dissemination is extremely rare**
- **Postherpetic neuralgia in 10% - 40% of cases**

Complications of Zoster

Common	Uncommon
• Postherpetic neuralgia • Ocular complications • Ophthalmic zoster • (uveitis, keratitis, scleritis, optic neuritis) • Pneumonitis • Scarring • Bacterial superinfection	• Cutaneous dissemination • Herpes gangrenosum • Hepatitis • Encephalitis • Motor neuropathies • Myelitis • Hemiparesis (granulomatous CNS vasculitis)

Prevalence and Duration of Pain

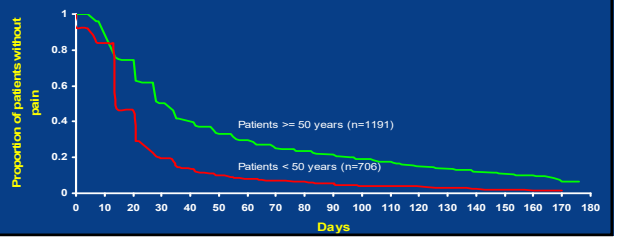


de Moragas et al. *Arch Derm.* 1957;75:193-196.

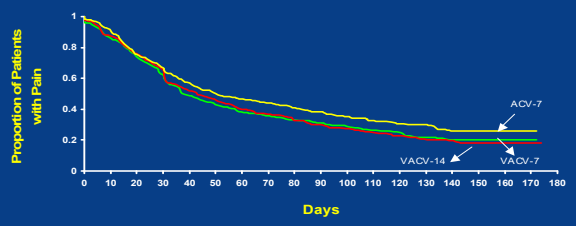
Goals of Therapy

- Accelerate cutaneous healing
- Accelerate loss of pain acute / chronic
- Prevent complications

Time to Cessation of Zoster-Associated Pain

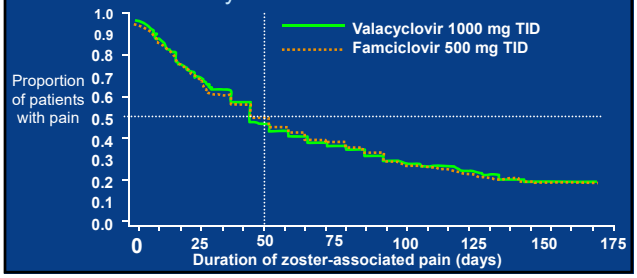


Time to Cessation of Zoster Associated Pain n = 1141



* Beutner, et al. Acyclovir versus Valacyclovir in the treatment of herpes zoster in patients > 50 years old.

Resolution of Pain in Herpes Zoster With Valacyclovir and Famciclovir



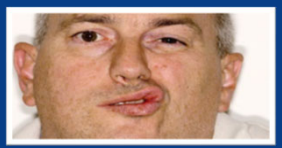
Summary of Efficacy of Concomitant Steroid Therapy with Acyclovir

- Accelerates resolution of acute neuritis
- Accelerates:
  - Return to usual activity P<0.001
  - Unaroused sleep P<0.0001
  - Cessation of analgesic use P<0.001
- Effect on chronic pain P=0.06

Question #5

What is the most likely etiologic agent?

A. HSV
B. VZV
C. CMV
D. EBV
E. HHV6



www.cdc.gov

METHODS OF PREVENTING / MODIFYING VARICELLA

Pre-exposure: Oka varicella vaccine

Post-exposure: VZIG (now available in US)

Oka varicella vaccine
(<3 days after exposure)

Acyclovir
(7-14 days after exposure)

Shingles Prevention Trial: Zostavax

- **Attenuated, live virus (approved 2006)**
- **Efficacy but waning of immunity with time**
  - **Burden Of Illness 61.1% (51.1 – 69.1%)**
  - **Post-Herpetic Neuralgia 66.5% (47.5 – 79%)**
  - **Incidence of Herpes Zoster 51.3% (44.2 – 57.6%)**

Second Generation Vaccine: Shingrix

- **Recombinant adjuvanted vaccine**
  - **Two shots**
  - **> 50 years of age**
- **Efficacy**
  - **Both PHN and incidence of shingles**
  - **>90% for >4 years**
- **Adverse events**
  - **Local reactogenicity: redness and pain ~ 50-70%**
  - **Systemic malaise/fever: ~30%**

Thank You

rwhitley@uab.edu

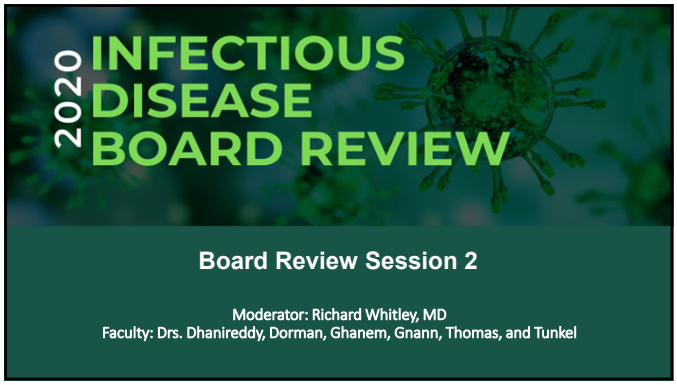
19

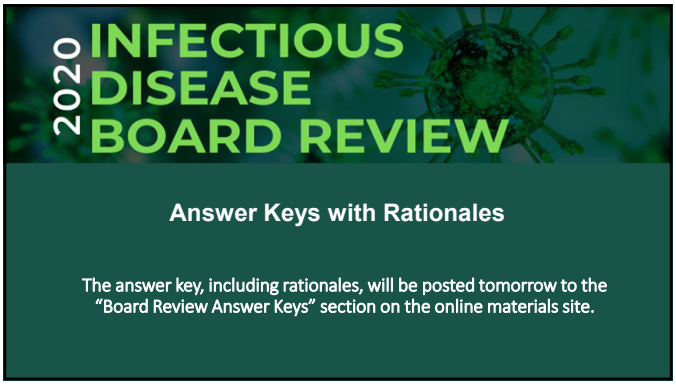
Board Review Session 2

Drs. Whitley (Moderator), Dhanireddy, Dorman, Ghanem, Gnann, Thomas, and Tunkel

19 – Board Review Session 2

Drs. Whitley (Moderator), Dhanireddy, Dorman, Ghanem, Gnann, Thomas, and Tunkel





#1

You are called by a 41-year-old friend who two days ago visited a religious community in central Pennsylvania that doesn't believe in vaccination.

Today he learned that, right after his visit, several members of that community had been diagnosed with chicken pox (varicella). Your friend is well and has no chronic health problems.

He can't remember ever having had chicken pox but is sure he didn't get the varicella vaccine.

#1

Which one of the following is the most appropriate intervention for your friend?

A) Varicella-zoster immune globulin

B) Valacyclovir

C) Varicella vaccine

D) Measure varicella antibody titer

E) Intravenous immune globulin

#2

You are consulted about three rugby players from the same team who have skin lesions. The skin lesions have been present for two to three days.

Each player has 10 to 20 raised, clustered lesions on the face, neck, and arms that are about 2 to 5 mm in diameter and filled with a clear yellow fluid; there is a small ring of erythema around the base of each lesion.

The athletes say the lesions are mildly uncomfortable but not pruritic; they are very minimally tender.

Three days before the lesions were noted by the first athlete, they had engaged in a rugby match after which they attended a party and bathed in a hot tub.

#2

Which one of the following is the most likely cause of the skin lesions?

A) Pseudomonas

B) Mycobacterium

C) Herpes simplex

D) Contact dermatitis

E) Molluscum

#3

A 50-year-old patient presents to the Hematology Service with paroxysmal nocturnal hemoglobinuria. They elect to treat the patient with eculizumab, and consult you for infectious disease advice. It is likely that the eculizumab therapy, if effective, will be continued for a long time, perhaps lifelong.

The patient has never had any significant illnesses and has no history of prior infection, has normal serum immunoglobulin levels, is HBV and HCV seronegative, and has no unusual occupational exposure.

#3

What preventive strategy would you recommend to reduce the infectious disease risks of eculizumab?

A) Trimethoprim sulfamethoxazole to prevent pneumocystis

B) Fluconazole to prevent candidiasis

C) Acyclovir to prevent HSV and VZV

D) Meningococcal quadrivalent and B vaccines

E) Test for latent tuberculosis

#4

A 47-year-old female in excellent health comes to consult you for a possible vaccine related complication. She reports that she receive an influenza immunization and a TdAP immunization on the instructions of her younger sister who had a newborn and wanted all visitors vaccinated.

Immediately after receiving the vaccinations in her left arm two weeks ago, her shoulder hurt. She has moderately severe pain on lifting her arm which is not relieved by non-steroidal anti-inflammatory drugs. The shoulder still hurts.

#4

She reports no fever and redness in the area of her shoulder. She has no trouble with strength in her arm or hand unless she raises her shoulder.

On examination, there is no warmth or redness of the shoulder but the patient has considerable pain when raising her left arm. No other joint is painful.

The patient is afebrile with a normal complete blood count.

#4

What diagnostic test would you order next?

A) Plain film of shoulder

B) Magnetic resonance image (MRI) of shoulder

C) Serum uric acid test

D) Joint washout for culture

E) Observation only for the next several weeks

#5

A 33-year-old man who emigrated from South Africa 2 years ago presents with fever, hemoptysis and a right apical cavity on CXR and is diagnosed with pulmonary tuberculosis.

Additional testing reveals he is HIV+ with an HIV RNA 122,000 copies/ml and a CD4 cell count of 47.

#5

What do you recommend?

A) Start TB meds first, then start ART within 2 weeks.

B) Start TB meds first, then start ART within 8 weeks.

C) Start ART first, then start TB meds within 2 weeks.

D) Start ART first, then start TB meds within 8 weeks.

#6

You are consulting on a hospitalized 53 y/o man with cavitary pneumonia.

Yesterday the result of a GeneXpert MTB/RIF test performed on sputum showed "MTB detected" and "rifampin resistance detected."

You started him on moxifloxacin, linezolid, clofazimine, pyrazinamide, and ethambutol for presumed multidrug-resistant (MDR)-TB, pending additional information about drug susceptibility. In discussions with the local health department TB program, the plan is to add bedaquiline.

#6

What additional bedaquiline-specific periodic safety monitoring will be required while the patient is receiving bedaquiline?

A) Periodic audiology examination to assess for high frequency hearing loss

B) Periodic serum bedaquiline drug levels to ensure that concentrations are within established target range

C) Periodic electrocardiogram to assess for QTc prolongation, and serum electrolytes

D) Visual acuity testing

E) 6-minute walk tolerance

#7

An asymptomatic male with HIV (CD4= 500 cells/mm3, Viral Load <20 copies/uL), on dolutegravir-lamivudine, has had multiple anonymous sexual exposures (oral, rectal and genital) over the past few weeks and requests that he be screened for sexually transmitted diseases.

You perform the following tests:

Syphilis
- RPR negative

Chlamydia: NAAT for rectal, and first catch urine:
- both negative

Gonorrhea: NAAT for oral, rectal and first catch urine:
- urine positive

#7

What is the best regimen for this patient's gonococcal infection?

A) Ceftriaxone 250 mg IM

B) Ceftriaxone 250 mg IM and azithromycin 1 gram PO

C) Cefixime 400 mg PO

D) Azithromycin 2 grams PO

E) Doxycycline 100 mg PO

#8

A 42-year-old recently divorced woman presents complaining of a vaginal discharge. She reports a new sex partner in the past month. She denies abdominal pain, nausea, vomiting, or a rash. She has a history of gastric reflux but is otherwise healthy.

On examination, a thin grey vaginal discharge is noted. Her cervix appears normal and there is no evidence of cervical motion tenderness or adnexal tenderness. A wet mount examination of a drop of the vaginal discharge reveals motile trichomonads but is otherwise normal. Testing for HIV performed two months earlier was negative.

#8

Which of the following is the most appropriate treatment for her infection?

A) Boric acid vaginal suppository

B) Metronidazole, single oral 2g dose

C) Metronidazole, 500 mg orally twice daily for one week

D) Paromomycin 6% topical vaginal cream

E) No therapy

#9

A 62-year-old male computer engineer from Seattle is 90 days post allo-HSCT for myelodysplastic syndrome and has been receiving valacyclovir prophylaxis because of a positive pretransplant test for antiHSV antibody.

The patient has had several episodes of severe graft versus host disease, two being associated with CMV detection in the blood by PCR, for which valganciclovir was substituted for valacyclovir for 2 to 3 week periods, ending 4 weeks ago.

#9

Two weeks ago the patient had the onset of fever and severe diarrhea. Reappearance of CMV in the blood by PCR has led to initiation of intravenous ganciclovir on the third day of diarrhea.

Persistence of diarrhea for seven days despite high dose steroids for presumed GVHD of the colon led to infectious disease consultation. Stool was negative for Clostridium difficile toxin by PCR and the CMV PCR in blood was unchanged over the first five days.

#9

What would be the most appropriate next step?

A) Oral metronidazole

B) Oral vancomycin

C) Change from ganciclovir to foscarnet

D) Colonoscopy

E) Stool for Strongyloides

#10

A 73 year old woman with T cell prolymphocytic leukemia has been treated with alemtuzumab (Campath) for 10 weeks and is awaiting a stem cell transplant. She is receiving trimethoprim-sulfamethoxazole and acyclovir prophylaxis.

During the tenth week of therapy, she develops low-grade fever and non-specific fatigue and myalgias. Her physical examination is unremarkable except for new shotty cervical adenopathy and some mild enlargement in her liver and spleen. Her hemoglobin, white blood count, and platelet count have fallen but she is not neutropenic. Her chest x-ray is normal.

She has not traveled since her diagnosis of leukemia and has no unusual exposures.

#10

What would be the next best step for diagnosing the likely cause of this syndrome?

A) Bone marrow biopsy

B) Serum PCR for toxoplasma

C) Serum PCR for CMV

D) Lymph node biopsy

E) CT scan of chest and abdomen

#11

A 64-year-old female with a history of chronic lymphocytic leukemia (CLL) for several years was recently diagnosed with Richter's transformation to diffuse large B cell lymphoma.

Her oncologist recommended starting R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine and prednisone) chemotherapy given the advanced stage disease.

The patient has a history of recurrent and severe sinopulmonary infections and hypogammaglobulinemia. As a result, she has been on monthly intravenous immunoglobulin (IVIG) for the past two years.

#11

The patient's hepatitis B serology obtained a year ago showed:

- HBsAg: nonreactive
- Total HBc Ab: positive
- HBsAb: positive
- HBV viral load: negative

Her oncologist referred her to be seen by you for further recommendations about the patient's hepatitis B.

#11

What is the most appropriate next step?

A) Treat only if monthly serum quantitative HBV viral load becomes positive while she gets treated with R-CHOP

B) Start tenofovir plus emtricitabine pre-R-CHOP

C) Start entecavir pre-R-CHOP

D) Administer a single hepatitis B vaccine booster dose

E) Review pre-IVIG hepatitis B serology before making a decision

2020 INFECTIOUS DISEASE BOARD REVIEW

PREVIEW QUESTION

#12

A 32 year old woman is referred for 'hepatitis' recognized by her primary care physician.

She is otherwise well.

She was born in Philippines but has lived in the USA for 2 years. She is a nurse on a medicine floor. Married with 2 children: 7 and 5 years old.

#12

She brings a lab slip with the following:

- Total anti-HAV pos;
- IgG anti-HBc pos;
- IgM anti-HBc neg;
- HBsAg pos; HBeAg pos;
- anti-HBe neg;
- HBV DNA 8.2 log IU/ML;
- ALT 24 U/L; AST 18 U/L;
- anti-HCV neg.

#12

Which of the following recommendations is most appropriate:

A) HBV vaccinate husband and children

B) Advise to use condoms

C) Test husband and children for HBsAg

D) Advise to stop work and initiate look-back investigation of a sample of patients

E) Advise against future pregnancies

#13

You treated a 54 year old man for chronic HCV infection with a direct acting regimen.

At baseline he was genotype 1a and HCV RNA was 6.5 log IU/ml. Baseline ALT was 92 U/L. He was HCV RNA undetectable after 4 weeks of treatment and again 12 weeks after treatment was done. ALT was 28 U/L. He is otherwise well.

Now he returns 2 years later because his primary tested him and his ALT is 84 U/L and HCV RNA is 6.8 log IU/ml and genotype 1a.

#13

Which is most likely?

A) He has HBV relapse from DAA treatment

B) He has HCV relapse

C) He was reinfected by HCV

D) He has steatohepatitis

#14

A previously healthy 30-year-old woman presented with right temporal headache, eye pain, diplopia and decreased vision in the right eye.

On exam, her temperature was 102°F. Her left eye had normal extraocular movement and vision. On the right, there was periorbital edema, proptosis, chemosis, and ptosis; the right eye was fixed in the midline.

Vision in the right eye was reduced to count fingers at 3 feet. She underwent a lumbar puncture; CSF analysis revealed glucose 69 mg/dL, protein 180 mg/dL, 3,000/mm^3 WBC (82% P, 18% L).

An MRI is ordered.

#14

#14

The most likely diagnosis is:

A) Superior sagittal sinus thrombosis

B) Cavernous sinus thrombophlebitis

C) Bacterial endophthalmitis

D) Mucormycosis

E) Right ethmoid sinusitis

#15

A previously healthy 60-year-old woman presents to the emergency room complaining of headaches, fevers, nausea, and vomiting for the past 4 days. Two days prior to her ER presentation, she noted difficulty with balance.

Earlier this morning, she noted left facial numbness. She denied any night sweats, photophobia, or neck stiffness. She has not traveled outside of the United States and has lived her entire life in Baltimore, Maryland.

She lives with her husband and two daughters in a row house. They own 2 cats and a dog. She denies smoking, alcohol use, or injection drug use.

#15

On physical examination, her temperature is 38.3°C, blood pressure is 120/60 mmHg, heart rate is 109 beats/minute, and respiratory rate is 13 breaths/minute. She is alert and oriented but appears uncomfortable. Higher cortical functions, extraocular movements and visual fields were intact. Limb tone, motor strength and reflexes were normal. Plantar responses were flexor.

Abnormalities included left facial hypoaesthesia, right facial weakness and left gaze-evoked nystagmus. She was noted to have gait ataxia. The remainder of her physical examination was unremarkable.

#15

- Her peripheral white cell count and differential were normal.
- A comprehensive metabolic panel was normal.
- Lumbar puncture and CSF examination revealed a lymphocytic pleocytosis with 500 white blood cells/mm^3 (94% lymphocytes). CSF glucose level was normal and protein level was slightly elevated. No organisms were visualized on Gram stain of the CSF. CT scan without IV contrast was unremarkable.
- Postgadolinium T1-weighted MRI images of the brain showed multiple ring-enhancing abscess-like lesions in the brainstem with mild meningeal enhancement.

#15

Which of the following is the most likely etiology of her clinical presentation?

A) Behcet's disease

B) Cytomegalovirus (CMV)

C) Herpes simplex virus type 2

D) Listeria monocytogenes

E) Mycobacterium tuberculosis

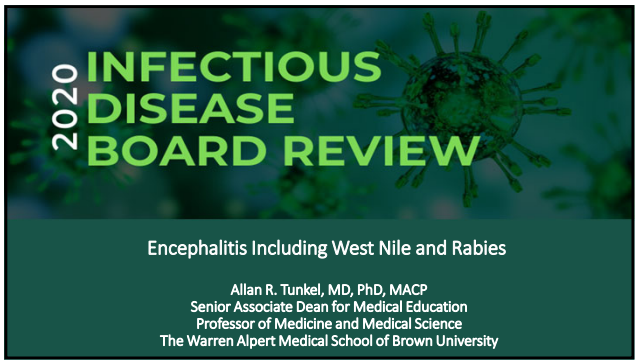
20

Encephalitis Including West Nile and Rabies

Dr. Allan Tunkel

20 –Encephalitis Including West Nile and Rabies

Speaker: Allan Tunkel, MD



Disclosures of Financial Relationships with Relevant Commercial Interests

- None

ENCEPHALITIS Definitions

- Encephalitis
  - Inflammation of brain parenchyma with neurologic dysfunction
  - Gold standard is pathologic examination and testing of brain tissue
  - Usually based on clinical, laboratory, and imaging
- Encephalopathy
  - Altered consciousness (confusion, disorientation, behavioral changes, cognitive impairment) ± inflammation
  - Usually metabolic or toxic conditions

ENCEPHALITIS Epidemiology

- ~20,000 cases annually in US
- >1 million cases annually worldwide
  - Rabies
  - Measles
  - Japanese encephalitis virus

ENCEPHALITIS Etiology

- California Encephalitis Project (CEP) reviewed 1,570 cases over 7-year period (CID 2006;43:1565)
- Confirmed or probable etiology in 16%
  - 69% viral
  - 20% bacterial
  - 7% prion
  - 3% parasitic
  - 1% fungal
- Possible etiology in 13%

Reasons Etiology not Identified

- Undiscovered pathogens
- Uncommon presentation by common pathogens
- Common presentation by uncommon pathogens
- Wrong test
- Wrong sample
- Wrong timing
- Not an infection

General Approach

- Can't test for everything
- Epidemiologic and clinical clues
- General diagnostic studies
- Neuroimaging clues
- Consider noninfectious etiologies

Tunkel et al. Clin Infect Dis 2008;47:303
Venkatesan et al. Clin Infect Dis 2013;57:1114

CASE #1

- 80-year-old man presents with a several day history of fever, headache, and personality change with progression to confusion
- On exam, temperature is 101ºF; he is disoriented and unable to follow commands
- CT scan of the head without contrast is negative
- CSF analysis reveals a WBC of 80/mm^3 (95% lymphs), glucose 70 mg/dL (serum 100 mg/dL), protein 120 mg/dL; Gram stain is negative

CASE #1

- Acyclovir is initiated
- MRI with gadolinium reveals enhancement in the left temporal lobe
- Results of initial cerebrospinal fluid (CSF) polymerase chain reaction (PCR) for HSV-1 and HSV-2 return negative
- After 3 days, the patient is now oriented to name and follows simple commands

QUESTION #1

What is the next step in the management of this patient?

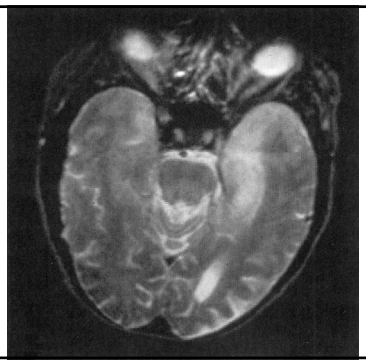
A. Perform a brain biopsy of the left temporal lobe
B. Obtain new CSF for HSV PCR testing
C. Send serum for HSV IgG antibodies
D. Repeat brain MRI
E. Discontinue acyclovir

Herpes Simplex Encephalitis

- Epidemiology
  - Among the most severe of all human viral infections of brain; >70% mortality with no or ineffective therapy
  - Accounts for10-20% of encephalitis viral infections
  - Occurs throughout the year and in patients of all ages
  - Increased risk in those with defects in TLR3 pathway?
  - Majority in adults caused by HSV-1
- Clinical features
  - Fever, personality change, dysphasia, autonomic dysfunction

Herpes Simplex Encephalitis

- Electroencephalography
  - Sensitivity of ~84%
  - Periodic lateralizing epileptiform discharges (PLEDs)
- Neuroimaging
  - Computed tomography (lesions in 50-75% of patients)
  - Magnetic resonance imaging (>90% of cases)
- Brain biopsy
  - Inflammation with widespread hemorrhagic necrosis
  - Intranuclear inclusions (50% of patients)
  - Reserve for patients not responding to acyclovir therapy



13

Herpes Simplex Encephalitis

14

- Cerebrospinal fluid (CSF) findings
  - Lymphocytic pleocytosis (mean of 100 cells/mm^3)
  - Presence of red blood cells (25% never have RBCs)
  - Elevated protein
  - Normal in 5-10% of patients on first evaluation
- CSF Polymerase Chain Reaction
  - Sensitivity 98%
  - Specificity 94%
  - Positive predictive value 95%
  - Negative predictive value 98%
  - If negative, may need new CSF sample in 3-7 days

Herpes Simplex Encephalitis

15

- Acyclovir is the antiviral agent of choice
  - Mortality of 19% at 6 months
  - Mortality of 28% at 18 months
  - Morbidity ~50%
- Dosage in adults is 30 mg/kg/day in 3 divided dosages (in those with normal renal function) for 14-21 days
- No added benefit on oral valacyclovir (3-month course) after standard course of acyclovir

Other Herpesviruses

16

- Varicella-zoster virus
  - Can occur without rash (zoster sine herpete)
  - Focal neurologic deficits and seizures
  - CSF antibodies; CSF PCR has sensitivity of only 30%
  - MRI/MRA large vessel vasculitis and ischemia
  - Acyclovir (however, no controlled studies) + ?corticosteroids (if vasculopathy)
- Epstein-Barr virus
  - Encephalitis and/or transverse myelitis
  - Serologic testing; CSF PCR (may have false-positives)
  - Corticosteroids?

Other Herpesviruses

17

- Human herpesvirus 6
  - Immunocompromised patients, but seen in children
  - CSF PCR (sensitivity >95%); high rate of detection in healthy adults (PPV only 30%)
  - Ganciclovir or foscarnet
- B virus
  - Bite or scratch from old world primates (macaques)
  - Vesicular eruption at site; neurologic disease in 3-7 days
  - Culture and PCR at site of bite; CSF PCR
  - Prophylactic valacyclovir
  - Therapy: acyclovir, valacyclovir, or ganciclovir

Other Herpesviruses

18

- Cytomegalovirus
  - Immunocompromised (especially HIV)
  - Evidence of widespread disease
  - CSF PCR (sensitivity 82-100%; specificity 86-100%)
  - MRI may reveal subependymal gadolinium enhancement and non-specific white matter changes
  - Ganciclovir + foscarnet

BioFire FilmArray

19

Bacteria	Viruses	Fungi
Escherichia coli K1	Cytomegalovirus	*Cryptococcus neoformans/gatti*
Haemophilus influenzae	Enterovirus	
Listeria monocytogenes	Herpes simplex virus 1	
Neisseria meningitidis	Herpes simplex virus 2	
Streptococcus agalactiae	Human herpesvirus 6	
Streptococcus pneumoniae	Human parechovirus	
	Varicella zoster virus	

CASE #2

20

- 72-year-old man presents in late August with complaints of fever, chills, and weakness beginning 1 week earlier; on the day of admission, he becomes confused
- He lives in central New Jersey, where he and his wife have a horse farm; they often noted mosquito and tick bites
- On presentation, he is somnolent and unable to provide a complete history, although denies headache and stiff neck

CASE #2

21

- T 103.1ºF, P 110, RR 16, BP 110/70 mmHg
- No rash or petechiae, neck supple, no adenopathy, lungs clear, heart without murmurs, abdomen normal
- On neurologic exam, he is oriented to person only. Cranial nerves intact. Motor strength 4/5 UE, and 3/5 LLE and 2/5 RLE. Sensation intact. Reflexes diminished in LE

QUESTION #2

22

Which of the following tests is most likely to establish the etiology of this patient's encephalitis?

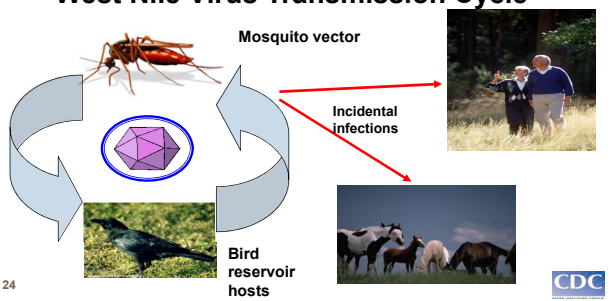
A. Serum IgM
B. Serum polymerase chain reaction
C. Cerebrospinal fluid IgM
D. Cerebrospinal fluid polymerase chain reaction
E. Brain MRI

West Nile Virus (WNV) Encephalitis

23

- First US cases reported in 1999 in New York City
- Birds are main reservoirs
- Mosquito vector
- Other modes of transmission
  - Transplanted organs
  - Blood transfusions
  - Breast milk
  - Transplacental
  - Occupational

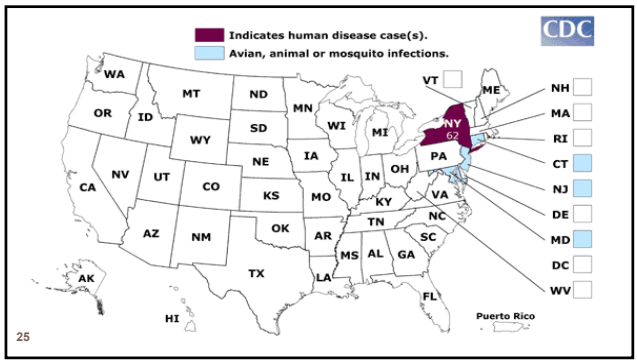
West Nile Virus Transmission Cycle

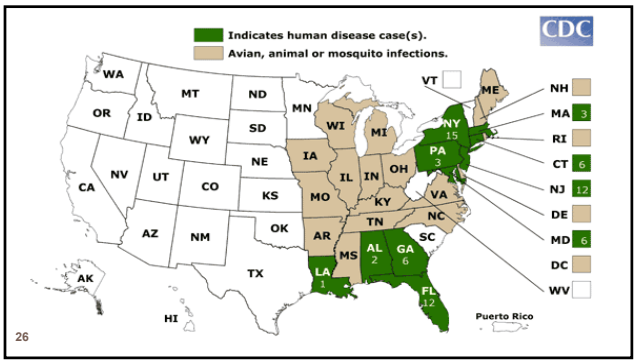


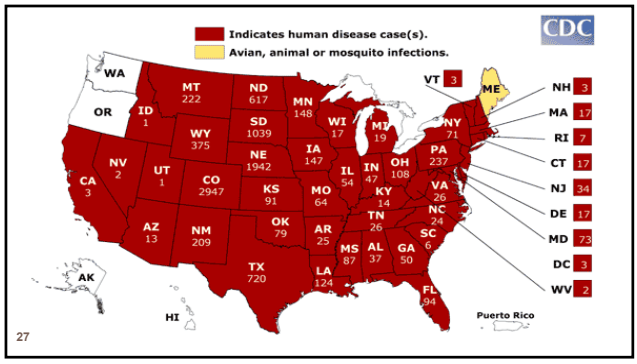
24

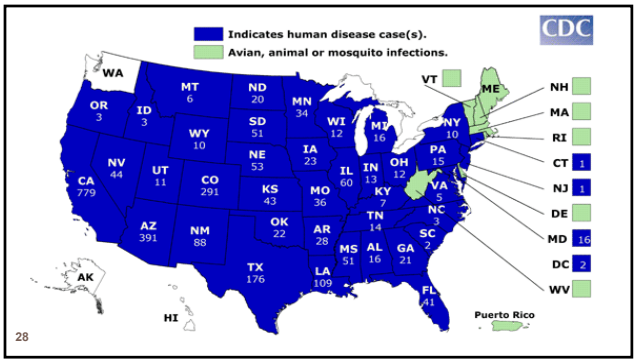
20 –Encephalitis Including West Nile and Rabies

Speaker: Allan Tunkel, MD



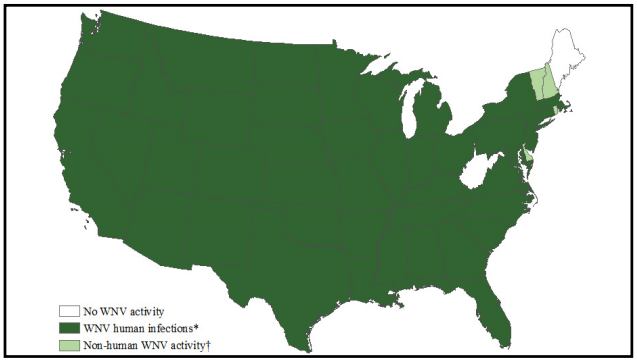


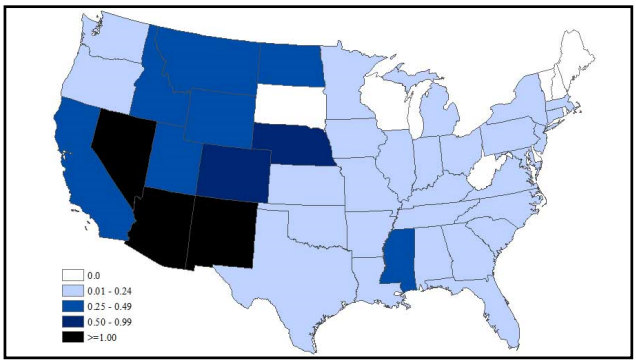




WNV Human Cases Reported To CDC

Year	Total Cases	Neuroinvasive	Deaths
2007	3630	1227	124
2009	720	386	32
2011	712	486	43
2012	5674	2873	286
2014	2122	1283	85
2016	2149	1308	106
2018	2544	1594	137
2019	958	626	54





West Nile Virus Clinical Syndromes

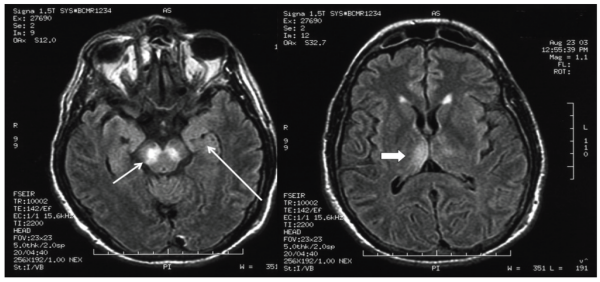
32

- No clinical illness or symptoms (~80%)
- West Nile Fever (~20%)
- Severe WNV Disease (1 in 150)
  - Meningitis
  - Encephalitis/Meningoencephalitis
  - Poliomyelitis-like flaccid paralysis

West Nile Virus Encephalitis

33

- Diagnosis
  - Serum IgM antibody (8-14 days of illness onset)
  - CSF reveals lymphocytic pleocytosis and elevated protein; glucose is normal
  - CSF IgM (positive in >90%)
  - CSF PCR (<60% sensitivity)
  - Neuroimaging



34

West Nile Virus Encephalitis

35

- Therapy
  - Supportive
  - Ribavirin, interferon alpha, and IVIG don't work

Other Arboviruses

36

- St. Louis encephalitis virus
  - Mosquito vector; bird reservoir
  - Endemic in western US; periodic outbreaks in eastern US
  - Urinary symptoms early; SIADH (one-third of cases)
  - Serology; CSF IgM
- Japanese encephalitis virus
  - Most common cause of mosquito-borne encephalitis worldwide (SE Asia, China, India, Nepal, Korea, Japan)
  - Mainly children; rice fields where vectors breed
  - Seizures and parkinsonian features; poliomyelitis-like flaccid paralysis
  - Serology; CSF IgM

Other Arboviruses

37

- Powassan virus
  - Tick vector (Ixodes scapularis in NE); rodent reservoir
  - Prevalence among animal hosts and vectors increasing
  - New England states
  - Serology; CSF IgM; metagenomic sequencing
- Tickborne encephalitis virus
  - Tick vector, rodent reservoir; drinking unpasteurized milk or cheese; solid organ transplantation; rituximab
  - Eastern Russia, central Europe
  - Poliomyelitis-like paralysis
  - Serology; CSF IgM
  - Anti-TBE immune globulin for post-exposure prophylaxis

Other Arboviruses

38

- La Crosse virus
  - Mosquito vector; chipmunk and squirrel reservoir
  - Midwest and eastern US; woodlands
  - 2nd most common arbovirus in US
  - Serology; CSF IgM; SIADH (~20%)
- Eastern equine encephalitis virus
  - Mosquito vector; bird reservoir in North America; organ transplantation
  - Primarily Atlantic and Gulf coast states
  - Abrupt onset with fulminant course; seizures common
  - High case-fatality rate (50-70%)
  - Serologic testing
  - High CSF WBC count (>1000 cells/mm^3)

Measles Virus

39

- Unvaccinated children and adults; worldwide
- Symptoms 1-6 months after exposure
- Decreased consciousness, focal signs, seizures
- Diagnosis
  - Serology
  - Culture and RT-PCR of nasopharynx and urine
  - CSF antibodies and RT-PCR (sensitivity and specificity unknown)
- Therapy
  - Supportive; ribavirin?

CASE #3

40

- 36-year-old man is on a hiking trip in northern California and is bitten on his lower leg by a skunk
- Upon presentation, he is afebrile and has several puncture wounds on his right lower extremity
- You irrigate with wounds with soap and povidone iodine, and administer a tetanus booster
- He has never been vaccinated against rabies

QUESTION #3

41

In addition to administration of rabies vaccine, what is the most appropriate management?

A. Rabies immune globulin at the bite sites
B. Rabies immune globulin in the deltoid muscle
C. Rabies immune globulin in the buttocks
D. Rabies immune globulin intraperitoneally
E. Nothing further is indicated

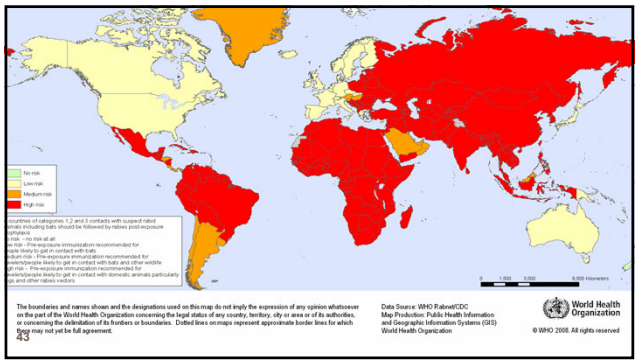
Rabies

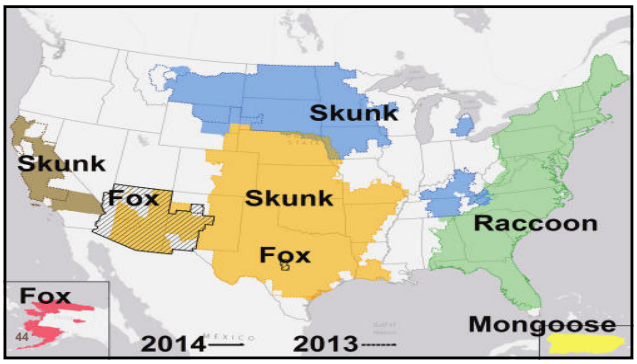
42

- Transmitted by bite of infected animal
  - Dogs are principal vector (98% of cases) worldwide
  - May be transmitted after unrecognized bites by bats
- Rare and sporadic in US – 125 cases from 1960-2018
  - 36 (28%) attributed to dog bite during international travel
  - 89 acquired in US; 62 (70%) attributed to bats
- Worldwide in distribution (50,000-100,000 annual deaths)
- Incubation period 20-90 days

20 –Encephalitis Including West Nile and Rabies

Speaker: Allan Tunkel, MD





Rabies

45

- Encephalitic (furious) form (80%)
  - Agitation alternating with lucidity
  - Hypersalivation
  - Hydrophobia
  - Bizarre behavior
  - Disorientation, stupor, coma, death
- Paralytic (dumb) form
  - Ascending paralysis; early muscle weakness
  - Later cerebral involvement

Rabies

46

- Diagnosis
  - Culture and RT-PCR of saliva
  - Immunofluorescent detection of viral antigens and RT-PCR in nuchal biopsy
  - CSF antibodies and RT-PCR
  - Brain biopsy (antigen detection/Negri bodies)
- Therapy
  - Supportive
  - Milwaukee Protocol has failed in 26 cases
  - Post-exposure prophylaxis (rabies immune globulin at bite site and vaccine)

CASE #4

47

- 22-year-old woman with no significant past medical or psychiatric history develops headache and low-grade fever followed by confusion and hallucinations
- On presentation, she is afebrile and disoriented; she has evidence of abnormal movements of her mouth and face
- CSF analysis reveals a WBC count of 20/mm^3, with normal glucose and protein
- Brain MRI is normal

CASE #4

48

- EEG reveals diffuse slowing
- CSF Gram stain and cultures, and PCR for HSV are negative
- A diagnosis of autoimmune encephalitis is considered and appropriate studies sent
- CSF returns positive for antibodies to the NR1 subunit of the N-methyl-D-aspartate receptor
- Corticosteroids and IV immune globulin are initiated

QUESTION #4

Which of the following studies should now be performed?

A. CT scan of the chest
B. CT scan of the abdomen
C. Carotid ultrasound
D. Renal ultrasound
E. Transvaginal ultrasound

ENCEPHALITIS
Noninfectious Etiologies

- Acute disseminated encephalomyelitis (ADEM)
  - 10-15% of encephalitis cases in US
  - Post-infectious (upper respiratory infections, measles, mumps, influenza, varicella, rubella, hepatitis C, HIV)
  - Post-immunization (smallpox, rabies, measles, rubella, oral polio, Japanese encephalitis, hepatitis B)
  - Symptoms 2-4 weeks after trigger
  - MRI bilateral asymmetric T2 hyperintensity in subcortical and deep white matter
  - Corticosteroids
- Anti-N-methyl-D-aspartate receptor (Anti-NMDAR) encephalitis

Anti-NMDAR Encephalitis

- Neuronal antibody-associated encephalitis
- In California Encephalitis Project, this entity exceeded that of any single viral entity in children and was also seen in adults
- Female to male ratio of about 8:2
- 37% of patients younger than 18 years at presentation

Anti-NMDAR Encephalitis

- Abnormal behavior (psychiatric symptoms)
- Cognitive dysfunction
- Seizures
- Movement disorders (orofacial dyskinesias)
- Decreased level of consciousness
- Autonomic instability
- May be associated with ovarian teratoma (in ~50% of patients older than 18 years)

Anti-NMDAR Encephalitis

- CSF analysis
  - Mild pleocytosis (median WBC 23/mm^3); normal glucose and protein
  - Specific IgG antibodies to GluN1 subunit of the NMDAR in CSF
  - Viral causes of encephalitis (e.g., HSV) are associated with development of NMDAR antibodies

Anti-NMDAR Encephalitis

- Neuroimaging
  - Abnormal in 50%, but nonspecific
  - T2 and FLAIR hyperintensity (hippocampi, cerebellar or cerebral cortex, frontobasal and insular regions, basal ganglia, brainstem)
- EEG
  - Diffuse or focal slowing
  - Occasional superimposed epileptic activity

Anti-NMDAR Encephalitis

- Therapy
  - First-line
    - Corticosteroids
    - Intravenous immunoglobulin
    - Plasma exchange
  - Second-line
    - Rituximab or cyclophosphamide
  - Female patients should be evaluated for ovarian teratoma; if present, remove
- 75% of patients have mild sequelae or fully recover; relapse in up to 24%

21

Immunizations: Domestic, Travel, and Occupational

Dr. Shireesha Dhanireddy

2020 INFECTIOUS DISEASE BOARD REVIEW

Immunizations:
Domestic, Travel, and Occupational

Shireesha Dhanireddy, MD
Professor, Allergy & Infectious Diseases
University of Washington

Disclosures of Financial Relationships with Relevant Commercial Interests

- None

Objectives

- Review vaccine guideline resources
- Review ACIP recommendations for routine immunizations
- Discuss travel immunizations
- Review vaccines in special populations

Key Sources

Only ACIP guidance for routine immunizations will be tested

https://www.cdc.gov/vaccines/schedules/hcp/adult.html

Key Sources

Only CDC guidance from yellow book for travel vaccines will tested

https://wwwnc.cdc.gov/travel/page/yellowbook-home

Egg Allergy

22 year old man with h/o egg allergy and no prior influenza vaccine presents for routine visit. He states he has had hives after eating eggs. No h/o anaphylaxis. **Which of the following is recommended?**

A. Defer vaccination and refer to an allergist for testing
B. Vaccinate with any inactivated influenza vaccine without monitoring
C. Vaccinate and monitor for 30 minutes after receiving any inactivated influenza vaccine
D. Vaccinate with only live attenuated influenza vaccine

Egg Allergy – ACIP Recommendations

- Egg allergy
  - 1.3% of children
  - 0.2% of adults
- Ok to get influenza vaccine if the following:
  - No reaction with cooked eggs
  - Only hives after exposure
- If have anaphylaxis, angioedema, respiratory distress or required epinephrine
  - CAN STILL RECEIVE VACCINE – but should be given by a provider who can recognize allergic reactions
  - 33 cases of anaphylaxis out of 25.1 million doses
  - 8/33 had symptoms within 30 min

Question: Measles Vaccine

71 year old man underwent unrelated HSCT for MDS AML 12 years ago which was relatively uncomplicated without GVHD and he has been off immunosuppression for 2 years. His primary care provider checks a rubeola serology as there is an outbreak in the community and patient is concerned regarding risk. The serology is negative. **Which of the following do you recommend?**

A. Vaccine is not recommended as it is live and there is risk of vaccine related disease
B. One dose of MMR vaccine recommended
C. Two doses of MMR vaccine recommended

Measles Vaccine

- Over 1000 cases of measles in the US in 2019 as of the end of June
- 90% of cases in unvaccinated or unknown states individuals

- Vaccine very effective!
  - 93% effective after 1 dose
  - 97% effective after 2 doses
  - Immunity is felt to be lifelong*

Measles Vaccine

Evidence of presumptive immunity

- Written documentation of adequate vaccination
  - 1+ doses of vaccine at ≥12mos
    - Pre-school age
    - Adults not at high risk
  - 2 doses
    - School age children
    - College students
    - Healthcare personnel
    - International travelers
- Lab evidence of immunity
- Lab confirmation of measles disease
- Birth prior to 1957

Measles Vaccine

Who doesn't need vaccine:

- Adults born before 1957 (except HCW – should receive during an outbreak)
- Those with laboratory evidence of immunity

Who needs 1 dose:

- Adults born after 1957 considered low risk without documented vaccine and no lab evidence of immunity or prior infection

Who needs 2 doses:

- Healthcare workers
- International travelers born in 1957 or later
- Persons attending colleges or post-high school educational institutions

Measles Vaccine

Measles vaccine may be administered post-transplant if:

- 2 years post transplant
- No active GVHD
- At least 1 year off immunosuppressive medications

Question: Measles Vaccine

71 year old man underwent unrelated HSCT for MDS AML 12 years ago which was relatively uncomplicated without GVHD and he has been off immunosuppression for 2 years. His primary care provider checks a rubeola serology as there is an outbreak in the community and patient is concerned regarding risk. The serology is negative. **Which of the following do you recommend?**

A. Vaccine is not recommended as it is live and there is risk of vaccine related disease
B. One dose of MMR vaccine recommended
C. Two doses of MMR vaccine recommended

Question: HPV Vaccine

An 24 year old healthy male presents for routine clinic visit. He is not on any medications. He smokes cigarettes. He is sexually active with both men and women and uses condoms consistently. Which of the following is correct regarding HPV vaccine?

A. He should receive 2 doses of HPV-9 spaced 6 months apart
B. He should receive 3 doses of HPV-9 at 0, 1, and 6 months
C. He does not need HPV vaccine as he is already sexually active
D. HPV vaccination is only recommended in males through age 21

HPV Vaccine

As of late 2016, only the nonavalent (9vHPV) vaccine is being distributed in the US

Nonavalent: Merck Gardasil 9®

- Types 6, 11, 16, 18, 31, 33, 45, 52, 58
- FDA-approved for females and males **9-45*** yrs
- Cost per dose $133-$193

HPV Vaccine Recommendations

- Routine vaccination at age 11 or 12 years*
- Recommended through age 26 for females **and males through age 21 (for now)** not previously vaccinated
- **Recommended for MSM and immunocompromised men (including persons with HIV infection) through age 26**
- **Up to age 45 through shared decision making**

* Vaccination series can be started at 9 years of age

MMWR 2015;64:300-4

Now 2 Doses Adequate in Some Populations

- For boys and girls age 9-14:
  - –2 dose schedule: 0, 6-12 months
- For those who are >14 or immunocompromised:
  - –3 dose schedule: 0, 1-2, 6 months
  - –2 dose schedule not yet tested in this group, stay tuned
- Hope to reduce costs and increase uptake!

Meites et al, MMWR 2016: 65(49); 1405-1408.
Iversen et al, JAMA 2016: 316(22); 2411-2421.

Question: HPV Vaccine

An 24 year old healthy male presents for routine clinic visit. He is not on any medications. He smokes cigarettes. He is sexually active with both men and women and uses condoms consistently. Which of the following is correct regarding HPV vaccine?

A. He should receive 2 doses of HPV-9 spaced 6 months apart
B. He should receive 3 doses of HPV-9 at 0, 1, and 6 months
C. He does not need HPV vaccine as he is already sexually active
D. HPV vaccination is only recommended in males through age 21

Question: Pneumococcal Vaccine

A 65 year old man with well controlled HIV presents to clinic for routine care. He received 13-valent conjugate pneumococcal vaccine 3 years ago and 23-valent polysaccharide vaccine 5 years ago. Which of the following is most accurate?

A. He does not need any further vaccination for pneumococcal disease
B. He needs a PCV13 alone
C. He needs a PCV13 followed 1 year later by a PPSV23
D. He needs a PPSV23 alone

Pneumococcal Disease

Age	Disease Incidence Cases/100,00 (# of cases)	Death Rate Deaths/100,000 (# of deaths)
<1	31.4 (142)	0.22 (1)
1	24.6 (112)	0.22 (1)
2-4	12.6 (171)	0.15 (2)
5-17	2.2 (111)	0.02 (1)
18-34	3.7 (261)	0.26 (18)
35-49	10.3 (670)	0.65 (42)
50-64	19.5 (1,068)	1.86 (102)
≥ 65	37.0 (1,291)	5.61 (196)
Total	12.9 (3,828)	1.22 (363)

Cox CM. CDC Manual for the Surveillance of Vaccine Preventable Diseases

Pneumococcal Vaccine in Adults: Who needs it?

- Persons ≥ 65 years of age
- Persons age 19-64 with:
  - – Chronic lung disease (**asthma** or COPD)
  - – Chronic heart disease (except HTN)
  - – Chronic liver disease
  - – CSF leak
  - – Smokers
  - – Diabetes
  - – Alcoholism
  - – Functional or anatomic asplenia
  - – Immunocompromising conditions

Pneumococcal Vaccine (PPSV23): Revaccination

- Not recommended for most persons
- Who should be revaccinated?
  - –Persons aged 19-64 with
    - Functional or anatomic asplenia
    - Immunocompromising conditions
- Multiple vaccinations not recommended

MMWR 2010. 59(34);1102-1106

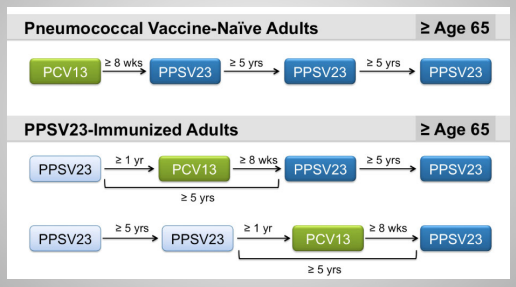
PPSV23 vs PCV13

- PPSV23 – contains polysaccharide antigens
- PCV13 – contains immunogenic proteins conjugated to pneumococcal polysaccharides

- PCV13 recommended for some immunocompromised (HIV) adults age < 65
- PCV13 recommended for persons ≥ 65 if not received already in adulthood

MMWR. 2015;64(34):944-7

Pneumococcal Vaccine Schedule in PWH



Question: Pneumococcal Vaccine

A 65 year old man with well controlled HIV presents to clinic for routine care. He received 13-valent conjugate pneumococcal vaccine 3 years ago and 23-valent polysaccharide vaccine 5 years ago. Which of the following is most accurate?

A. He does not need any further vaccination for pneumococcal disease
B. He needs a PCV13 alone
C. He needs a PCV13 followed 1 year later by a PPSV23
D. He needs a PPSV23 alone

Question: Hepatitis B Vaccine

A 35 year old woman with recently diagnosed HIV now on ART with VL UD and CD4 count 650 presents for f/u. She is HBV non-immune (HBsAb negative, HBcAb negative, HBsAg negative). She completes 3 doses of standard-dose HBV vaccine. Which of the following is most accurate?

A. She needs an additional dose of vaccine as she has HIV
B. She should have received double-dose vaccine as she has HIV
C. You should check HBsAb 1-2 months after completion, and give additional dose of vaccine if remains non-immune

ACIP Recommendations for HBV Immunization in PWH

- Recombivax®: 3 dose series (0, 1, 6 months) 10 µg/mL IM **(AII)**

OR

- Engerix®: 3 dose series (0, 1, 6 months) 20 µg in 1.0 mL IM **(AII)**

OR

- Heplisav®: 2-dose series (0, 1 month) 20 µg in 0.5 mL IM **(CIII)**

Anti-HBs should be assessed 1-2 months after completion of series

Safety and efficacy of Heplisav® has not been studied in individuals with HIV

Question

A 35 year old woman with recently diagnosed HIV now on ART with VL UD and CD4 count 650 presents for f/u. She is HBV non-immune (HBsAb negative, HBcAb negative, HBsAg negative). She completes 3 doses of standard-dose HBV vaccine. Which of the following is most accurate?

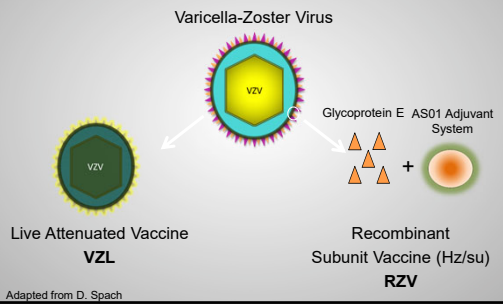
A. She needs an additional dose of vaccine as she has HIV
B. She should have received double-dose vaccine as she has HIV
C. You should check HBsAb 1-2 months after completion, and give additional dose of vaccine if remains non-immune

Question: Zoster Vaccine

A 62 year old woman with a self-reported history of shingles 10 years ago and type II diabetes presents to clinic. She received the live-attenuated zoster vaccine (ZVL) 2 years ago. What do you recommend regarding the zoster vaccine?

A. Vaccine not indicated given her history of zoster
B. Vaccine not indicated as she has received ZVL
C. Check VZV titer to confirm history. If negative, proceed with vaccination
D. Recommend recombinant zoster vaccine

Zoster Vaccines



ACIP Recommendations for Zoster Vaccine

- RZV is preferred over ZVL
- Healthy adults ≥ 50 years
  - Regardless of prior h/o HZ
  - No need to wait any specific period of time after HZ to give RZV (just not during acute episode)
- 2 doses, 2-6 months apart
- Wait a minimum of 8 weeks after giving ZVL to give RZV
- ACIP not recommending use in immunocompromised persons (except low-dose immunosuppression)

Question: Zoster Vaccine

A 62 year old woman with a self-reported history of shingles 10 years ago and type II diabetes presents to clinic. She received the live-attenuated zoster vaccine (ZVL) 2 years ago. What do you recommend regarding the zoster vaccine?

A. Vaccine not indicated given her history of zoster
B. Vaccine not indicated as she has received ZVL
C. Check VZV titer to confirm history. If negative, proceed with vaccination
D. Recommend recombinant zoster vaccine

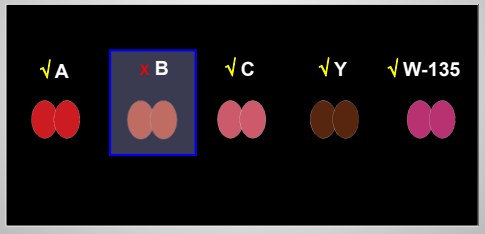
Question: Meningococcal Vaccine

44 year old woman hospitalized with anemia and thrombocytopenia diagnosed with complement-mediated HUS. Treatment with eculizumab is being considered. She is told she will need vaccine(s) prior to initiation of therapy.

A. Give meningococcal conjugate vaccine (MCV4)
B. Give meningococcal polysaccharide vaccine (MPSV4)
C. Give meningococcal B vaccine only
D. Give both MCV4 and meningococcal B vaccines

Meningococcal Quadrivalent Vaccines

Serogroups Included in Vaccine: A, C, Y, W-135

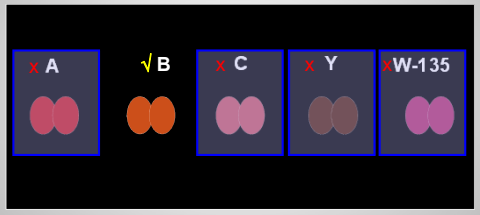


Meningococcal Quadrivalent Vaccines

Serogroups Included in Vaccine: A, C, Y, W-135

- *Menactra* (MCV4)
  - Conjugate vaccine
  - Approved for ages 9 months to 55 years
- *Menveo* (MCV4)
  - Conjugate vaccine
  - Approved for ages 2 months to 55 years
- *Menomune* (MPSV4) – *NO LONGER AVAILABLE*
  - Polysaccharide vaccine
  - Approved for persons >2 years of age

Meningococcal B Vaccines



Meningococcal Group B Vaccines
Serogroups Included in Vaccine: B

- MenB-4C (*Bexsero*)
  - Recombinant vaccine
  - For ages 10 to 25 years
  - 2 dose series ≥1 month apart
- MenB-FHbp (*Trumenba*)
  - Recombinant vaccine
  - For ages 10 to 25 years
  - Healthy adolescents and young adults: 2 doses at 0, 6 months
  - Adults at risk for meningococcal disease: 3 doses at 0, 1-2, 6 months
  - Vaccinated during serogroup B meningococcal disease outbreaks: 3 doses at 0, 1-2, 6 months

ACIP Meningococcal B Vaccine Recommendation
Adolescents and Young Adults

- Recommended fo
  increased risk, pr
  - Meningococcal
  - Asplenia
  - Complement d
  - On eculizumab
  - Microbiologist
    Neisseria meni
- Same vaccine should be used for all doses


BREAKING TOP STORY

Meningococcus returns to OSU: Student being treated for disease

BENNETT HALL Corvallis Gazette-Times Oct 27, 2017

CDC. MMWR. 2015;64:1171-6.

Eculizumab

- Soliris (eculizamab) 1000-2000x increased risk of meningococcal meningitis
- CDC recommendations –
  - –Immunize with both quadrivalent and B vaccines at least 2 weeks prior to giving eculizumab if possible
  - –Repeat immunization every 5 years while on eculizumab
- Risk remains increased despite vaccination

Question: Tdap

A 27 year old pregnant woman presents for her routine obstetrics visit at her 32 week gestation visit. She is G2P1. She has a healthy 2 year old daughter at home. Which statement is correct regarding Tdap in pregnancy?

A. She should receive a Tdap today only if she has not received in the past 5 years.
B. She should receive Tdap only if she did not receive during her prior pregnancy
C. She should receive Tdap today

Tdap Recommendations

WHO
- All adolescents aged 11 through 18 years (age 11-12 preferred)
- All adults aged 19 through 64 who have not received a dose
- All adults aged ≥ 65 years (2/2012)
- All pregnant women during each pregnancy

WHAT
- Boostrix preferred for adults ≥ 65 years (but either okay)

WHEN
- Regardless of interval between last Td if has not received Tdap
- During each pregnancy for pregnant women – optimum timing is 3rd trimester (27-34 weeks)

MMWR 2013;62:131-135

Question: Tdap

A 27 year old pregnant woman presents for her routine obstetrics visit at her 32 week gestation visit. She is G2P1. She has a healthy 2 year old daughter at home. Which statement is correct regarding Tdap in pregnancy?

A. She should receive a Tdap today only if she has not received in the past 5 years.
B. She should receive Tdap only if she did not receive during her prior pregnancy
C. She should receive Tdap today

Question: Hepatitis A

A couple in their 30's plans to adopt a 2 year old girl from Ethiopia. They have a regular babysitter and another 7 year old child.

Who should receive the Hepatitis A vaccine?

A.Both parents
B.Mother only
C.Both parents and 7 year old child
D.Both parents, 7 year old child, and babysitter

Hepatitis A

- Vaccine recommended for all close personal contacts, including regular babysitters of children adopted from high/intermediate endemic areas
- Timing – ideally at ***least 2 weeks prior to arrival*** of child but within first 60 days of arrival

Hepatitis A

Hepatitis A

- Universal vaccination for children since 2006 (between 12-23 months)
- 3 formulations of vaccine available – Havrix, Vaqta, Twinrix (with Hep B vaccine)
  - Havrix and Vaqta are 2 doses 0, and 6-12 months apart
- Duration of protection is unknown but felt to be lifelong
  - No need to check antibody titers after vaccination
  - Negative titer does not mean lack of immunity

Hepatitis A Vaccination in Adults

- Travelers
- Men who have sex with men
- Persons who use illicit drugs
- Persons who work with nonhuman primates
- Persons who anticipate close contact with an international adoptee
- Persons with chronic liver disease
- Post-exposure prophylaxis for healthy persons
- **Persons living homeless**

Question: Hepatitis A

A couple in their 30's plans to adopt a 2 year old girl from Ethiopia. They have a regular babysitter and another 7 year old child.

Who should receive the Hepatitis A vaccine?

A. Both parents

B. Mother only

C. Both parents and 7 year old child

D. Both parents, 7 year old child, and babysitter

Question: Travel

27 year old female aid worker for a relief organization is planning a 2 month trip to Nigeria in May. She recently completed graduate school. Prior travel to Brazil for vacation 11 years ago. Vaccine history - received all childhood vaccines and yellow fever vaccine 11 years ago. She should receive the following vaccines:

A. Yellow fever, Hep A, Typhoid, meningococcal, Japanese encephalitis, cholera

B. Hep A, Typhoid, meningococcal, cholera

C. Hep A, Typhoid

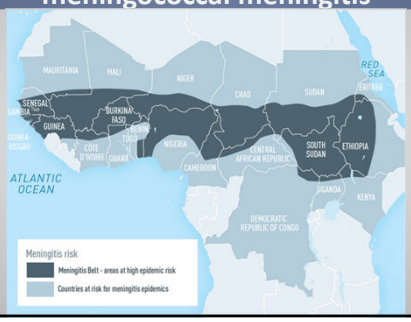
D. Yellow fever, Hep A

Yellow Fever

Yellow Fever Vaccine

- Recommended for ≥ 9 months traveling to or living in areas of risk or countries requiring vaccine for entry
- In 2014, WHO concluded that single dose fellow fever vaccine provides lifelong protection and no booster needed
  - Exceptions if ongoing risk and the following
    - pregnant when initially vaccinated
    - underwent HSCT after initial vaccine
    - HIV+

Areas of frequent epidemics of meningococcal meningitis



Meningococcal Vaccine and Travel

- Quadrivalent meningococcal vaccine recommended for travelers to the meningitis belt during dry season (Dec-June)
  - For ages 2 months – 55 years --> MenACWY (conjugate vaccine) recommended
  - For ≥ 56 years who have received conjugate vaccine before, Men ACWY recommended
  - For ≥ 56 years who are vaccine naïve, then MPSV4 (polysaccharide vaccine) recommended
- Meningitis B vaccine not recommended for travel
- Approx 7-10 days after vaccine for the development of protective antibody levels

Meningococcal Vaccine and Travel for Umrah or Hajj

- Travelers to Saudi Arabia for Umrah or Hajj are required to provide documentation of meningococcal vaccination at least 10 days before arrival
  - –No more than 3 years before for polysaccharide vaccine
  - –No more than 9 years before for conjugate

Typhoid Vaccine

- Highest risk for travelers to South Asia (6-30 x more than other destinations)
- Increased risk in West Africa, particularly in rural areas
- 2 vaccines available in US
  - Oral, live attenuated (given at least 1 wk before travel); age 6 and above, q 5 years if ongoing risk or travel
  - IM, polysaccharide (given at least 2 wks before travel); age 2 and above, q 2 years if ongoing risk or travel
  - Both 50-80% effective
- Indicated in travelers
- Delay vaccine >72 hrs after antibacterial medications

Japanese Encephalitis

JEV

- 35,000-50,000 cases/year
- 20-30% mortality
- 30-50% with neurologic sequelae
- Very low risk in travelers *(< 1 case per million travelers)*
- Risks are extended travel > 1 month, rural areas, irrigated areas (rice paddies), or going to an outbreak area
- Vaccine 2 doses, 28 days apart. 2nd dose should be given at least a week prior to travel
- 2 months or older
  - Smaller dose for children under 3
  - ? Booster dose for ≥ 17 years if risk and > 1 year since prior vaccine

Cholera Vaccine

- Approved in 2016
- Single-dose vaccine recommended for adults 18-64 years travelling to an area of active transmission (where cases have been reported in the past year)
- Cholera in travelers is extremely rare
- Risk factors: aid workers in outbreak settings
- Vaccine 90% effective in preventing severe diarrhea (declined to 80% after 3 month

Question: Travel

27 year old female aid worker for a relief organization is planning a 2 month trip to Nigeria in May. She recently completed graduate school. Prior travel to Brazil for vacation 11 years ago. Vaccine history - received all childhood vaccines and yellow fever vaccine 11 years ago. She should receive the following vaccines:

A. Yellow fever, Hep A, Typhoid, meningococcal, Japanese encephalitis, cholera
B. Hep A, Typhoid, meningococcal, cholera
C. Hep A, Typhoid
D. Yellow fever, Hep A

Question: Travel

A 30 year old male is planning on traveling to Angola. He presents to a travel clinic prior to travel and receives appropriate vaccines. One week later, he develops fever, ataxia, confusion, and then seizure.

Which vaccine is most likely responsible for this clinical syndrome?

A. Typhoid vaccine
B. Pneumococcal vaccine
C. Yellow fever vaccine
D. Japanese encephalitis
E. Malaria vaccine

Yellow Fever Vaccine

- YEL-AND (yellow fever vaccine associated neurologic disease)
  - Can dx by amplification of vaccine-type virus from CSF
- YEL-AVD (yellow fever vaccine associated viscerotropic disease)
  - Fever, N/V, malaise, myalgia, dyspnea
  - Jaundice, renal/hepatic impairment, rhabdo, decreased platelets, respiratory distress, hypotension, DIC
  - Diagnosis - isolate virus from blood

Question: Travel

A 30 year old male is planning on traveling to Angola. He presents to a travel clinic prior to travel and receives appropriate vaccines. One week later, he develops fever, ataxia, confusion, and then seizure.

Which vaccine is most likely responsible for this clinical syndrome?

A. Typhoid vaccine
B. Pneumococcal vaccine
C. Yellow fever vaccine
D. Japanese encephalitis
E. Malaria vaccine

Vaccines Post-Exposure

Question: Rabies

A 25 year old spelunker was bitten by a bat 6 days ago. He has never received rabies vaccine in the past.

What do you recommend?

A. Observation as too late to benefit from immunization or immune globulin
B. He should receive HRIG + vaccine today, then in 3, 7, and 14 days (total 4 doses).
C. He should receive HRIG + vaccine today, and day 14 as he is already a week past exposure
D. He should receive HRIG + vaccine today, then in 3, 7, 14, and 28 days (total 5 doses)

Question: Rabies vaccine in previously vaccinated patient

A 25 year old spelunker was bitten by a bat 6 days ago. *He received rabies vaccine series 5 years ago*.

What do you recommend?

A. He does not need HRIG or additional vaccine
B. He does not need HRIG, but should receive vaccine today and in 3 days
C. He should receive HRIG + vaccine today in 3 days
D. He should receive HRIG + vaccine today, then in 3, 7, and 14 days

Rabies

- Nearly uniformly fatal disease, acute, progressive encephalomyelitis
- Incubation period 1-3 months, but can be days to years
- 1-2 cases/year in US since 1960

Rabies Vaccine

- Recommendations revised 3/2010
- Pre-exposure prophylaxis
  - Vaccination on day 0, 7, and 21 OR 28 days
- Post-exposure
  - Vaccination day 0 (ASAP after exposure), 3, 7, 14
  - If received pre-exposure vaccine, should receive 2 doses PEP vaccine (day 0,3)
  - If immunocompromised, 5 doses of vaccine on day 0, 3, 7, 14, 28

Rabies Immune Globulin (HRIG)

- Clean wound
- Full dose around and into the wound (if any remaining, give at site distant from vaccine)
- If pre-vaccinated, no RIG

Question: Rabies

A 25 year old spelunker was bitten by a bat 6 days ago. He has never received rabies vaccine in the past.

What do you recommend?

A. Observation as too late to benefit from immunization or immune globulin
B. He should receive HRIG + vaccine today, then in 3, 7, and 14 days.
C. He should receive HRIG + vaccine today, and day 14 as he is already a week past exposure
D. He should receive HRIG + vaccine today, then in 3, 7, 14, and 28 days.

Question: Rabies

A 25 year old spelunker was bitten by a bat 6 days ago. He has never received rabies vaccine in the past.

What do you recommend?

A. Observation as too late to benefit from immunization or immune globulin
B. He should receive HRIG + vaccine today, then in 3, 7, and 14 days.
C. He should receive HRIG + vaccine today, and day 14 as he is already a week past exposure
D. He should receive HRIG + vaccine today, then in 3, 7, 14, and 28 days.

Question: Rabies vaccine in previously vaccinated patient

A 25 year old spelunker was bitten by a bat 6 days ago. *He received rabies vaccine series 5 years ago*.

What do you recommend?

A. He does not need HRIG or additional vaccine
B. He does not need HRIG, but should receive vaccine today and in 3 days
C. He should receive HRIG + vaccine today in 3 days
D. He should receive HRIG + vaccine today, then in 3, 7, and 14 days

Question: Post-Exposure

A 50 year old man living homeless is notified by public health that 2 people living in his tent community were diagnosed with hepatitis A in the last week. He does not know if he has been vaccinated but he is not in routine medical care. He denies any symptoms. Which of the following is most appropriate:

A. He does not need vaccine as he is asymptomatic
B. He should receive Hep A vaccine as soon as possible
C. He should receive combination Hep A and Hep B vaccine as he is likely non-immune to both

Hepatitis A Post-Exposure Prophylaxis

- No PEP needed if healthy and previously vaccinated
- PEP should be given immediately (within 14 days of exposure)
- No data available for combination HepA/HepB vaccine for PEP in HAV outbreak setting (contains only half the Hep A antigen compared to HAV vaccine – so not recommended after exposure)
- If non-immune, should complete 2-dose vaccine series (2nd dose at least 6 months after 1st dose)
- Immune globulin + vaccine (at separate sites) for immunocompromised and those with chronic liver disease
- For infants < 12 months, immune globulin only ASAP (within 2 weeks)

Question: Post-Exposure

A 35 year old man living homeless is notified by public health that 2 people living in is tent community were diagnosed with hepatitis A in the last week. He does not know if he has been vaccinated but he is not in routine medical care. He denies any symptoms. Which of the following is most appropriate:

A. He does not need vaccine as he is asymptomatic
B. He should receive Hep A vaccine as soon as possible
C. He should receive combination Hep A and Hep B vaccine as he is likely non-immune to both

Vaccines Post-Exposure

- ***Varicella exposure***
  - If no evidence of immunity and no contraindications (ie not severely immunocompromised) → Give vaccine ideally 3-5 days after exposure
  - For non-immune immunocompromised hosts and pregnant women, passive immunization with VariZIG is recommended
- ***Hepatitis B exposure***
  - If unvaccinated or incompletely vaccinated, Hep B vaccine dose + HBIG (can be given at a different injection site) as soon as possible after exposure
- ***Meningococcal exposure***
  - Chemoprophylaxis for close contacts (household members, child-care personnel, persons directly exposed to oral secretions)
  - Vaccination of population in outbreak

Exposure: Anthrax

If exposure to aerosolized *Bacillus anthracis* spores
•60 days of antimicrobial prophylaxis +
•3 doses of anthrax vaccine

Contraindications for vaccine
•Pregnant women when risk of anthrax exposure low

Precautions for use in:
•Individuals with latex allergy
•H/o anthrax
•Immunocompromised individuals
•Moderate to severe illness from anthrax

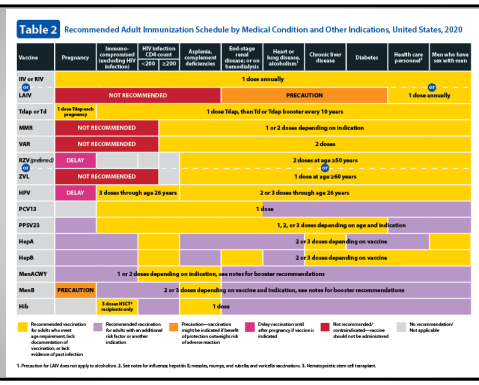


Table 2 Recommended Adult Immunization Schedule by Medical Condition and Other Indications, United States, 2020

Vaccine	Pregnancy	Immunocompromising conditions (including HIV infection)	HIV infection – CD4 count <200	HIV infection – CD4 count ≥200	Asplenia, complement deficiencies	End-stage renal disease, hemodialysis	Heart or lung disease, alcoholism	Chronic liver disease	Diabetes	Health-care personnel	Men who have sex with men
IIV or RIV	1 dose annually										
LAIV	NOT RECOMMENDED				PRECAUTION					1 dose annually	
Tdap or Td	1 dose Tdap each pregnancy	1 dose Tdap, then Td or Tdap booster every 10 years									
MMR	NOT RECOMMENDED	1 or 2 doses depending on indication									
VAR	NOT RECOMMENDED	2 doses									
RZV (preferred)	DELAY	2 doses at age ≥50 years									
ZVL	NOT RECOMMENDED	1 dose at age ≥60 years									
HPV	DELAY	3 doses through age 26 years			2 or 3 doses through age 26 years						
PCV13	1 dose										
PPSV23	1, 2, or 3 doses depending on age and indication										
HepA	2 or 3 doses depending on vaccine										
HepB	2 or 3 doses depending on vaccine										
MenACWY	1 or 2 doses depending on indication, see notes for booster recommendations										
MenB	PRECAUTION	2 or 3 doses depending on vaccine and indication, see notes for booster recommendations									
Hib	3 doses HSCT recipients only	1 dose									

Recommended vaccination for adults who meet age requirement/lack documentation of vaccination or evidence of past infection
Recommended vaccination for adults with an additional risk factor or another indication
Precaution—vaccination might be indicated if benefit of protection outweighs risk of adverse reaction
Delay vaccination until after pregnancy if vaccine is indicated
Not recommended/contraindicated—vaccine should not be administered
No recommendation/Not applicable

1. Precaution for LAIV does not apply to alcoholism. 2. See notes for influenza; hepatitis B; measles, mumps, and rubella; and varicella vaccinations. 3. Hematopoietic stem cell transplant.

Vaccinations for Immunocompromised Hosts: Levels of Immunosuppression

- ***High-level Immunosuppression***
  - Combined primary immunodeficiency disorder
  - Receiving cancer chemotherapy
  - Within 2 months after SOT
  - HIV with CD4 count < 200 in adolescents/adults and < 15% in children
  - Daily steroid therapy ≥ 20mg (or > 2mg/kg/day for pts < 10kg) of prednisone or equivalent for ≥ 14 days
  - Certain biologic immune modulators or rituximab
  - HSCT (duration of high level immunosuppression variable)
- ***Low-level immunosuppression***
  - Asymptomatic HIV with CD4 count 200-499 for adolescents/adults and 15-24% in children
  - Lower doses of steroids
  - MTX ≤ 0.4mg/kg/week, azathioprine ≤ 3mg/kg/day, 6-mercaptopurine ≤ 1.5mg/kg/day

Vaccinations for Persons with HIV

<u>If CD4 count > 200</u>
Inactivated influenza
Tdap
Pneumococcal
Meningococcal
HBV
HPV
MMR
Varicella

<u>If CD4 count < 200</u>
Inactivated influenza
Tdap
Pneumococcal
Meningococcal
HBV
HPV
~~MMR~~
~~Varicella~~

Vaccinations for Persons with HIV

•Meningococcal vaccine
  – 0, 8 weeks; then q5 years thereafter
•Pneumococcal vaccine age 19-64
  – PCV13 once, then PPSV23 at least 8 weeks later
  – Repeat PPSV23 5 years later
•No recommendations for either zoster vaccine

Vaccinations for Asplenic Persons

- Live influenza vaccine contraindicated
- Special recommendations
  - Hib (even as adults if not immunized previously or prior to elective splenectomy)
  - MenACWY (q 5 years) and MenB (no recs for booster doses)
  - PCV13 once as adult, followed by PPSV23 at least 8 weeks later; repeat PPSV23 5 years later
- Above vaccines should be given at least 2 weeks prior to elective splenectomy, if possible

Vaccinations for Healthcare Workers

25 year old nursing student is being seen in student health clinic for routine visit. She brings medical records indicating that she received her first dose of hepatitis B vaccine 18 months ago and the second vaccine 1 month thereafter. She asks today if she requires additional doses. No other medical problems and she is not on any other medications.

Which of the following is most appropriate?

A. No additional doses of HBV vaccination needed
B. Restart HBV vaccine series
C. Check hepatitis B surface Ab titer to assess immunity
D. Give 3rd dose of HBV vaccine series today

Vaccines for Healthcare Workers

- Hepatitis B
  - Pre-vaccine serologies not indicated unless born in geographic regions with prevalence ≥ 2%, MSM, PWID, immunosuppressed, liver disease NOS
  - All HCP should be vaccinated with at least 3 doses
  - Should have post-vaccination anti-HBs ≥ 10 mIU/mL (drawn 1-2 months after last dose of vaccine)

Vaccines for Healthcare Workers

Hepatitis B	If you don't have documented evidence of a complete hepB vaccine series, or if you don't have an up-to-date blood test that shows you are immune to hepatitis B (i.e., no serologic evidence of immunity or prior vaccination) then you should • Get the 3-dose series (dose #1 now, #2 in 1 month, #3 approximately 5 months after #2). • Get anti-HBs serologic tested 1–2 months after dose #3.
Flu (Influenza)	Get 1 dose of influenza vaccine annually.
MMR (Measles, Mumps, & Rubella)	If you were born in 1957 or later and have not had the MMR vaccine, or if you don't have an up-to-date blood test that shows you are immune to measles or mumps (i.e., no serologic evidence of immunity or prior vaccination), get 2 doses of MMR (1 dose now and the 2nd dose at least 28 days later). If you were born in 1957 or later and have not had the MMR vaccine, or if you don't have an up-to-date blood test that shows you are immune to rubella, only 1 dose of MMR is recommended. However, you may end up receiving 2 doses, because the rubella component is in the combination vaccine with measles and mumps. For HCWs born before 1957, see the MMR ACIP vaccine recommendations.
Varicella (Chickenpox)	If you have not had chickenpox (varicella), if you haven't had varicella vaccine, or if you don't have an up-to-date blood test that shows you are immune to varicella (i.e., no serologic evidence of immunity or prior vaccination) get 2 doses of varicella vaccine, 4 weeks apart.
Tdap (Tetanus, Diphtheria, Pertussis)	Get a one-time dose of Tdap as soon as possible if you have not received Tdap previously (regardless of when previous dose of Td was received). Get Td boosters every 10 years thereafter. Pregnant HCWs need to get a dose of Tdap during each pregnancy.
Meningococcal	Those who are routinely exposed to isolates of *N. meningitidis* should get one dose.

Resources

- www.cdc.gov/vaccines/recs/ACIP/default.htm
- www.immunize.org/acip

THANK YOU

sdhanir@uw.edu

22

Acute Hepatitis

Dr. David L. Thomas

22 – Acute Hepatitis

Speaker: David Thomas, MD, MPH

2020 INFECTIOUS DISEASE BOARD REVIEW

Acute Hepatitis

David L. Thomas, MD
Stanhope Bayne Jones Professor of Medicine
Johns Hopkins University
Chief of Infectious Diseases
Johns Hopkins School of Medicine

Disclosures of Financial Relationships with Relevant Commercial Interests

- None

Acute Hepatitis

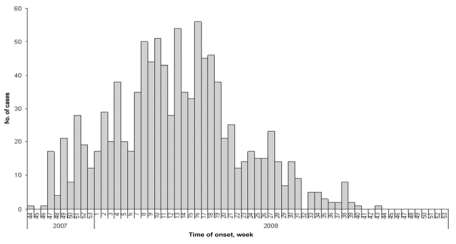
- 42 year old female has malaise and RUQ pain; she just returned from 6 month stay at an IDP camp in north Uganda. She endorses tick and other 'bug' bites and swam in the Nile. 1st HAV vaccine 2 days before departure. Prior HBV vaccine series.
- Exam shows no fever, vitals are normal. RUQ tender. Mild icteric. ALT 1245 IU/ml; TB 3.2 mg/dl; WBC 3.2k nl differential.

Question #1

Which test result is most likely positive?

A. Ebola PCR
B. IgM anti-HEV
C. IgM anti-HAV
D. Schistosomiasis "liver" antigen
E. 16S RNA for Rickettsial organism

1. There are HEV outbreaks, eg. North-Ugandan IDP Camp



Teshale CID 2010

2. Vaccination works vs immune globulin to prevent hepatitis A *even after* exposure

End Points	Per-Protocol Population		Modified Intention-to-Treat Population†	
	Vaccine Group (N=568)	Immune Globulin Group (N=522)	Vaccine Group (N=740)	Immune Globulin Group (N=674)
	number (percent)			
Clinical				
Primary				
Any symptom plus IgM-positive and ALT ≥ twice ULN	25 (4.4)	17 (3.3)	26 (3.5)	18 (2.7)
Secondary				
Any symptom plus IgM-positive and ALT ≥ twice ULN or HAV RNA–positive on PCR‡	29 (5.1)	19 (3.6)	30 (4.1)	20 (3.0)
Jaundice plus IgM-positive and ALT ≥ twice ULN or HAV RNA–positive on PCR	18 (3.2)	12 (2.3)	19 (2.6)	12 (1.8)

Victor NEJM 2007

3. Boards aren't in alphabetical order

Hepatitis E: Key Epidemiologic Points

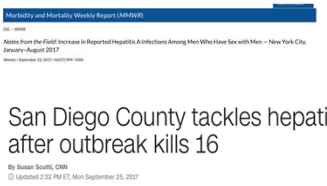
- –Outbreaks – contaminated water in Asia/Africa
- –Sporadic - undercooked meat (BOAR, deer, etc)
- –Overseas travel typical
- –USA: endemic rare, genotype 3, IgG serology positive far more than can be explained by cases - can be hard to interpret

Hepatitis E: Key Clinical Points

- –Diagnosis: RNA PCR; IgM anti-HEV
- –Fatalities in pregnant women
- –Can be chronic in transplant (rarely in HIV)
- –GBS and neurologic manifestations (vs other hep viruses)
- –Pancreatitis

Hepatitis A: Key Epidemiologic Points

- There are outbreaks all over the world now: <u>people</u>


Morbidity and Mortality Weekly Report (*MMWR*)

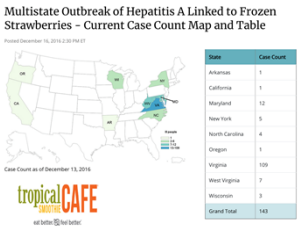
Notes from the Field: Increase in Reported Hepatitis A Infections Among Men Who Have Sex with Men — New York City, January–August 2017

San Diego County tackles hepatitis A after outbreak kills 16

By Susan Scutti, CNN
Updated 2:32 PM ET, Mon September 25, 2017

Hepatitis A: Key Epidemiologic Points

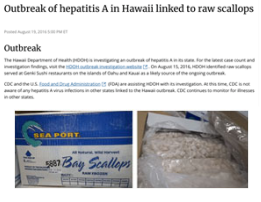
- There are outbreaks all over the world now: <u>places/products</u>


Multistate Outbreak of Hepatitis A Linked to Frozen Strawberries – Current Case Count Map and Table

Case Count as of December 13, 2016

State	Case Count
Arkansas	1
California	1
Maryland	12
New York	5
North Carolina	4
Oregon	1
Virginia	109
West Virginia	7
Wisconsin	3
Grand Total	143

tropical SMOOTHIE CAFE


Outbreak of hepatitis A in Hawaii linked to raw scallops

Outbreak

Hepatitis A: Key Clinical Points

- There are outbreaks all over the world now
- The most common cause of acute hepatitis in USA
- Clinical syndrome
  - –fulminant on HCV
  - –relapsing: symptoms/jaundice recur <12 mo

Vaccination to Prevent Hepatitis A

- *Pre-exposure:* vaccinate
  - Inactivated vaccines USA (HAVRIX,VAQTA)(TWINRIX)
  - HCV or HBV positive persons/chronic liver disease/homeless/MSM/PWID/Travelers/HIV pos/adoptee exposure
  - All children receive hepatitis A vaccine at age 1 since 2006
- *Post-exposure:* vaccinate (and possibly IG)
  - Unless > 40 years or immunosuppressed then IG is 'preferred' (see slide 7)
  - Close exposure (sex or IDU partner) not casual (eg office worker)

Victor NEJM 2007; MMWR May 19, 2006 / 55(RR07) MMWR October 19, 2007 / 56(41);1080-1084

Case 2: Tired and jaundiced

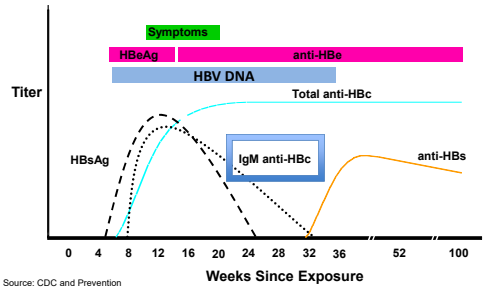
- 21 year old male presents with fatigue and dark urine. PMH neg; MSM, Hx STD, not very careful and at least 1 new ptr. No IDU. No rashes. No penile ulcer or discharge.
- Exam shows no fever, vitals are normal. Mild icteric. ALT 1945 IU/ml; AST 1239 IU/ml; TB 4.2 mg/dl; WBC 3.2k nl differential.
- Total HAV pos; HAV IgM neg; HCV RNA neg; IgM anti-HBc pos; HBsAg pos; RPR neg

Question #2

Which is easiest to justify medically?

A. Anti-HBs for partner
B. Repeat HBsAg in 1 month to see if cleared
C. Discuss TAF/FTC for HBV and HIV PREP
D. HIV testing
E. Repeat HCV RNA with test for HCV antibodies

1. Diagnose acute HBV infection with IgM anti-HBc



2. Recognize HIV can co-occur

- Shared risk factors
- HIV/HBV coinfection is common
- TDF/TAF active against HIV and HBV so status of both needed
- Test for other STD

3. No treatment is needed for acute HBV prevention by HBIG + vaccine

- HBsAg and anti-HBs screening of partners
- Vaccine and HBIG if susceptible

Acute Viral Hepatitis B Key Points

- Most linked to sex, drugs, nosocomial
  - –Nosocomial (fingerstick devices, etc)
  - –Most transmissible (HBV>HCV>HIV)
- Clinical
  - –Acute immune complex disease
  - –Diagnose: IgM anti-core, HBsAg and HBV DNA
  - –New infection vs reactivation (can be IgM pos)

Acute Viral Hepatitis Delta Key Points

- HDV
  - –HBV coinfection
    - Fulminant with acute HBV
  - –HBV superinfection
    - Acute hepatitis in someone with chronic HBV
  - –Test for HDV RNA

Acute Viral Hepatitis C Key Points

- HCV
  - –IDU link (hepatitis in Appalachia)
  - –HIV pos MSM
  - –Acute RNA pos but AB neg or pos
  - –"most likely" in IDU or HIV pos MSM with neg HBsAg

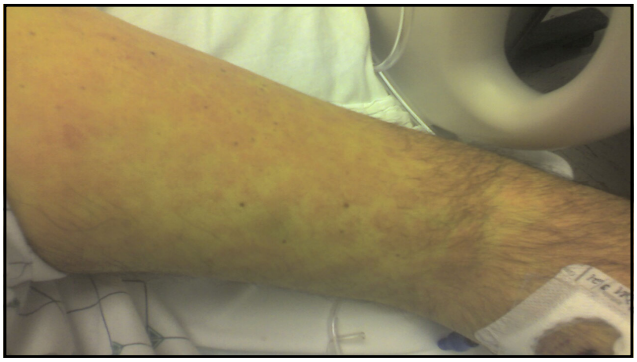
Cox CID 2005

Case 3. 48 year-old with jaundice

- 48 year old found minimally responsive and brought by friends to ED
  - – 1 week malaise, chills, headaches, leg pain and weakness
  - – Eats disposed "food"
- PMH – ETOH, IDU, kidney stones
- SH – homeless
- Baltimore for 20 years, previously Missouri
- FH, ROS non-contributory

Case 3. 48 year-old with jaundice, con't

- T 39.1; BP 80/50; P 110; 95% 4L; sleepy
- Icteric, non-injected, no murmurs or lymphadenopathy
- Diffuse red maculopapular rash
- WBC 98,000 (79 P, 4 B, 5 My/Meta); Hb 7.7; Plt 31,000
- Creatinine 3.9; UA 1+pro; Bicarb 8; INR 2.5; Tbili 41 (direct 31); ALT/AST 146/213
- HCV Ab pos, HIV Ab neg



Case 3. 48 year old with jaundice

The cause of his illness is:

A. Acute hepatitis A
B. Babesia microti
C. Ehrlichia chaffeensis
D. Leptospira icterohaemorrhagiae
E. Zika

Leptospirosis

1. Exposure to fresh water (eg rafting in Hawaii or Costa Rico) OR rats (Baltimore)

Leptospirosis

2. Systemic findings (kidney, eyes, skin, muscle, lungs)

Liver and muscle: flu, adeno, EBV, HIV, malaria, Rickettsia/Ehrlichiosis, tularemia, TSS, coxsackie

Leptospirosis

3. Liver enzymes < bilirubin

Case 4. Hepatitis in the Coast Guard*

- 40 y/o coast guard presents with 1 fever and watery diarrhea
- Has B cell lymphoma; s/p CHOP x4 and 1 week post rituximab
- Lives on E Shore of MD, recent travel to NC with fresh water swimming; extensive travel before including SW USA (recurrent), S America (1 yr); daughter just returned from Ecuqador 1 wk before onset. Has dog, no ticks noted

**Courtesy J Rocco*

Pilot Case History, con't

- T 38.1, Vitals nl; no rash, neuro- WNL
- Hb 11 g/L, WBC 600 (ANC 320), Plt 35,000
- Creat 3.5; no rbc casts
- AST 600, ALT 320, Alk Phos nl, alb 2.6, TBR 2.2
- Ferritin: 180,000

Hepatitis in a pilot

What agent caused this illness?

A. Leptospira icterohaemorrhagiae
B. Hepatitis A virus
C. EBV
D. Ehrlichia chaffeensis
E. Hepatitis G (GB virus C)

Hepatitis with bacterial infections

1. Think Rickettsia/Ehrlichia with exposure, low PMN, and especially low platelets

Hepatitis with bacterial infections

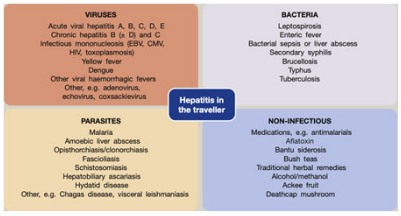
2. Coxiella burnetti and spirochetes (syphilis and lepto) also in ddx but tend to be cholestatic

Hepatitis with bacterial infections

3. Hepatitis F or G are WRONG answers

Hepatitis with travel to developing country

There is a broad differential



Jones Medicine 2017

Hepatitis with travel

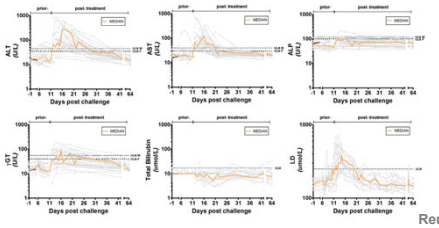
Viral: remember dengue (below), Chickungunya, or Zika

Ref.	Patients	Raised AST	Raised ALT	AST > ALT	Hyper-bilirubinemia	> 10 fold rise (AST, ALT)
Kuo et al[37]	270	93.30%	82.20%	+	7.20%	11.1%, 7.4%
Souza et al[39]	1585	63.40%	45%	+	-	3.4%, 1.8%
Itha et al[41]	45	96%	96%	Equal	30%	-
Wong et al[40]	127	90.60%	71.70%	+ in 75.6%	13.4%	10.2%, 9.5%
Parkash et al[33]	699	95%	86%	+	-	15%
Trung et al[36]	644	97%	97%	+	1.7%	-
Lee et al[14]	690	86%	46%	-	-	1%
Karoli et al[34]	138	92%		+	48%	-
Saha et al[35]	1226				16.9%	

Samanta World J Cases 2015

Hepatitis with travel

Malaria –



Acute human challenge studies

Reuling Ebio Med 2018

Case 5. Hepatitis in Pregnancy

- 24yo 33 wks gestation with nausea and vomiting and RUQ pain. Taking acetaminophen 1gm q 4-6; has dog and bird; recent visit to mom in NC.
- T 37.2; BP 158/110;2/6 SEM; RUQ tender; no rash.
- Plt 103K; Hct 26; WBC 6.6 10%L; PMN 82%; G 85; creat 0.6; ALT 225; AST 559; TB 1.4; CRP 15.8; PT WNL; fibrinogen NL.

Hepatitis in pregnancy

What is the best diagnosis?

A. HELLP
B. Acute fatty liver of pregnancy
C. HAV infection
D. HSV infection
E. HEV

Hepatitis in pregnancy

1. Rule out HSV
   ~50% have muco-cutaneous lesions

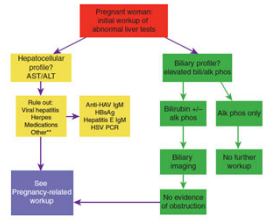


Figure 1. Workup of abnormal liver test in pregnant woman. **Other differential diagnosis to consider if clinically appropriate: AIH, Wilson disease.

ACOG 2016

Hepatitis in pregnancy

2. HELLP
   – HTN and can occur post partum
   – Fibrinogen high vs. sepsis and AFLP

3. AFLP – severe and low glucose, inc INR, low fibrinogen (Swansea criteria)

Case 6. Fulminant hepatitis

- 65 year old man with hx of jaundice. 2 weeks before finished amoxacillin/clavulanate acid for sinusitis. Hx of HTN on HCTZ and rosuvastatin. ETOH: 2 drinks per day.
- TB24; ALT 162 U/L; AST 97 U/L ALK P 235 U/L. IgM anti-HAV neg; IgM anti-HBc neg; HCV RNA neg. RUQ US neg.

Question: Fulminant Hep

Which of the following is the most likely cause of hepatitis:

A. **toxicity from amox/clav**
B. **alcohol**
C. **porphyria flare**
D. **leptospirosis**
E. **statin**

Drug related liver toxicity

1. Amoxicillin/clavulanate is most common
- **Cholestatic or mixed**
- **Often AFTER stopping**
- **1/2500 Rx**
- **DRB1*1501**
- **clavulanate>amoxicillin**

Rank	Agent	Year of FDA Approval	No. (%)†	Major Phenotypes
1	Amoxicillin-clavulanate	1984	91 (10.1)	Cholestatic or mixed hepatitis
2	Isoniazid	1952	48 (5.3)	Acute hepatocellular hepatitis
3	Nitrofurantoin	1953	42 (4.7)	Acute or chronic hepatocellular hepatitis
4	TMP-SMZ	1973	31 (3.4)	Mixed hepatitis
5	Minocycline	1971	28 (3.1)	Acute or chronic hepatocellular hepatitis
6	Cefazolin	1973	20 (2.2)	Cholestatic hepatitis
7	Azithromycin	1991	18 (2.0)	Hepatocellular, mixed, or cholestatic hepatitis
8	Ciprofloxacin	1987	16 (1.8)	Hepatocellular, mixed, or cholestatic hepatitis
9	Levofloxacin	1996	13 (1.4)	Hepatocellular, mixed, or cholestatic hepatitis
10	Diclofenac	1988	12 (1.3)	Acute or chronic hepatocellular hepatitis
11	Phenytoin	1946	12 (1.3)	Hepatocellular or mixed hepatitis
12	Methyldopa	1962	11 (1.2)	Hepatocellular or mixed hepatitis
13	Azathioprine	1968	10 (1.1)	Cholestatic hepatitis

http://livertox.nlm.nih.gov; Hoofnagle NEJM 2019

Drug related liver toxicity

2. Watch for hypersensitivity

Dilantin, Abacavir, Nevirapine,

http://livertox.nlm.nih.gov

Acute hepatitis in HIV

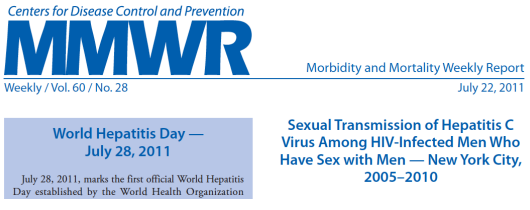
46 y/o HIV pos male, CD4+ lymphocyte 235/ml^3, HIV RNA undetect; HBsAg pos; no symptoms on TDF/FTC/RAL. Liver enzymes increased from ALT of 46 to 1041 IU/L. TB was 2.3. He has a long history of various ART regimens. He is sexually active with other men.

Acute hepatitis in HIV

Which of the following is the most likely cause of hepatitis:

A. **toxicity from the RAL**
B. **acute HCV infection**
C. **IRIS**
D. **resistant HBV**
E. **HDV**

Recognize acute HCV in HIV POS MSM



22 – Acute Hepatitis

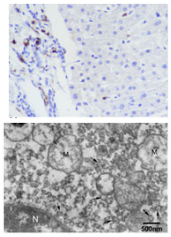
Speaker: David Thomas, MD, MPH

Hepatitis in 2020: SARS-CoV-2

Table 2. Laboratory and radiographic findings of patients with COVID-

	All patients (N = 788)
Leukocytes, $\times 10^9$/L	4.8 (3.8-6.0)
Neutrophils, $\times 10^9$/L	3.0 (2.2-4.0)
Lymphocytes$\times 10^9$/L	1.2 (0.9-1.6)
≥0.8$\times 10^9$/L	654 (83.0)
<0.8$\times 10^9$/L	134 (17.0)
Platelets, $\times 10^9$/L	181 (147-221)
≥100$\times 10^9$/L	761 (96.6)
<100$\times 10^9$/L	27 (3.4)
Hemoglobin, g/L	138.0 (127.0-151.0)
International normalized ratio	1.02 (0.97-1.09)
Albumin, g/L	41.4 (38.3-43.8)
Alanine aminotransferase, U/L	21.1 (15.0-33.0)
Aspartate aminotransferase, U/L	25.0 (19.6-33.0)

Hao Am J Gastro 2020



Wang J Hepatol 2020

Acute Hepatitis Summary

- Acute A: vaccine effective
- HEV: chronic in transplant and/or boar
- HIV: acute HCV in MSM
- Ehrlichial or rickettsial
- Find the lepto case (jaundice>hepatitis)

BREAK

Case 4. Hepatitis in a pilot

- 70 y/o pilot presents with 1 week of fever, diarrhea and sweats, then "collapse"
- Tooth extraction 1 month before, E. Shore of Maryland and extensive travel, chelation "treatment"
- T 38.1, 135/70, 85, 18, 97% on 2L; few small nodes, soft systolic M, petechial rash on legs, neuro- WNL

Pilot Case History, con't

- Hct 33%, WBC 1.4 K (81% P 10% L), Plt 15,000
- Creat 2.8
- AST 495, ALT 159, Alk Phos 47, alb 2.6, TBR 0.8
- CPK 8477
- CXR: infiltrate LLL

Hepatitis in a pilot

What agent caused this illness?

A. Leptospira icterohaemorrhagiae
B. Hepatitis A
C. EBV
D. Ehrlichia chaffeensis
E. Hepatitis G (GB virus C)

23

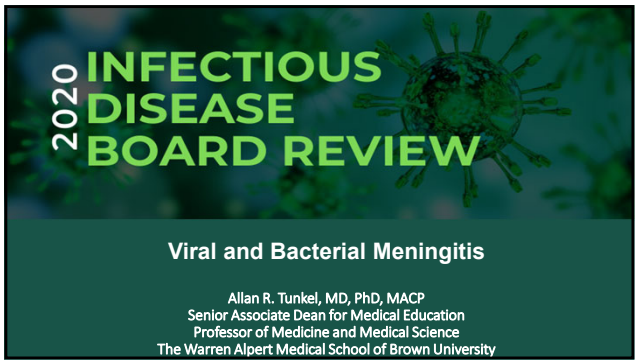
Viral and Bacterial Meningitis

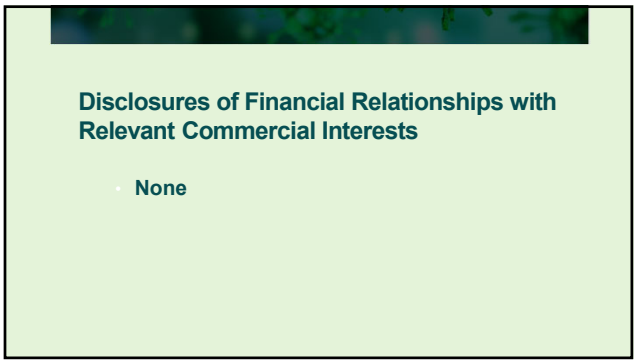
Dr. Allan Tunkel

Page left blank intentionally.

23 –Viral and Bacterial Meningitis

Speaker: Allan Tunkel, MD





CASE #1

- 38-year-old woman presents with a 2-day history of fever, headache and stiff neck; similar episodes have occurred every 3-4 months over several years, with spontaneous abatement after 4-5 days
- She is sexually active only with her husband of 8 years, and has 2 children at home (ages 2 and 5 years)
- On exam, T 99.8ºF and other vital signs are normal; she has evidence of meningismus, but is alert and oriented and with no focal findings
- Laboratory studies are normal
- CSF analysis reveals a WBC of 70/mm^3 (100% lymphs), glucose of 60 mg/dL, and protein of 100 mg/dL; Gram stain negative

QUESTION #1

Which of the following is the most likely etiology of this patient's meningitis?

A. Coxsackie A virus
B. Coxsackie B virus
C. Human immunodeficiency virus
D. Herpes simplex virus type 2
E. Human herpesvirus 6

VIRAL MENINGITIS Major Etiologies

- Enteroviruses
- Mumps virus
- Herpesviruses
- Lymphocytic choriomeningitis virus
- Others
  - Arboviruses
  - Human immunodeficiency virus
  - Adenovirus
  - Parainfluenza virus types 2 and 3

Cerebrospinal Fluid Findings in Viral Meningitis

CSF Parameter	Viral
Opening pressure	≤ 250 mm H_2O
WBC count	50-1000/mm^3
WBC differential	Lymphocytes
Glucose	>45 mg/dL
CSF: serum glucose	>0.6
Protein	<200 mg/dL
Gram stain	Negative

Enteroviruses

- Leading cause of "aseptic" meningitis syndrome
- Accounts for 85-95% of cases with identified etiology
- 30,000-75,000 cases annually in US (low estimate)
- Summer/fall seasonality; outbreaks reported
- Fecal-oral spread
- ~100 serotypes; 14 account for 80% of isolates
- CEMA (chronic enteroviral meningoencephalitis in agammaglobulinemia)
- Rituximab

Enteroviruses

- Clinical clues
  - Time of year
  - Outbreak in community
  - Other recognizable enteroviral syndromes
- Specific etiologies
  - Scattered maculopapular rash: echovirus 9
  - Herpangina: coxsackievirus A
  - Pericarditis/pleuritis: coxsackievirus B
  - Rhombencephalitis: enterovirus 71

Enteroviruses

- Symptoms and signs
  - Fever, headache, nuchal rigidity (>50%), photophobia
- Diagnosis
  - Neutrophils may predominate in CSF early (up to 48 hrs)
  - CSF virus isolation (sensitivity 65-75%)
  - Virus isolation from throat or rectum
  - PCR (sensitivity 86-100%; specificity 92-100%)
- Therapy
  - Supportive

Mumps Virus

- Common in unimmunized populations
- Occurs in 10-30% of mumps patients overall
- Peak in children 5-9 years of age; males>females
- Can occur in patients without parotitis; 40-50% have no evidence of salivary gland enlargement
- Symptoms and sign usually follow onset of parotitis (if present) by ~5 days
- Diagnosis
  - Serology
  - CSF RT-PCR
  - CSF culture (sensitivity 30-50%)

Herpes Simplex Virus

- Self-limited syndrome
- Most commonly with primary HSV-2 genital infection
  - 36% of women
  - 13% of men
- Less likely with recurrence of genital herpes
- Recurrent benign lymphocytic meningitis (Mollaret)
  - Most caused by HSV-2
  - Few or at least 10 episodes lasting 2-5 days followed by spontaneous recovery
  - Fever, headache, photophobia, meningismus

Herpes Simplex Virus

- Diagnosis
  - Lymphocytic pleocytosis (<500 cells/mm^3); normal glucose, elevated protein
  - CSF PCR
- Therapy
  - Usually self-limited; unclear if antiviral therapy alters course of mild meningitis
  - Suppressive therapy (valacyclovir) not indicated for recurrent disease; associated with a higher frequency of meningitis after cessation of active drug

Lymphocytic Choriomeningitis Virus

- Now rarely reported as an etiologic agent
- Transmitted to humans by contact with rodents (hamsters, rats, mice) or their excreta
- Risk groups
  - Laboratory workers
  - Pet owners
  - Persons living in impoverished or unhygienic places
  - Rodent breeding factory
- No evidence of human-to-human transmission

CASE #2

- 60-year-old man with chronic kidney disease immigrated from Brazil to the US and underwent a cadaveric renal transplant
- Prior to transplant, he had episodes of recurrent epigastric pain. At the time, his WBC was 6,500/mm^3 with 15% eosinophils
- After transplant, he received immunosuppressive therapy

CASE #2

- Presented 1 month later with headache, meningismus and altered mental status, and a temperature of T 39°C
- Lumbar puncture had WBC 2500/mm^3 (98% neutrophils), glucose 20 mg/dL, and protein 450 mg/dL
- Placed on empiric antimicrobial therapy with vancomycin, ampicillin, and ceftriaxone
- Cultures of blood and CSF grew *Escherichia coli*

Question #2

Which of the following diagnostic tests would most likely establish the pathogenesis of *E. coli* meningitis in this patient?

A. MRI of the head and sinuses
B. Right upper quadrant ultrasound
C. Serial stool examinations
D. Cisternography
E. Colonoscopy

EPIDEMIOLOGIC FEATURES OF PNEUMOCOCCAL MENINGITIS

- Most common etiologic agent in US (58% of cases)
- Mortality of 18-26%
- Associated with other suppurative foci of infection
  - Pneumonia (25%)
  - Otitis media or mastoiditis (30%)
  - Sinusitis (10-15%)
  - Endocarditis (<5%)
  - Head trauma with CSF leak (10%)

EPIDEMIOLOGIC FEATURES OF MENINGOCOCCAL MENINGITIS

- Children and young adults; mortality 3-13%
- Serogroups A, B, C, W, and Y
- Serogroup B disease in recent outbreaks (Princeton, UC-Santa Barbara, Providence College)
- Predisposition in those with congenital deficiencies in terminal complement components (C5-C8, and perhaps C9) and properdin deficiencies
- Increased risk: MSM, HIV infection, eculizumab

EPIDEMIOLOGIC FEATURES OF GROUP B STREPTOCOCCAL MENINGITIS

- Important etiologic agent in neonates; mortality 7-27%
- Early-onset septicemia associated with prematurity, premature rupture of membranes, low birth weight
- Late onset meningitis (> 7 days after birth)
- Disease in adults associated with the following:

Diabetes mellitus	Parturient women
Cardiac, hepatic, renal disease	Malignancy
Collagen-vascular disorders	Alcoholism
HIV infection	Corticosteroid use

EPIDEMIOLOGIC FEATURES OF *LISTERIA* MENINGITIS

- Rare etiology in US (2-8%); mortality 15-29%
- Outbreaks associated with consumption of contaminated cole slaw, raw vegetables, milk, cheese, processed meats, cantaloupe, diced celery, ice cream, hog head cheese
- Common in neonates
- Low in young, previously healthy persons (4-10%)
- Disease in adults associated with:

Elderly	Alcoholism
Malignancy	Immune suppression
Diabetes mellitus	Hepatic and renal disease
Iron overload	Collagen-vascular disorders
HIV infection	Biologic therapies

EPIDEMIOLOGIC FEATURES OF AEROBIC GRAM-NEGATIVE BACILLARY MENINGITIS

- *Klebsiella* species, *Escherichia coli*, *Serratia marcescens*, *Pseudomonas aeruginosa*, *Acinetobacter baumannii*, *Salmonella* species
- Isolated from CSF of patients following head trauma or neurosurgical procedures
- Cause meningitis in neonates, the elderly, immunocompromised patients, and in patients with gram-negative septicemia
- Associated with disseminated strongyloidiasis in the hyperinfection syndrome

EPIDEMIOLOGIC FEATURES OF *HAEMOPHILUS INFLUENZAE* MENINGITIS

- Causes 7% of cases in US; mortality 3-7%
- Capsular type b strains were previously in >90% of serious infections; children <6 years of age (peak 6-12 months)
- Concurrent pharyngitis or otitis media in >50% of cases
- Disease in persons >6 years of age associated with:

Sinusitis or otitis media	Pneumonia
Sickle cell disease	Splenectomy
Diabetes mellitus	Immune deficiency
Head trauma with CSF leak	Alcoholism

OTHER BACTERIAL ETIOLOGIES OF MENINGITIS

Bacterial Etiology	Risk Factors
Staphylococcus aureus	Neurosurgery, trauma, diabetes mellitus, alcoholism, hemodialysis, injection drug use, malignancy
Staphylococcus epidermidis	CSF shunts and drains
Diphtheroids (e.g., *Cutibacterium acnes*)	CSF shunts and drains
Anaerobes	Contiguous foci in head and neck
Streptococcus salivarius	Spinal anesthesia, myelogram
Streptococcus suis	Vietnam, eating undercooked pig blood or pig intestine, pig exposure

INCIDENCE OF BACTERIAL MENINGITIS (UNITED STATES)

Organism	Incidence (cases per 100,000)		
	1986	1995	2006-2007
H. influenzae	2.9	0.2	0.08
S. pneumoniae	1.1	1.1	0.81
N. meningitidis	0.9	0.6	0.19
Group B streptococcus	0.4	0.3	0.25
L. monocytogenes	0.2	0.2	0.05

23 –Viral and Bacterial Meningitis

Speaker: Allan Tunkel, MD

CEREBROSPINAL FLUID FINDINGS IN BACTERIAL VERSUS VIRAL MENINGITIS

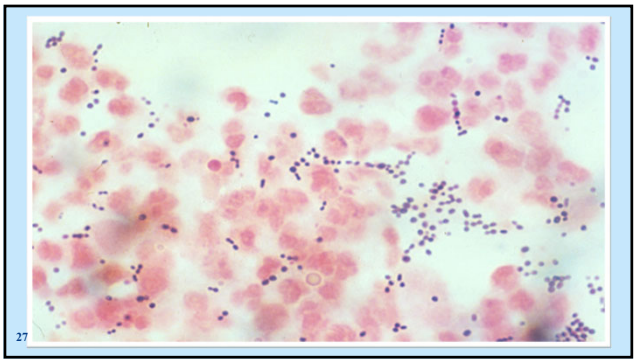
25

CSF Parameter	Bacterial	Viral
Opening pressure	200-500 mm H_2O	≤ 250 mm H_2O
WBC count	1000-5000/mm^3	50-1000/mm^3
WBC differential	Neutrophils	Lymphocytes
Glucose	<40 mg/dL	>45 mg/dL
CSF: serum glucose	≤ 0.4	>0.6
Protein	100-500 mg/dL	<200 mg/dL
Gram stain	(+) in 60-90%	Negative

CASE #3

26

- A 35-year-old woman presents to the hospital with a 2-day history of fever, chills, headache, and confusion. She has a history of diabetes mellitus and recently delivered a healthy child
- T 40.5°C, P 140, RR 32, BP 90/60 mmHg
- Obtunded, stiff neck
- WBC 30,000/mm^3 (40% bands), platelets 20,000/mm^3
- Lumbar puncture revealed an opening pressure of 280 mm H_2O, WBC 2500/mm^3 (99% segs), glucose 20 mg/dL, and protein 400 mg/dL



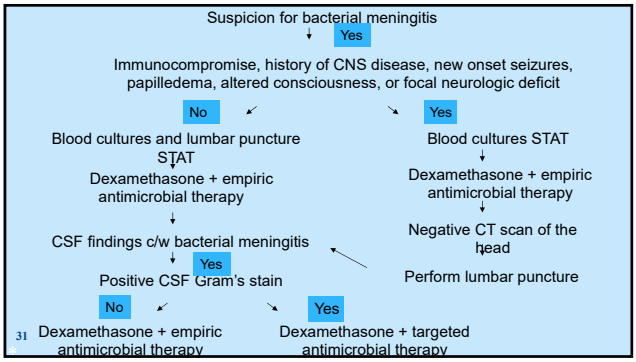
27

Question #3

28

In addition to adjunctive dexamethasone, which of the following regimens should be initiated?

A. Ampicillin + gentamicin
B. Ampicillin + ceftriaxone
C. Vancomycin + ampicillin
D. Vancomycin + ceftriaxone
E. Vancomycin + trimethoprim-sulfamethoxazole



31

EMPIRIC ANTIMICROBIAL THERAPY OF PURULENT MENINGITIS

30

Age	Antimicrobial Therapy
<1 month	Ampicillin + cefotaxime; ampicillin + cefepime
1-23 months	Vancomycin + a third-generation cephalosporin[a]
2-50 years	Vancomycin + a third-generation cephalosporin[a,b,c]
Older than 50 years	Vancomycin + ampicillin + a third-generation cephalosporin[a]

[a]ceftriaxone or cefotaxime
[b]some experts would add rifampin if dexamethasone is also given
[c]add ampicillin if Listeria is suspected

EMPIRIC ANTIMICROBIAL THERAPY OF PURULENT MENINGITIS

Predisposing Condition	Antimicrobial Therapy
Immunocompromise	Vancomycin + ampicillin + either meropenem or cefepime
Basilar skull fracture	Vancomycin + a third generation cephalosporin[a]
Head trauma or after neurosurgery	Vancomycin + either ceftazidime or cefepime or meropenem
Cerebrospinal fluid shunt or drain	Vancomycin + either ceftazidime or cefepime or meropenem

[a]ceftriaxone or cefotaxime

TARGETED ANTIMICROBIAL THERAPY IN BACTERIAL MENINGITIS

Microorganism	Antimicrobial Therapy
S. pneumoniae	Vancomycin + a third-generation cephalosporin[a,b]
N. meningitidis	Third-generation cephalosporin[a]
H. influenzae	Third-generation cephalosporin[a]
L. monocytogenes	Ampicillin or penicillin G[c]

[a]ceftriaxone or cefotaxime
[b]addition of rifampin may be considered, especially if dexamethasone given
[c]addition of an aminoglycoside may be considered

ANTIMICROBIAL THERAPY IN BACTERIAL MENINGITIS

Organism	Antimicrobial Therapy
Streptococcus pneumoniae	
PCN MIC ≤0.06 μg/mL	Penicillin G or ampicillin
PCN MIC ≥0.12 μg/mL	
CTX[a] MIC <1.0 μg/mL	Third-generation cephalosporin[a]
CTX[a] MIC ≥1.0 μg/mL	Vancomycin + a third-generation cephalosporin[a,b]

[a]ceftriaxone or cefotaxime
[b]consider addition of rifampin if ceftriaxone MIC >4 μg/mL

ANTIMICROBIAL THERAPY IN BACTERIAL MENINGITIS

Organism	Antimicrobial Therapy
Neisseria meningitidis	
PCN MIC <0.1 μg/mL	Penicillin G or ampicillin
PCN MIC 0.1-1.0 μg/mL	Third-generation cephalosporin[a]
Haemophilus influenzae	
β-lactamase-negative	Ampicillin
β-lactamase-positive	Third-generation cephalosporin[a]

[a]ceftriaxone or cefotaxime

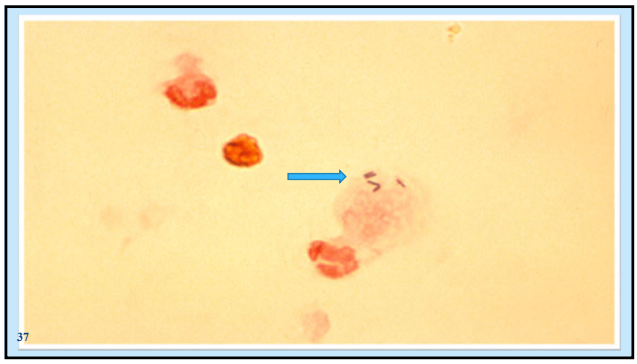
ANTIMICROBIAL THERAPY IN BACTERIAL MENINGITIS

Organism	Antimicrobial Therapy
Pseudomonas aeruginosa	Ceftazidime or cefepime or meropenem
Acinetobacter baumannii	Meropenem or colistin (formulated as colistimethate sodium)[a] or polymyxin B[a]
Streptococcus agalactiae	Ampicillin or penicillin G[b]
Listeria monocytogenes	Ampicillin or penicillin G[b]
Staphylococcus aureus	
MSSA	Nafcillin or oxacillin
MRSA	Vancomycin

[a]might also need to be administered by intraventricular or intrathecal routes
[b]addition of an aminoglycoside should be considered

CASE #4

- 60-year-old male with chronic lymphocytic leukemia presented with fever, headache, ataxia, and altered mental status. Recently traveled to an outdoor family picnic in rural Virginia. He is allergic to penicillin (anaphylaxis)
- T 102°F, P 120, RR 24, BP 100/60 mmHg
- He was obtunded and had nuchal rigidity
- WBC was 25,000/mm^3 (30% bands)
- LP revealed a WBC 1500/mm^3 (50 neutrophils, 50% lymphocytes), glucose 30 mg/dL, and protein 200 mg/dL



37

Question #4

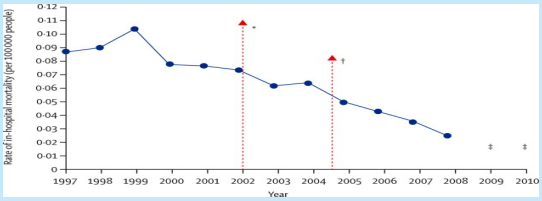
Which of the following antimicrobial regimens should be initiated?

A. Vancomycin
B. Trimethoprim-sulfamethoxazole
C. Chloramphenicol
D. Moxifloxacin
E. Daptomycin

ADJUNCTIVE DEXAMETHASONE IN BACTERIAL MENINGITIS

- Attenuates subarachnoid space inflammatory response resulting from antimicrobial-induced lysis
- Recommended for infants and children with *Haemophilus influenzae* type b meningitis and considered for pneumococcal meningitis in childhood, given before or with parenteral antimicrobial therapy
- Recommended in adults with pneumococcal meningitis
- Administer at 0.15 mg/kg IV every 6 hours for 4 days in adults concomitant with or just before first antimicrobial dose

IN-HOSPITAL MORTALITY FOR PNEUMOCOCCAL MENINGITIS



Castelblanco et al. Lancet ID 2014;14:813

24

Chronic Hepatitis

Dr. David Thomas

24 – Chronic Hepatitis

Speaker: David Thomas, MD, MPH

2020 INFECTIOUS DISEASE BOARD REVIEW

Chronic Hepatitis

David L. Thomas, MD
Stanhope Bayne Jones Professor of Medicine
Johns Hopkins University
Chief of Infectious Diseases
Johns Hopkins School of Medicine

Disclosures of Financial Relationships with Relevant Commercial Interests

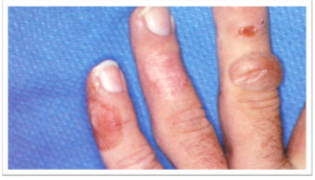
- None

Chronic Hepatitis and Liver Disease

- HCV
- HBV (and delta)
- Other forms
- HIV coinfection
- NB: extra slides are included for updated information

Hepatitis C and a rash

A 44 year old, anti-HCV and HCV RNA positive man feels bad after a recent alcohol binge. He has a chronic rash on arms that is worse and elevated ALT and AST.



OConnor Mayo Clin Proc 1998

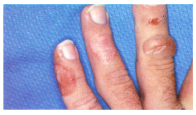
HCV with a rash

The most likely dx is:

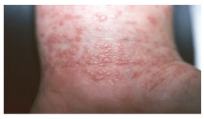
A. Cirrhosis due to HCV and alcohol
B. Vibrio vulnificus
C. Porphyria cutanea tarda
D. Essential mixed cryoglobulinemia
E. Yersinia infection

Compare

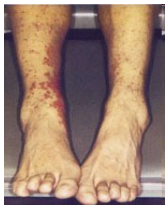
Porphyria cutanea tarda



Lichen planus



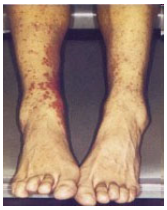
Cryoglobulin vasculitis



blogspot.com; OConnor Mayo Clin Proc 1998

More HCV and rash

55 year old with cirrhosis untreated 1a HCV and



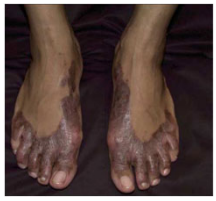
HCV with a rash

What can you counsel:

A. **Rash will likely improve with HCV treatment**
B. **Cryoglobulin blood level closely tracks disease**
C. **Needs a renal biospy**
D. **Needs steroids before HCV treatment**

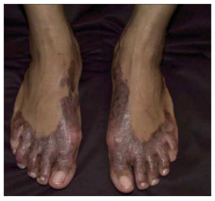
HCV and rash

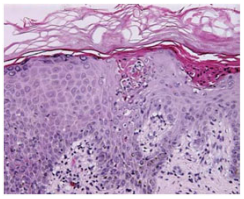
46 year old woman with cirrhosis untreated 1b HCV and



HCV and rash

46 year old woman with cirrhosis untreated 1b HCV and





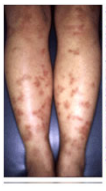
HCV with a rash

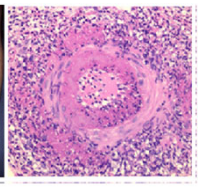
The most likely dx is:

A. **Necrolytic acral erythema**
B. **Porphyria cutanea tarda**
C. **Essential mixed cryoglobulinemia**
D. **Secondary syphilis**
E. **Pemphigus psoriaticus**

HBV and rash

46 year old woman HBsAg pos, anti-HCV neg





Chen Rheum 2014

HBV with a rash

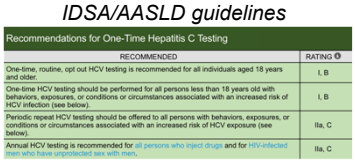
The most likely dx is:

A. Necrolytic acral erythema
B. Porphyria cutanea tarda
C. Essential mixed cryoglobulinemia
D. Polyarteritis nodosa
E. Secondary syphilis vasculitis

Who needs an HCV antibody test?

A. 33 year old woman with normal ALT and negative test during pregnancy at 28
B. 55 year old man s/p HCV treatment
C. 24 year old pregnant woman with no risk factors
D. Former PWID who was HCV negative 1 yr ago
E. HIV positive MSM with negative HCV antibody test 5 years ago and no risk factors

IDSA/AASLD guidelines



Recommendations for One-Time Hepatitis C Testing

RECOMMENDED	RATING
One-time, routine, opt out HCV testing is recommended for all individuals aged 18 years and older.	I, B
One-time HCV testing should be performed for all persons less than 18 years old with behaviors, exposures, or conditions or circumstances associated with an increased risk of HCV infection (see below).	I, B
Periodic repeat HCV testing should be offered to all persons with behaviors, exposures, or conditions or circumstances associated with an increased risk of HCV exposure (see below).	IIa, C
Annual HCV testing is recommended for all persons who inject drugs and for HIV-infected men who have unprotected sex with men.	IIa, C

USPSTF 2020

RECOMMENDATION The USPSTF recommends screening for HCV infection in adults aged 18 to 79 years. (B recommendation)

JAMA. doi:10.1001/jama.2020.1123
Published online March 2, 2020.

54 y/o with HCV antibodies and RNA

54 year old Caucasian man was anti-HCV pos after elevated ALT noted by primary. Brief IDU when 20-21; moderate ETOH; otherwise well.

HCV RNA 4 million IU/L; Genotype 1a; ALT 42 IU/ml; AST 65 IU/ml; TB 1.6 mg/dl; Alb 3.9 mg/dl; Hb – 13.4 mg/dl; PLT 110,000; creatinine 1.2 mg/dl; HBsAg pos; anti-HBc pos. HIV neg

54 y/o with HCV antibodies and RNA

Which of the following is the next appropriate step:

A. Treat with oral regimen for 12 weeks
B. Check HCV 1a resistance test
C. Elastography
D. Confirm HCV antibody test
E. Repeat skin exam looking for acral necrolysis

HCV NS5 RAS testing is uncommonly recommended

Treatment naive	*Treatment experienced*
• Genotype 1a and elbasvir/grazoprevir	• 1a and ledipasvir/sofosbuvir 'considered'
• Genotype 3 AND cirrhosis for sofosbuvir/velpatasvir	• Genotype 3 and sofosbuvir/velpatasvir

NB: no PI resistance testing
Clinically sig is >100-fold in vitro

Wyles, HCVguidelines.org

Staging is needed for chronic HCV

1. Drug approvals
2. Rule out cirrhosis
   - Treatment duration and safety
   - Screen for HCC and/or varices

Hcvguidelines.org

Staging is needed for chronic HCV

Accepted staging methods	Not for routine staging
1. Liver biopsy	1. Viral load
2. Blood markers	2. HCV genotype
3. Elastography	3. Ultrasound
4. Combinations of 1-3	4. CT scan or MRI

Hcvguidelines.org

Liver staging pearls

- FIB4 is great value

Liver staging pearls

$$\text{FIB 4} = \frac{\text{Age (yrs) x AST (U/L)}}{\text{Platelet count } (10^9/\text{L}) \text{ x ALT (U/L)}^{1/2}}$$

847 liver biopsies with chronic HCV

	Liver Biopsy (METAVIR)		
FIB4 Index	F0-F1-F2	F3-F4	Total
<1.45	94.7% (n = 521)	5.3% (n = 29)	550
1.45-3.25	73.0% (n = 168)	27.0% (n = 62)	230
>3.25	17.9% (n = 12)	82.1% (n = 55)	67
Total	82.8% (n = 701)	17.2% (n = 146)	847

Sterling Hepatology 2006; Vallet-Pichard Hepatology 2007

Liver staging pearls

- Fib -4 is great value
  - (but doesn't work for insurance approval)
- Transient elastography balances sensitivity and specificity

Validity of Noninvasive Tests for Cirrhosis*

Test	% Sens	% Spec	AUROC
Fibrotest[1] >.56	85	74	.86
Fibrotest > .73	56	81	-
FIB4[2], >1.45	87	61	.87
APRI[3], >1.0	51	91	0.73
Elastography 12.5 kPa	89	91	0.95

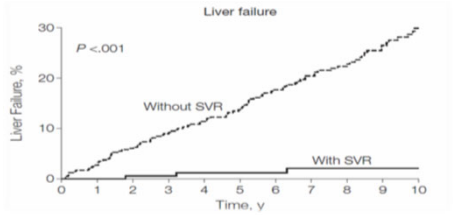
Singh Gastro 2017; Chou Ann Intern Med 2013; Castera Gastro 2012

54 year old with HCV

Elastography (17.3 kPa) and Fib-4 (5.5) consistent with cirrhosis. Ultrasound and UGI are ok and you recommend treatment but he wants to know why. Which is NOT true of successful treatment?

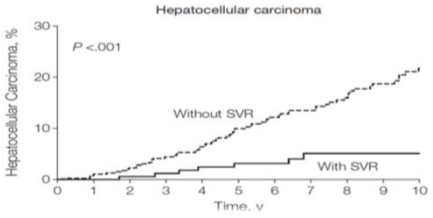
A. **reduces risk of reinfection**
B. **reduces risk of death**
C. **reduces risk of HCC**
D. **reduces risk of liver failure**

SVR reduces clinical outcomes



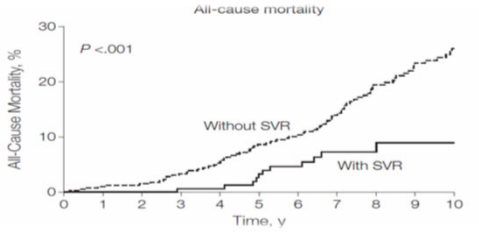
Van der Meer, *JAMA* 2012. Backus, *Clin Gastro* 2011. Imazeki, *Hepatology* 2003. Shiratori, *Ann Intern Med* 2005. Veldt, *Ann Intern Med* 2007. Berenguer, *Hepatology* 2009.

SVR reduces clinical outcomes



Van der Meer, *JAMA* 2012. Backus, *Clin Gastro* 2011. Imazeki, *Hepatology* 2003. Shiratori, *Ann Intern Med* 2005. Veldt, *Ann Intern Med* 2007. Berenguer, *Hepatology* 2009.

SVR reduces clinical outcomes



Van der Meer, *JAMA* 2012. Backus, *Clin Gastro* 2011. Imazeki, *Hepatology* 2003. Shiratori, *Ann Intern Med* 2005. Veldt, *Ann Intern Med* 2007. Berenguer, *Hepatology* 2009.

AASLD — HCV Guidance: Recommendations for Testing, Managing, and Treating Hepatitis C — IDSA Infectious Diseases Society of America

Home | Test, Evaluate, Monitor | Treatment-Naive | Treatment-Experienced | Unique & Key Populations | About

RECOMMENDED	DURATION	RATING
Daily fixed-dose combination of elbasvir (50 mg)/grazoprevir (100 mg) for patients without baseline NS5A RASs[b] for elbasvir	12 weeks	I, A
Daily fixed-dose combination of glecaprevir (300 mg)/pibrentasvir (120 mg)[c]	12 weeks	I, A
Daily fixed-dose combination of ledipasvir (90 mg)/sofosbuvir (400 mg)	12 weeks	I, A
Daily fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg)	12 weeks	I, A

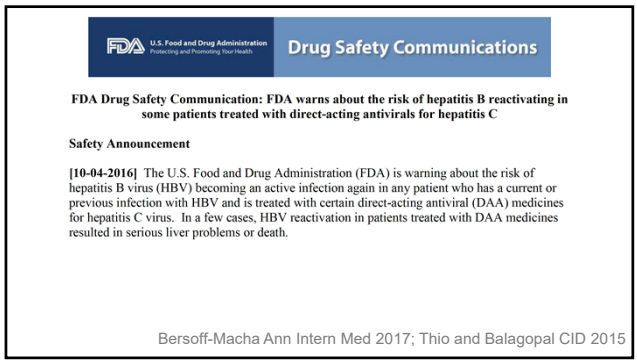
54 y/o with HCV antibodies, RNA, and cirrhosis

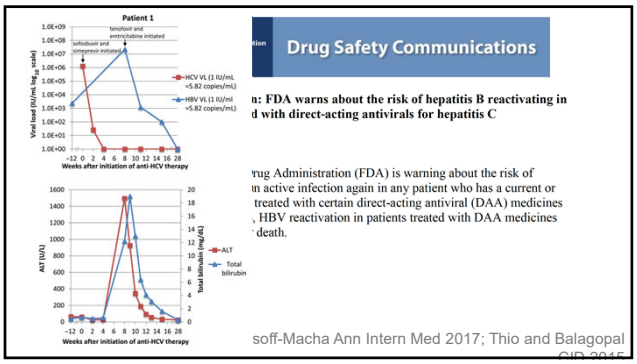
Treatment is given with glecaprevir and pibrentasvir

Treatment week 8: HCV RNA undet; ALT 1279 IU/L; AST 987 IU/L; TB 3.2 mg/dl.

Which test is likely to be most helpful?

A. Glecaprevir level
B. HCV resistance test
C. GGT
D. HBV DNA
E. Liver biopsy with EM





Flare of HBV with DAA treatment of HCV

- All are tested for HBV
  - HBsAg pos: treat per HBV guidelines
  - Anti-HBc pos: monitor

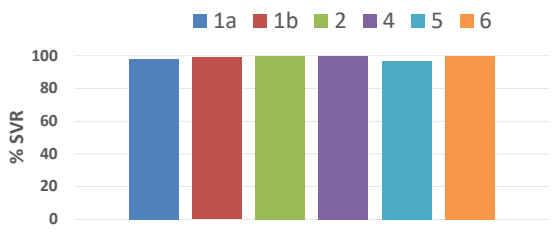
Bersoff-Macha Ann Intern Med 2017; Thio and Balagopal CID 2015

A. Glecaprevir and pibrentasvir
B. Sofosbuvir and velpatasvir
C. Sofosbuvir and ledipasvir
D. Elbasvir and grazoprevir

Which 2 regimens are pangenotypic?

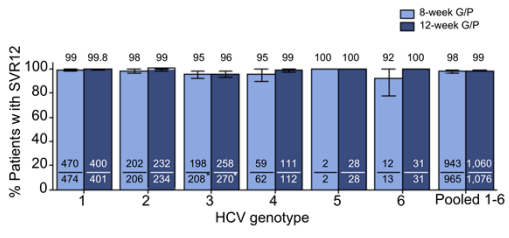
1. **A and B**
2. **A and C**
3. **B and C**
4. **C and D**

Sofosbuvir and velpatasvir for 12 weeks among 624 patients with chronic hepatitis C



Feld NEJM 2015

Glecaprevir and pibrentasvir for chronic hepatitis C



Puoti J Hepatol 2018

A. Glecaprevir and pibrentasvir
B. Sofosbuvir and velpatasvir
C. Sofosbuvir and ledipasvir
D. Elbasvir and grazoprevir

Which regimens are approved for ESRD?

1. A and B
2. A and C
3. A, B and C
4. A, B, C and D

A. Glecaprevir and pibrentasvir
B. Sofosbuvir and velpatasvir
C. Sofosbuvir and ledipasvir
D. Elbasvir and grazoprevir

Which regimens have concerns with TDF?

1. A and B
2. B and C
3. A, B and C
4. A, B, C and D

A. Glecaprevir and pibrentasvir
B. Sofosbuvir and velpatasvir
C. Sofosbuvir and ledipasvir
D. Elbasvir and grazoprevir

Which regimen is recommended with etravirine?

1. A
2. B
3. C
4. D

		Ledipasvir/ Sofosbuvir (LDV/SOF)	Sofosbuvir/ Velpatasvir (SOF/VEL)	Elbasvir/ Grazoprevir (ELB/GRZ)	Glecaprevir/ Pibrentasvir (GLE/PIB)	Sofosbuvir/ Velpatasvir/ Voxilaprevir (SOF/VEL/VOX)
Protease Inhibitors	Boosted Atazanavir	A	A			
	Boosted Darunavir	A	A			
	Boosted Lopinavir	ND, A	A			ND
NNRTIs	Doravirine		ND		ND	ND
	Efavirenz				ND	ND
	Rilpivirine					
	Etravirine	ND	ND	ND	ND	ND
Integrase Inhibitors	Bictegravir		ND	ND	ND	
	Cobicistat-boosted elvitegravir	C	C			C
	Dolutegravir					ND
	Raltegravir					ND
	Maraviroc	ND	ND	ND	ND	ND
NRTIs	Abacavir		ND	ND		ND
	Emtricitabine					
	Lamivudine		ND	ND		ND
	Tenofovir disoproxil fumarate	B, C	B, C			C, D
	Tenofovir alafenamide	D	D	ND		D

Green indicates coadministration is safe; yellow indicates a dose change or additional monitoring is warranted; and red indicates the combination should be avoided.

ND: No data

Slide 40 of 44

HCV treatment summary 2020

- Two pangenotypic regimens: SOF VEL and GP
- No change for HIV (avoid drug interactions)
- Watch for HBV relapse at week 8
- No change for acute
- No change for renal insufficiency
- Test, don't treat during pregnancy

Chronic hepatitis B

31 yr old Asian woman is referred to see you because she had a positive HBsAg test. She is otherwise feeling fine.

HBsAg pos, HBeAg neg, anti-HBe pos, ALT 78 IU/ml, AST 86 IU/ml, TB 0.8, albumin 4.2 g/dl, INR 1.

24 – Chronic Hepatitis

Speaker: David Thomas, MD, MPH

Which of the following tests is not recommended?

A. HIV test
B. HBV resistance
C. HBV genotype
D. Hepatitis Delta testing
E. Quantitative HBV DNA level

The work up of CHB may include ultrasound

US starts at 50 for Asian women

Surveillance recommended		
Population group	**Threshold incidence for efficacy of surveillance (> .25 LYG)(%/year)**	**Incidence of HCC**
Asian male hepatitis B carriers over age 40	0.2	0.4-0.6%/year
Asian female hepatitis B carriers over age 50	0.2	0.3-0.6%/year
Hepatitis B carrier with family history of HCC	0.2	Incidence higher than without family history
African/North American Blacks with hepatitis B	0.2	HCC occurs at a younger age
Cirrhotic hepatitis B carriers	0.2-1.5	3-8%/yr
Hepatitis C cirrhosis	1.5	3-5%/yr
Stage 4 primary biliary cirrhosis	1.5	3-5%/yr
Genetic hemachromatosis and cirrhosis	1.5	Unknown, but probably > 1.5%/year
Alpha 1-antitrypsin deficiency and cirrhosis	1.5	Unknown, but probably > 1.5%/year
Other cirrhosis	1.5	Unknown
Surveillance benefit uncertain		
Hepatitis B carriers younger than 40 (males) or 50 (females)	0.2	< 0.2%/yr
Hepatitis C and stage 3 fibrosis	1.5	< 1.5%/yr
Non-cirrhotic NAFLD	1.5	< 1.5%/yr

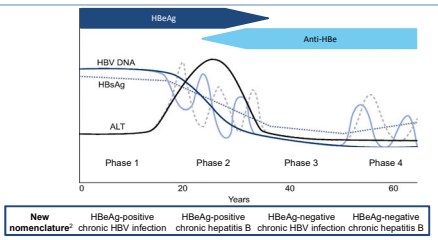
Use testing to define disease phase

- The natural history of chronic HBV infection has been schematically divided into five phases

Chronic hepatitis B	HBeAg positive		HBeAg negative		
	Phase 1	Phase 2	Phase 3	Phase 4	Phase 5
Chronic HBV infection	Chronic HBV infection	Chronic hepatitis B	Chronic HBV infection	Chronic hepatitis B	Resolved HBV infection
HBsAg	High	High/ intermediate	Low	Intermediate	Negative
HBeAg	Positive	Positive	Negative	Negative	Negative
HBV DNA	$>10^7$ IU/mL	10^4–10^7 IU/mL	<2,000 IU/mL*	>2,000 IU/mL	<10 IU/mL‡
ALT	Normal	Elevated	Normal	Elevated†	Normal
Liver disease	None/minimal	Moderate/ severe	None	Moderate/ severe	None§
Old terminology	Immune tolerant	Immune reactive HBeAg positive	Inactive carrier	HBeAg negative chronic hepatitis	HBsAg negative /anti-HBc positive

*HBV DNA levels can be between 2,000 and 20,000 IU/mL in some patients without signs of chronic hepatitis; †Persistently or intermittently, based on traditional ULN (~40 IU/L). ‡cccDNA can frequently be detected in the liver; §Residual HCC risk only if cirrhosis has developed before HBsAg loss.
EASL CPG HBV. J Hepatol 2017;67:370–98

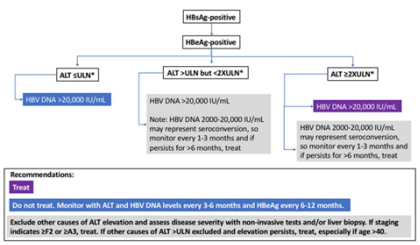
Use testing to define disease phase[1]



New nomenclature[2]	HBeAg-positive chronic HBV infection	HBeAg-positive chronic hepatitis B	HBeAg-negative chronic HBV infection	HBeAg-negative chronic hepatitis B

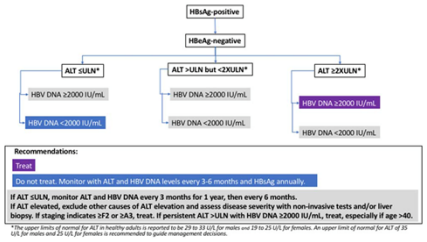
1. Lok A, et al. J Hepatol 2017;67:847–61;
2. EASL CPG HBV. J Hepatol 2017;67:370–98

Treat when high replication *and* disease HBeAg positive



AASLD guidelines, Terrault Hepatology 2018

HBeAg negative is 2,000 IU vs 20,000 IU



AASLD guidelines, Terrault Hepatology 2018

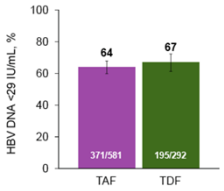
Four preferred treatments for chronic hepatitis B

HBeAg Positive	Peg-IFN*	Entecavir†	Tenofovir Disoproxil Fumarate†	Tenofovir Alafenamide‡
% HBV-DNA suppression (cutoff to define HBV-DNA suppression)§	30-42 (<2,000-40,000 IU/mL) 8-14 (<80 IU/mL)	61 (<50-60 IU/mL)	76 (<60 IU/mL)	73 (<29 IU/mL)
% HBeAg loss	32-36	22-25	—	22
% HBeAg seroconversion	29-36	21-22	21	18
% Normalization ALT	34-52	68-81	68	—
% HBsAg loss	2-7 11 (at 3 years posttreatment)	4-5	8	1
HBeAg Negative	**Peg-IFN**	**Entecavir**	**Tenofovir Disoproxil Fumarate†**	**Tenofovir Alafenamide‡**
% HBV-DNA suppression (cutoff to define HBV-DNA suppression)‖	43 (<4,000 IU/mL) 19 (<80 IU/mL)	90-91 (<50-60 IU/mL)	93 (<60 IU/mL)	90 (<29 IU/mL)
% Normalization ALT¶	59	78-88	76	81
% HBsAg loss	4 6 (at 3 years posttreatment)	0-1	0	<1

TAF 25 mg with or without FTC

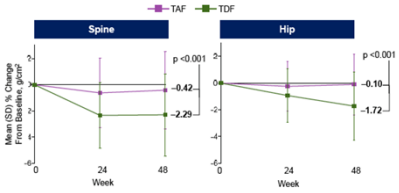
AASLD guidelines, Terrault Hepatology 2018

TAF is as effective and safer than tenofovir DF for chronic hepatitis B



Chan Lancet Gastro 2016

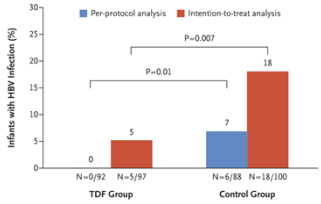
TAF is as effective and safer than tenofovir DF for chronic hepatitis B



Chan Lancet Gastro 2016

Treat HBV in pregnant women if HBV DNA level above 200,000 IU/ml

Rec for all pregnant women to have quantitative HBV DNA TEST



Terrault Hepatology 2015; Pan NEJM 2016

Treatment of HBV changes with renal insufficiency

- **GFR 30-60** mL/min/1.73 m^2 **: TAF preferred**
- **GFR <30-10: TAF OR entecavir 0.5 q 3d**
- **GFR <10 no dialysis: entecavir 0.5**
- **Dialysis: TDF 300/wk PD or entecavir 0.5mg/wk or TAF 25mg PD**

It is hard to stop HBV treatment

- **If HBeAg conversion noted and no cirrhosis *consider* stopping after 6 months**
- **HBeAg neg when treatment started and all with cirrhosis stay on indefinitely**

HIV/HBV coinfected need treatment for both

- All are treated and tested for both
- HBV-active ART
- Entecavir less effective if LAM exposure
- Watch switch from TAF/TDF containing regimen

What if HBV levels stay detectable?

- Continue monotherapy, ideally with TAF or TDF
- Rising levels (breakthrough)
  - Add second drug or switch esp if initial Rx with ETV

Hepatitis serology in the oncology suite

You are called about 62 year old Vietnamese scientist who is in oncology suite where he is about to get R-CHOP for Non Hodgkins lymphoma. Baseline labs: normal AST, ALT, and TBili. Total HAV detectable; anti-HBc pos; HBsAg neg; anti-HCV neg.

What do you recommend?

A. Hold rituximab
B. Hold prednisone
C. Entecavir 0.5 mg
D. HCV PCR
E. HBV DNA

Rituximab, high-dose prednisone, and BM transplant high risk for HBV reactivation

- If HBsAg pos, prophylaxis always recommended
- If anti-HBc pos but HBsAg neg, prophylaxis still recommended with high risk exposures
- Use TAF or ETV

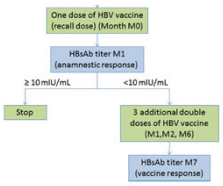
AASLD Terrault Hepatology 2018

Isolated anti-core antibodies usually reflect occult hepatitis B in high risk groups

- Most often true positive test in HIV pos or with HBV risk
- Primary responses to vaccination
- 29 anti-HBc and 40 negative for anti-HBc
  - anamnestic response in anti-HBc pos (24%) vs anti-HBc neg (10%)
  - 50% anti-HBc pos also tested positive for anti-Hbe
  - Anti-HBs seroconversion in ~60% both groups

Gandhi JID 2005; Terrault Hepatology 2018; Piroth CID 2018

HBV vaccination recommended in persons with isolated anti-HBc



Gandhi JID 2005; Terrault Hepatology 2018; Piroth CID 2018

HBV Prevention is with vaccine and sometimes HBIG

Pre-exposure:

- vaccinate and get post vaccination titers (<2 months) if exposure likely

Post Exposure:

- vaccinate if not already done or not known to respond
- add HBIG when infection likely
- infants of HBsAg pos mothers get immediate vaccination and HBIG

MMWR / January 12, 2018 / Vol. 67 / No. 1; Medical Letter JAMA 2018

How do we prevent HBV?

Vaccine	Formulations	Dose	Schedule	Cost[a]
Hepatitis B				
Heplisav-B (Dynavax)	0.5 mL solution in single-dose vials	≥18 yrs[b]: 0.5 mL IM	2 doses (0 and 1 mo)	$230.00
Engerix-B (GSK)	0.5, 1 mL suspension in single-dose vials, prefilled syringes	Birth-19 yrs: 0.5 mL IM[c] ≥20 yrs: 1 mL IM[c]	3 doses (0, 1, and 6 mos)[d]	66.90 169.50
Recombivax HB (Merck)	0.5, 1 mL suspension in single-dose vials, prefilled syringes	Birth-19 yrs: 0.5 mL IM[c] ≥20 yrs: 1 mL IM[c]	3 doses (0, 1, and 6 mos)[d,e]	69.60 181.40
Hepatitis A/B				
Twinrix (GSK)	1 mL suspension in single-dose vials, prefilled syringes	≥18 yrs: 1 mL IM	3 doses (0, 1, and 6 mos)[f]	298.50

MMWR / January 12, 2018 / Vol. 67 / No. 1; Medical Letter JAMA 2018

A final case of chronic hepatitis in transplant recipient

51 y/o HTN, and ankylosing spondylitis s/p renal transplant presents with elevated liver enzymes. Pred 20/d; MMF 1g bid; etanercept 25mg twice/wk; tacro 4mg bid.

HBsAg neg, anti-HBs pos, anti-HBc neg; anti-HCV neg; HCV RNA neg; CMV IgG neg; EBV neg; VZV neg. ALT 132 IU/ml, AST 65 IU/ml; INR 1. ALT and AST remained elevated; HBV, HCV, HAV, CMV, EBV serologies remain neg.

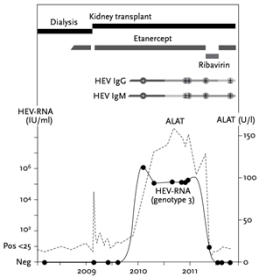
Barrague Medicine 2017

Which test is most likely abnormal

1. HEV PCR
2. HCV IgM
3. Tacrolimus level
4. Adenovirus PCR
5. Delta RNA PCR

Chronic HEV in transplant recipient

- Europe (boar)
- Can cause cirrhosis
- Tacrolimus associated
- Ribavirin may be effective



Barrague Medicine 2017

24 – Chronic Hepatitis

Speaker: David Thomas, MD, MPH

Chronic Hepatitis for the Boards Summary

- **HCV-associated conditions: PCT or cryoglobulinemia**
- **HBV-associated: PAN**
- **HCV: staging or treatment outcome**
- **HBV: relapse post rituximab**
- **Guess b and good luck**

25

Brain Abscess, Cavernous Sinus Thrombosis, and Subdural and Epidural Empyema

Dr. Allan Tunkel

25 – Brain Abscess, Cavernous Sinus Thrombosis, and Subdural and Epidural Empyema

Speaker: Allan Tunkel, MD

2020 INFECTIOUS DISEASE BOARD REVIEW

Brain Abscess, Cavernous Sinus Thrombosis, Subdural Empyema and Epidural Abscess

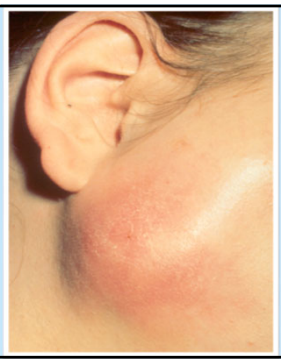
Allan R. Tunkel, MD, PhD, MACP
Senior Associate Dean for Medical Education
Professor of Medicine and Medical Science
The Warren Alpert Medical School of Brown University

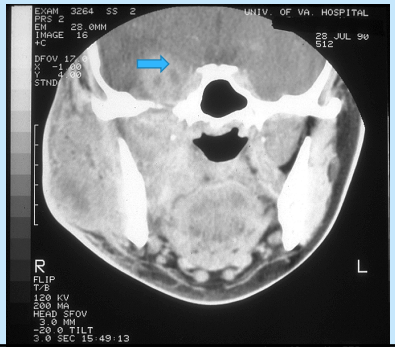
Disclosures of Financial Relationships with Relevant Commercial Interests

- None

CASE #1

- 24-year-old female who presented with pain and swelling on the right side of her jaw that had been progressing over the last several weeks. She was unable to open her mouth. She denied fever or headache, and had no past hospitalizations or illnesses. The patient had not been to the dentist within 10 years.
- T 99.8ºF, P 88, RR 14, BP 110/80
- Exam revealed swelling and erythema along her right mandible





Question #1 (Case #1)

Which of the following empiric antimicrobial regimens should be initiated?

A. Ceftriaxone + metronidazole
B. Vancomycin + cefepime
C. Trimethoprim-sulfamethoxazole
D. Voriconazole
E. Liposomal amphotericin B

25 – Brain Abscess, Cavernous Sinus Thrombosis, and Subdural and Epidural Empyema

Speaker: Allan Tunkel, MD

Answer #1 (Case #1)

Which of the following empiric antimicrobial regimens should be initiated?

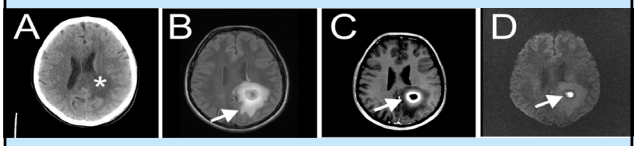
A. Ceftriaxone + metronidazole
B. Vancomycin + cefepime
C. Trimethoprim-sulfamethoxazole
D. Voriconazole
E. Liposomal amphotericin B

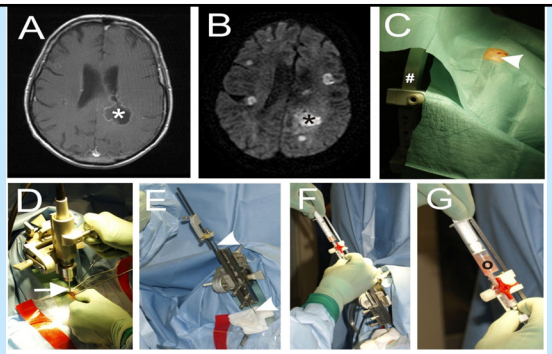
PREDISPOSING CONDITIONS FOR BRAIN ABSCESS

Condition	Relative Frequency (%)
Contiguous focus of infection (otitis media, mastoiditis, sinusitis, face or scalp infection, dental sepsis, osteomyelitis, penetrating head injury)	30-50
Hematogenous spread (lung abscess, empyema, congenital heart disease, bronchiectasis, infective endocarditis, compromised host, hereditary hemorrhagic telangiectasia)	~35
Cryptogenic	10-35

PRINCIPLES OF BRAIN ABSCESS MANAGEMENT

- MR imaging is the diagnostic procedure of choice; diffusion-weighted imaging increases diagnostic accuracy (sensitivity and specificity 96% for differentiation from cancers [PPV 98%; NPV 92%])
- Lumbar puncture is contraindicated
- Biopsy or aspiration (via stereotactic guidance) is needed for microbiologic diagnosis
- Begin empiric antimicrobial therapy based on underlying condition and pathogenesis of spread of infection to brain





EMPIRIC ANTIMICROBIAL THERAPY OF BRAIN ABSCESS

Predisposing Condition	Antimicrobial Regimen
Otitis media or mastoiditis	Metronidazole + a third-generation cephalosporin[a]
Sinusitis	Vancomycin + metronidazole + a third-generation cephalosporin[a]
Dental sepsis	Third-generation cephalosporin[a] + metronidazole
Penetrating trauma or post-neurosurgical	Vancomycin + a third or fourth generation cephalosporin
Lung abscess, empyema, bronchiectasis	Third-generation cephalosporin[a] + metronidazole + trimethoprim-sulfamethoxazole
Bacterial endocarditis	Vancomycin[b]

[a]ceftriaxone or cefotaxime
[b]additional agents may be used based on other likely microbial etiologies

25 – Brain Abscess, Cavernous Sinus Thrombosis, and Subdural and Epidural Empyema

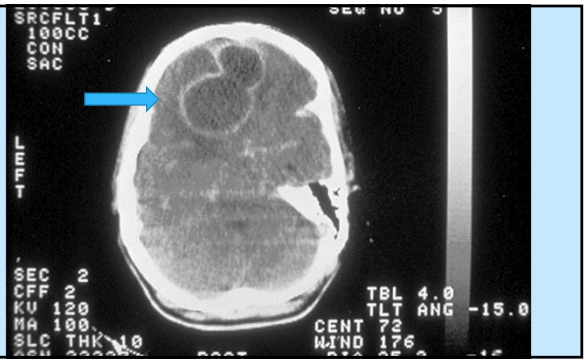
Speaker: Allan Tunkel, MD

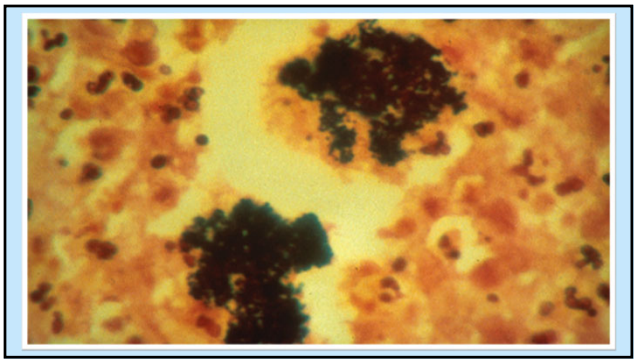
EMPIRIC ANTIMICROBIAL THERAPY OF BRAIN ABSCESS

Predisposing Condition	Antimicrobial Regimen
Unknown	Vancomycin + metronidazole + a third or fourth generation cephalosporin
Transplant recipients	Add voriconazole, plus trimethoprim-sulfamethoxazole or sulfadiazine
HIV-infected patients	Add pyrimethamine + sulfadiazine; consider isoniazid, rifampin, pyrazinamide, and ethambutol for possible tuberculosis

CASE #2

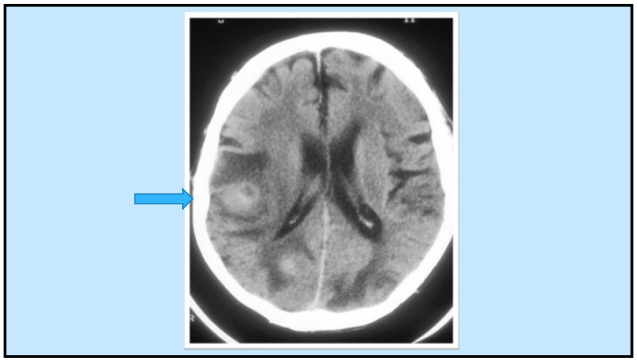
- 21-year-old member of a motorcycle gang thrown from his bike, and suffered a depressed skull fracture
- In the OR, a large subdural hematoma was evacuated
- Discharged in 5 days
- Returned by mother 5 days later because of bizarre behavior
- No headache, afebrile

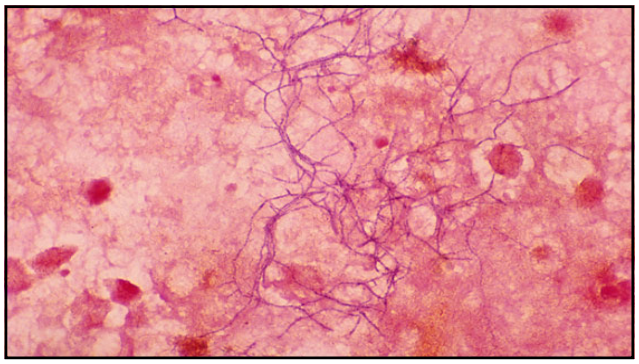




CASE #3

- 78-year-old male with multiple myeloma on chronic prednisone therapy; underwent aortic valve replacement with a bioprosthesis 5 years earlier; presented with new-onset seizures
- T 100.4° F, P 96, RR 18, BP 110/70 mmHg; Exam (-)
- CT scan revealed multiple ring-enhancing lesions
- TEE - no vegetations and normal bioprosthesis
- Empirically placed on vancomycin + ampicillin + gentamicin
- Blood cultures negative

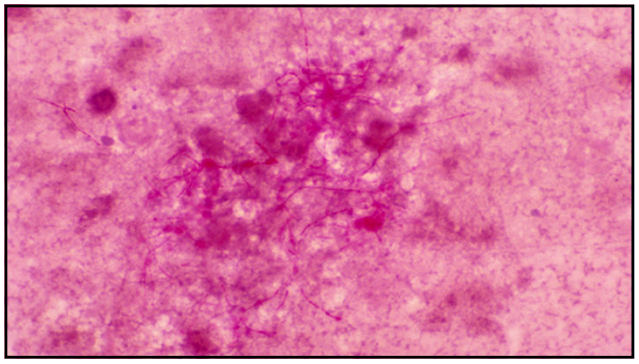




Question #2 (Case #3)

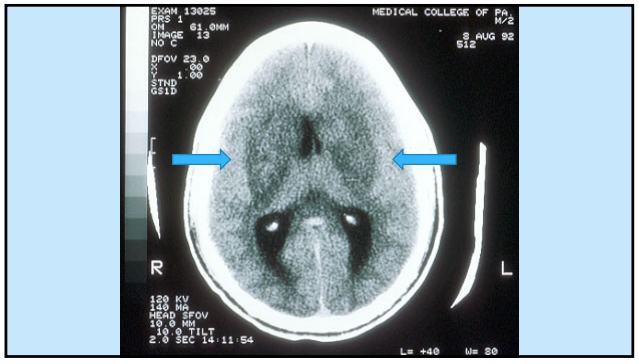
Which of the following antimicrobial regimens should be initiated?

A. Penicillin + metronidazole
B. Trimethoprim-sulfamethoxazole
C. Daptomycin
D. Liposomal amphotericin B + 5-FC
E. Voriconazole



CASE #4

- 24-year-old injection drug user who, while injecting intravenous drugs with his girlfriend, fell out of the second story window of his apartment. When he did not return for 48 hours, she found him unresponsive on the ground and called fire rescue
- T 103°F, P 150, RR 32, BP 110/76 mmHg
- On exam, he was comatose without evidence of head trauma
- WBC 13,000/mm^3, profound metabolic acidosis



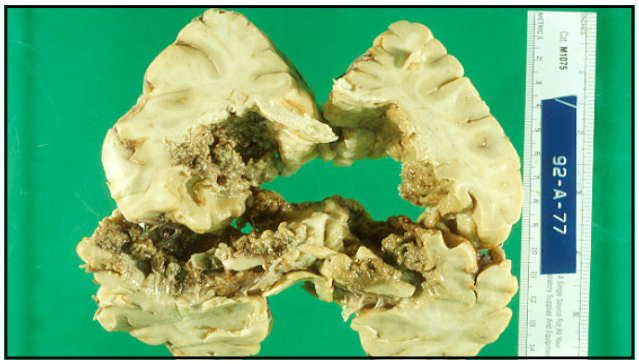
Question #3 (CASE #4)

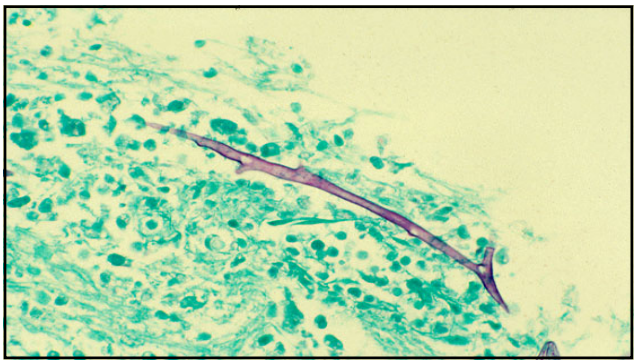
The most likely etiologic agent of the patient's CNS lesions is which of the following?

A. Staphylococcus aureus
B. Pseudomonas aeruginosa
C. Nocardia asteroides
D. Candida albicans
E. Rhizopus arrhizus

25 – Brain Abscess, Cavernous Sinus Thrombosis, and Subdural and Epidural Empyema

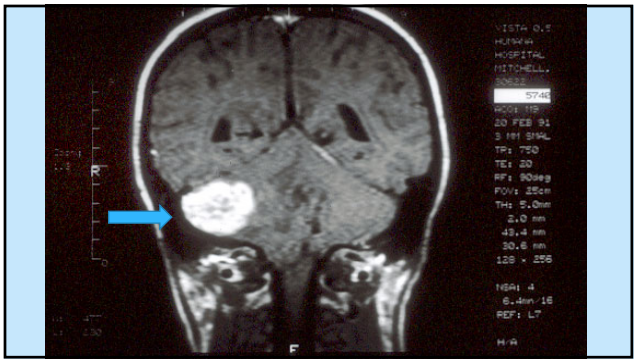
Speaker: Allan Tunkel, MD

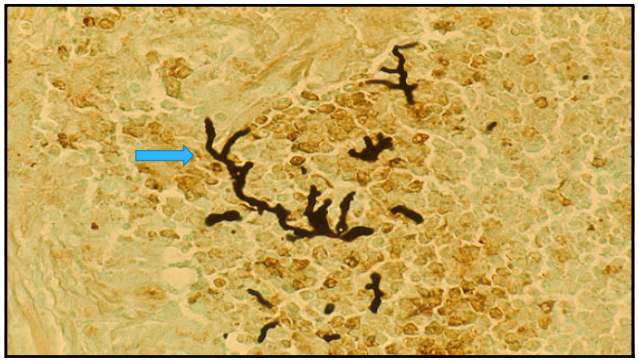




CASE #5

- 11-year-old boy with chronic granulomatous disease on chronic TMP-SMX therapy noted the onset of a mild headache which lasted 10 minutes.
- Two weeks later at a routine physician visit, the patient had no complaints and denied recurrence of the headache
- On examination, the patient had normal vital signs and a normal neurologic examination
- The physician ordered an MR imaging of the head



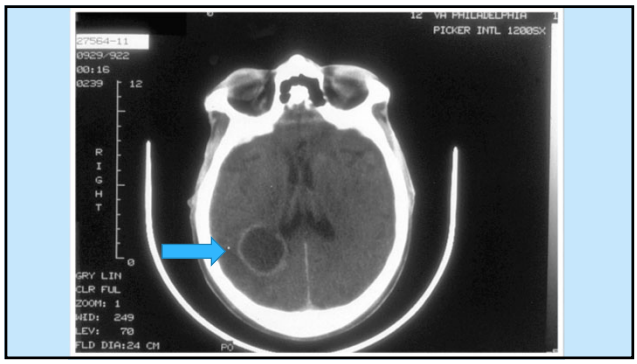


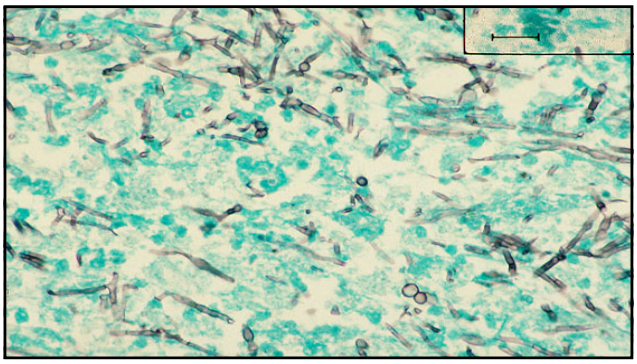
CASE #6

- 80-year-old male with CLL on chronic prednisone therapy presented to the VA Hospital with sepsis and ARDS. Course complicated by VDRF and multiple nosocomial infections, including candidemia for which he received 4 weeks of IV amphotericin B. After completing the course of therapy, he developed altered mental status
- T 101^0 F, P 100, RR 20, BP 120/76
- Neurologic exam left-sided hyperreflexia and Babinski

25 – Brain Abscess, Cavernous Sinus Thrombosis, and Subdural and Epidural Empyema

Speaker: Allan Tunkel, MD





PRINCIPLES OF BRAIN ABSCESS MANAGEMENT

- Optimal management usually requires a combined medical and surgical approach (aspirate if >2.5 cm)
- Fungal brain abscess often requires combined medical and surgical therapy
- Initiate corticosteroids with evidence of cerebral edema or mass effect causing increased ICP

ANTIMICROBIAL THERAPY OF BRAIN ABSCESS

Organism	Antimicrobial Therapy
Actinomyces sp.[a]	Penicillin G
Bacteroides fragilis[a]	Metronidazole
Enterobacteriaceae[a]	Third or fourth generation cephalosporin
Fusobacterium sp.[a]	Metronidazole
Pseudomonas aeruginosa	Ceftazidime or cefepime or meropenem
Staphylococcus aureus	Nafcillin, oxacillin, or vancomycin
Strep. milleri; [a] other streptococci[a]	Penicillin G

[a]depending on pathogenesis of infection, may be isolated as part of a mixed infection

ANTIMICROBIAL THERAPY OF BRAIN ABSCESS

Organism	Antimicrobial Therapy
Nocardia asteroides	Trimethoprim-sulfamethoxazole or sulfadiazine; combination therapy for immunocompromised patients and those failing standard therapy
Mycobacterium tuberculosis	Isoniazid + rifampin + pyrazinamide ± ethambutol

ANTIMICROBIAL THERAPY OF BRAIN ABSCESS

Organism	Antimicrobial Therapy
Aspergillus sp.	Voriconazole
Candida sp.	Amphotericin B preparation[a]
Mucorales	Amphotericin B preparation
Scedosporium spp.	Voriconazole

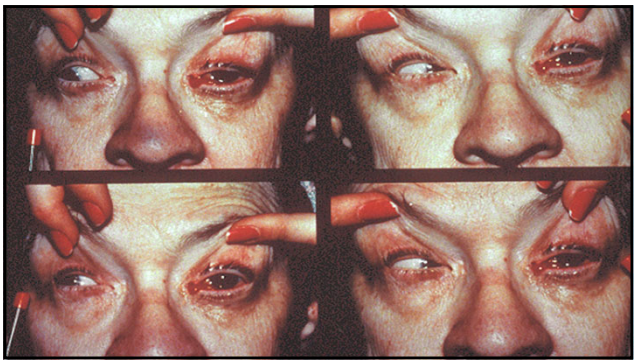
[a]Addition of 5-flucytosine should be considered

25 – Brain Abscess, Cavernous Sinus Thrombosis, and Subdural and Epidural Empyema

Speaker: Allan Tunkel, MD

CASE #7

- 79-year-old female is transferred from a nursing home for failure to thrive as a result of decreased oral intake. A nasogastric tube is placed via the left nares for enteral hyperalimentation
- One week into her hospital course, the patient develops fever to 101.5° F, and left periorbital edema and chemosis
- CT scan of the head without contrast reveals opacification of the sphenoid sinus



Question #4 (CASE #7)

Which of the following studies should be performed to establish the diagnosis?

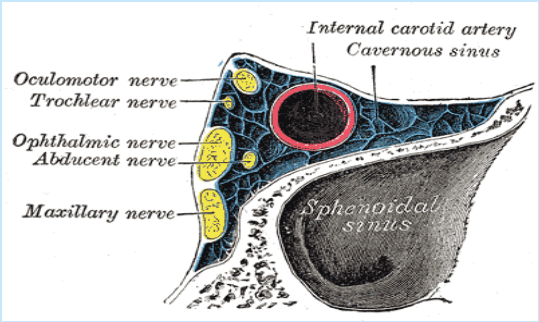
A. CT scan of the head and sinuses with contrast
B. MR imaging with MR venography
C. Cerebral angiography
D. Positron emission tomography of the head
E. Lumbar puncture

EPIDEMIOLOGY AND ETIOLOGY OF SEPTIC CAVERNOUS SINUS THROMBOSIS

Risk Factors	Etiologic Agents
Paranasal sinusitis	Staphylococci (60-70%)
Facial infection	Streptococci (~17%)
Dental infection	Gram-negative bacilli (~5%)
	Pneumococci (~5%)
	Bacteroides sp. (~2%)

CLINICAL FEATURES OF SEPTIC CAVERNOUS SINUS THROMBOSIS

Symptoms	Signs
Headache (52%)	Periorbital edema (73%)
Facial pain	Chemosis
Vision loss	Papillitis
Fever	Oculomotor palsies
Double vision	Proptosis



Tunkel AR. Principles and Practice of Infectious Diseases, 8th ed. 2015.

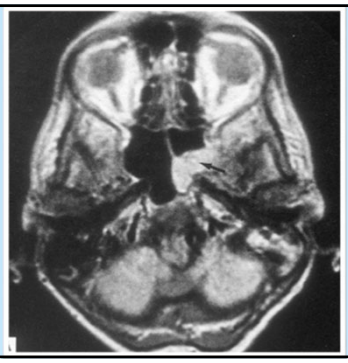
25 – Brain Abscess, Cavernous Sinus Thrombosis, and Subdural and Epidural Empyema

Speaker: Allan Tunkel, MD

RADIOLOGIC FINDINGS IN SEPTIC CAVERNOUS SINUS THROMBOSIS

MR imaging

- Noninvasive diagnostic procedure of choice
- MRA and MRV can directly visualize cerebral vasculature
- Fullness in cavernous sinus region
- Paranasal sinus fluid

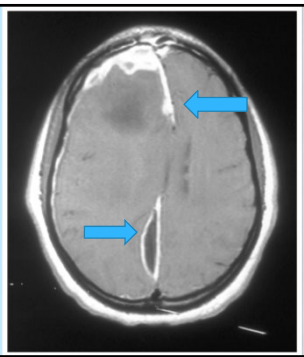


MANAGEMENT OF SEPTIC CAVERNOUS SINUS THROMBOSIS

- Culture and drainage of infected sinuses
- Antimicrobial therapy (vancomycin + metronidazole + 3rd or 4th generation cephalosporin)
- Anticoagulation
  - Cavernous sinus thrombosis
  - Lateral sinus thrombosis?
  - Superior sagittal sinus thrombosis?

CASE #8

- 22-year-old man with a history of paranasal sinusitis presents with fever, severe headache, neck pain, and seizure
- On physical examination, T 102° F and he is lethargic
- Laboratory studies normal



Question #5 (CASE #8)

In addition to appropriate antimicrobial therapy, what other management should be performed?

A. Lumbar puncture
B. External ventricular drain
C. Dexamethasone
D. Burr hole drainage
E. Craniotomy

25 – Brain Abscess, Cavernous Sinus Thrombosis, and Subdural and Epidural Empyema

Speaker: Allan Tunkel, MD

CRANIAL SUBDURAL EMPYEMA AND CRANIAL EPIDURAL ABSCESS

Risk Factors	Etiologic Agents
Sinusitis (50-80%)	Staphylococci (10-15%)
Otogenic	Streptococci (25-45%)
Head trauma	Gram-negative bacilli (3-10%)
Neurosurgery	Other anaerobes (8%)
Hematogenous	Others (8%)
Meningitis	Unknown (20%)

CRANIAL SUBDURAL EMPYEMA AND CRANIAL EPIDURAL ABSCESS

Subdural Empyema (acute course)

- Fever
- Headache
- Depressed consciousness
- Hemiparesis
- Seizures
- Nuchal rigidity
- Gaze palsies/ataxia

Epidural Abscess (indolent course)

- Headache
- Fever
- Seizures
- Focal neurologic signs
- Altered mental state

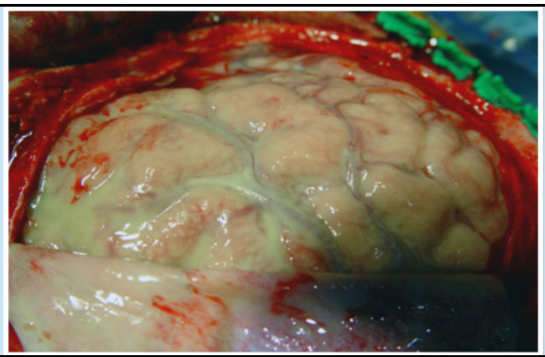
PRINCIPLES OF MANAGEMENT OF CRANIAL SUBDURAL EMPYEMA

- MR imaging (diagnostic procedure of choice) provides better clarity of detail and can differentiate empyema from most sterile effusions and chronic hematomas; diffusion-weighted imaging adds to value of MRI
- Surgical therapy (burr holes or craniotomy) is imperative; better outcome with craniotomy
- Empiric antimicrobial therapy based on pathogenesis of infection

SURGICAL MANAGEMENT OF CRANIAL SUBDURAL EMPYEMA

Surgical Procedure	Mortality Rate
Burr hole(s)	23.3%
Craniectomy	11.5%
Craniotomy	8.4%

Nathoo et al. Neurosurgery 2001;49:872



EPIDEMIOLOGY OF SPINAL EPIDURAL ABSCESS

- Usually occurs secondary to hematogenous dissemination (~50% of cases)
- Contiguous foci (~1/3rd of cases)
- Unidentified source (20-40% of cases)
- Diabetes mellitus identified in up to 50% of patients

25 – Brain Abscess, Cavernous Sinus Thrombosis, and Subdural and Epidural Empyema

Speaker: Allan Tunkel, MD

ETIOLOGY OF SPINAL EPIDURAL ABSCESS

Organism	Relative Frequency (%)
Staphylococci	50-90
Streptococci	8-17
Gram-negative bacilli	12-17
Other anaerobes	2
Other	2
> 1 organism	5-10
Unknown	6

CLINICAL STAGES OF SPINAL EPIDURAL ABSCESS

I. Back pain and tenderness at the level of infection
II. Radicular pain and paresthesias
III. Impaired spinal cord function; motor paresis and sensory deficits
IV. Complete paralysis

PRINCIPLES OF MANAGEMENT OF SPINAL EPIDURAL ABSCESS

- MR imaging is the diagnostic procedure of choice; can visualize the spinal cord and epidural space, and can identify accompanying osteomyelitis, intramedullary spinal cord lesions, and joint space infection
- Empiric antimicrobial therapy should include an antistaphylococcal agent and coverage for gram-negative bacilli

PRINCIPLES OF MANAGEMENT OF SPINAL EPIDURAL ABSCESS

- Surgical therapy imperative in the presence of neurologic dysfunction (best if <24-36 hours of complete paralysis)
- Nonsurgical therapy only for patients with an unacceptably high surgical risk or no neurologic deficits at diagnosis; patient must be followed carefully for clinical deterioration

2020 INFECTIOUS DISEASE BOARD REVIEW

GW | Office of Continuing Education in the Health Professions

25th Annual

COMPREHENSIVE REVIEW *for* INFECTIOUS DISEASE BOARD PREPARATION

DAY 3

COURSE DIRECTORS:
John E. Bennett, MD
Henry Masur, MD

COURSE CO-DIRECTORS:
Paul Auwaerter, MD
David N. Gilbert, MD
Roy M. Gulick, MD, MPH
Andrew Pavia, MD
Richard J. Whitley, MD

www.IDBoardReview.com

MONDAY, AUGUST 24, 2020

#	Start		End	Presentation	Speaker(s)
26	9:45 AM	-	10:15 AM	**Daily Question Preview 3**	*Roy Gulick, MD (Moderator)*
27	10:15 AM	-	10:45 AM	**Upper Gastrointestinal Infections**	*Herbert Dupont, MD*
28	10:45 AM	-	11:30 AM	**Clinical Manifestations of Human Retroviral Diseases and Slow Viruses**	*Frank Maldarelli, MD*
29	11:30 AM	-	12:00 PM	**Lower Gastrointestinal Infections**	*Herbert Dupont, MD*
	12:00 PM	-	12:15 PM	***BREAK***	
30	12:15 PM	-	12:30 PM	**HIV Diagnosis**	*Frank Maldarelli, MD*
31	12:30 PM	-	1:15 PM	**Antiretroviral Therapy**	*Roy Gulick, MD*
32	1:15 PM	-	1:30 PM	**HIV Drug Resistance**	*Frank Maldarelli, MD*
33	1:30 PM	-	2:00 PM	**Antiretroviral Therapy for Special Populations**	*Roy Gulick, MD*
	2:00 PM	-	2:15 PM	***BREAK***	
34	2:15 PM	-	3:00 PM	**Board Review Session 3**	*Drs. Gulick (Moderator), Bell, Dupont, Maldarelli, Saag, and Weinstein*
35	3:00 PM	-	4:00 PM	**Hospital Epidemiology**	*Robert Weinstein, MD*
36	4:00 PM	-	4:45 PM	**Antifungal Drugs**	*John Bennett, MD*
	4:45 PM	-	5:00 PM	***BREAK***	
37	5:00PM	-	5:45 PM	**Non AIDS-Defining Complications of HIV/AIDS**	*Michael Saag, MD*
38	5:45 PM	-	6:15 PM	**Syndromes in the ICU that ID Physicians Should Know**	*Taison Bell, MD*
39	6:15 PM	-	7:00 PM	**Photo Opportunity II: More Photos and Questions to Test Your Board Preparation**	*John Bennett, MD*

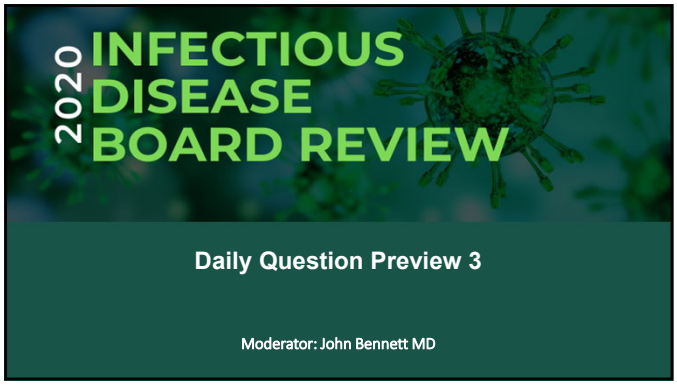
26

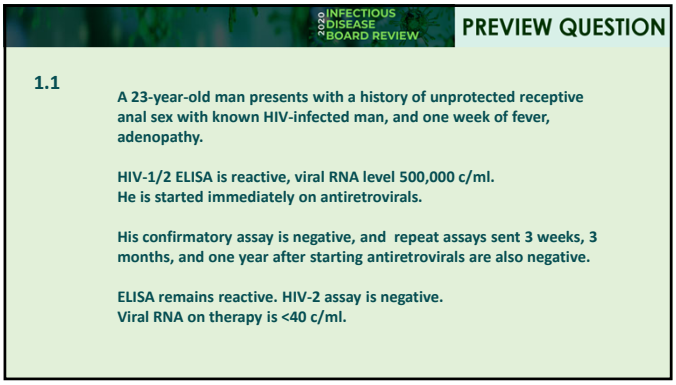
Daily Question Preview 3

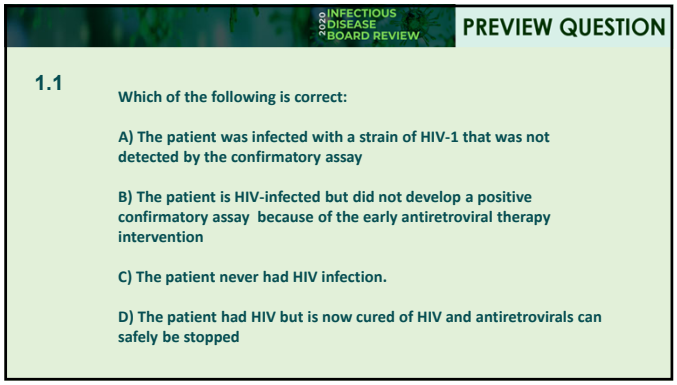
Dr. Roy Gulick (Moderator)

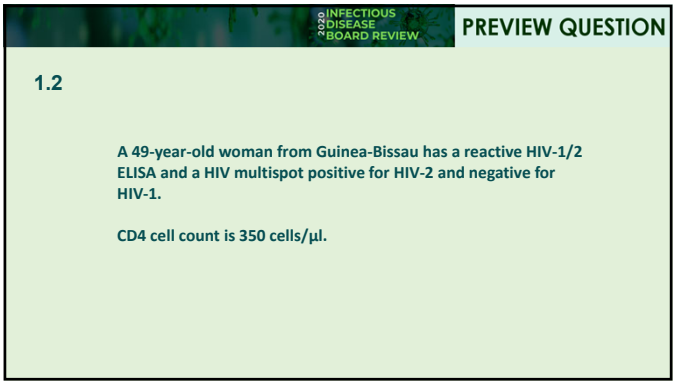
26 – Daily Question Preview 3

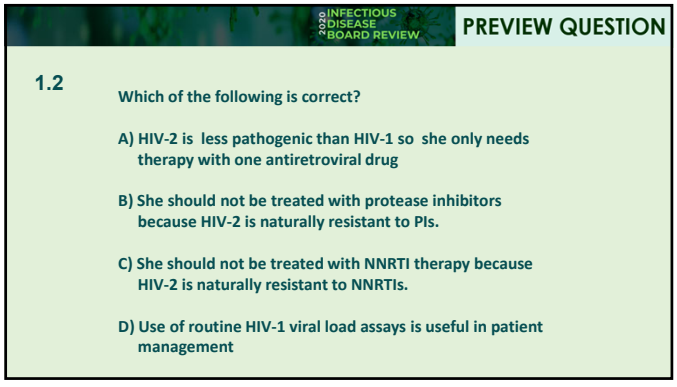
Speaker: John Bennett, MD

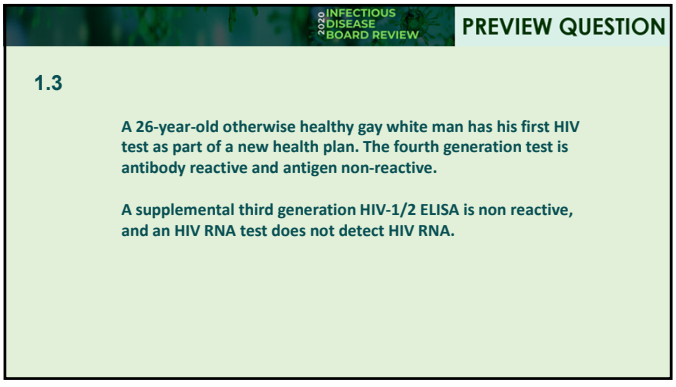












26 – Daily Question Preview 3

Speaker: John Bennett, MD

INFECTIOUS DISEASE BOARD REVIEW 2020

PREVIEW QUESTION

1.3

The most likely explanation for these results is

A) This person HIV infected and is an elite non-controller

B) This person is HIV infected but is in the window period for HIV infection

C)This person is infected with an HIV variant that is not detected by the supplemental test

D) This person is not HIV infected

INFECTIOUS DISEASE BOARD REVIEW 2020

PREVIEW QUESTION

1.4

A 27-year-old female commercial sex worker working in Washington, DC, visits your clinic and requests PrEP.

She shows you her home HIV test, which she took yesterday, and which is non-reactive. She has normal laboratory results and a negative pregnancy test.

INFECTIOUS DISEASE BOARD REVIEW 2020

PREVIEW QUESTION

1.4

Which of the following is most appropriate next step?

A) She can immediately initiate PrEP with tenofovir-FTC with no additional testing

B) She requires additional testing with fourth generation Ag/Ab HIV test to determine whether she is infected with a non-B subtype of HIV-1 that is not detected by the home HIV test.

C) She requires additional testing with fourth generation HIV test to determine whether she has early HIV infection not detected by the home HIV test.

D) She should not initiate PrEP because PrEP does not work well in women

INFECTIOUS DISEASE BOARD REVIEW 2020

PREVIEW QUESTION

1.5

83-Year-Old Man with Bloody Diarrhea Develops Renal Failure.
He has a one week history of diarrhea with stools containing blood; he undergoes colonoscopy which looks like ischemic colitis

As his diarrhea improves his urine output decreases

Serum creatinine is 9, platelet count of 50,000, hematocrit 20 and LDH 1,000.

Stool culture on Sorbitol MacConkey Agar grows no sorbitol-negative E. coli and stool sample is positive for Shiga toxin 2 by EIA

He is treated with Eculizumab, a humanized monoclonal antibody inhibits the terminal sequence of complement

INFECTIOUS DISEASE BOARD REVIEW 2020

PREVIEW QUESTION

1.5

Colonoscopy Shows "Ischemic Colitis"

Peripheral Smear Shows Red Cell Fragments

INFECTIOUS DISEASE BOARD REVIEW 2020

PREVIEW QUESTION

1.5

What is the likely cause of dysentery and renal failure in the elderly man?

A) Ischemic bowel disease

B) Non-O157 Shigatoxin producing E. coli (STEC)

C) O157:H7 strain of STEC

D) Shigella dysenteriae 1 (Shiga bacillus)

E) Campylobacter jejuni

26 – Daily Question Preview 3

Speaker: John Bennett, MD

INFECTIOUS DISEASE BOARD REVIEW 2020

PREVIEW QUESTION

1.6

A patient develops numbness of lips, burning and tingling of his extremities, and abdominal pain and vomiting 30 minutes after a meal in Jamaica, progressing to respiratory failure.

What is the likely diagnosis?

A) Scombroid

B) Paralytic shellfish poisoning

C) Ciguatera

D) Neurotoxic shellfish poisoning

E) Monosodium glutamate toxicity

INFECTIOUS DISEASE BOARD REVIEW 2020

PREVIEW QUESTION

1.7

A 35-year-old woman develops diarrhea, cramps and is passing bloody stools with fever while snorkeling with her family in Cozumel, Mexico.

INFECTIOUS DISEASE BOARD REVIEW 2020

PREVIEW QUESTION

1.7

What is the preferred treatment for this patient With dysenteric traveler's diarrhea?

A) Azithromycin 1,000 mg

B) Ciprofloxacin 500 mg twice daily X 3 days

C) Levofloxacin 500 mg

D) Rifaximin 200 mg three times/d for 3 days

E) Oral fluids only

INFECTIOUS DISEASE BOARD REVIEW 2020

PREVIEW QUESTION

1.8

A 43-year-old HIV+ man has CD4 900-1200 and HIV RNA consistently <200 copies over the last 11 years.

Do you recommend starting ART?

A) Yes, all current guidelines recommend starting.

B) No, he's a long-term non-progresser and doesn't need ART.

C) No, he should wait until his viral load level is confirmed >200 copies/ml.

D) No, he should wait until CD4 is confirmed <500.

INFECTIOUS DISEASE BOARD REVIEW 2020

PREVIEW QUESTION

1.9

You have been monitoring a 36 year old HIV+ man with CD4 ~350, VL 636,000 who is now ready to start ART, but wants the "simplest regimen possible."

Which of these regimens do you recommend?

A) zidovudine/lamivudine + darunavir (boosted)

B) tenofovir/emtricitabine/rilpivirine

C) abacavir/lamivudine + efavirenz

D) lamivudine/dolutegravir

E) tenofovir/emtricitabine + dolutegravir

INFECTIOUS DISEASE BOARD REVIEW 2020

PREVIEW QUESTION

1.10

A 52-year-old woman is admitted for progressive SOB, is intubated, undergoes BAL and is found to have PCP. HIV Ab test is positive, CD4 103, HIV RNA 135,000 copies/ml. She is day 4 of IV trimethoprim-sulfa and corticosteroids and still intubated.

When should she start ART?

A) Immediately

B) In the next 2 weeks

C) After completing 21 days of trimethoprim-sulfa

D) At her first outpatient clinic visit

26 – Daily Question Preview 3

Speaker: John Bennett, MD

PREVIEW QUESTION

1.11 A 55-year-old treatment-naïve man with HIV disease, CD4 320 and HIV RNA 67,000 cps/ml

Lab testing reveals: toxoplasma Ab+; CMV Ab+; HAV total Ab+; HBV surface Ag+, core Ab+, surface Ab-; HCV Ab-; RPR NR

Of the following, which ART regimen would you recommend?

A) abacavir/lamivudine/dolutegravir

B) abacavir/lamivudine + atazanavir (boosted)

C) tenofovir (TAF or TDF)/emtricitabine + zidovudine

D) tenofovir (TAF or TDF)/emtricitabine + darunavir (boosted)

PREVIEW QUESTION

1.12

A 34-year-old HIV-negative nurse sustains a needlestick from an HIV-positive patient who has not taken ART for 2 years.

Which of these post-exposure (PEP) regimens do you recommend?

A) tenofovir (TDF)/emtricitabine

B) tenofovir (TDF)/emtricitabine + integrase inhibitor

C) tenofovir (TAF)/emtricitabine + integrase inhibitor

D) tenofovir (TDF)/emtricitabine + protease inhibitor

PREVIEW QUESTION

1.13

A hospitalized patient with nosocomial Influenza A was treated promptly with oseltamivir.

She should be placed on:

A) Standard Precautions in any room

B) Standard Precautions in a private room

C) Contact Precautions

D) Droplet Precautions

E) Airborne Precautions

PREVIEW QUESTION

1.14

A 47-year-old male with acute myeloid leukemia and an neutrophil count below 100/mcl for the past three weeks has been febrile for 10 days, first treated with piperacillin-tazobactam

Had been on prophylactic micafungin but a blood culture is growing a yeast on Gram stain.

PREVIEW QUESTION

1.14

The most likely echinocandin-resistant yeast is which of the following:

A) Candida parapsilosis

B) Candida glabrata

C) Candida auris

D) Trichosporon asahii

E) Candida krusei

PREVIEW QUESTION

1.15

45 year-old male 6 weeks post stem cell transplant for myelodysplasia, with a history of chronic hepatitis C was discharged home to Florida on cyclosporine, mycophenylate, prednisone, Bactrim (tmp/smz), citalopram and voriconazole.

Diffuse nonpruritic erythema developed over his sun exposed skin.

26 – Daily Question Preview 3

Speaker: John Bennett, MD

INFECTIOUS DISEASE 2020 BOARD REVIEW

PREVIEW QUESTION

1.15

The most probable cause was:

A) Porphyria cutanea tarda

B) Graft versus host disease

C) Drug interaction

D) Voriconazole

E) Bactrim allergy

INFECTIOUS DISEASE 2020 BOARD REVIEW

PREVIEW QUESTION

1.16

A 55-year-old man presents with R hip pain

H/o COPD requiring steroids frequently
HIV diagnosed 17 years ago

On TDF / FTC / EFV for 10 years; originally on IND / AZT / 3TC
Initial HIV RNA 340,000; CD4 43 cells/ul
Now HIV RNA < 50 c/ml; CD4 385 cells/ul

Electrolytes NL; Creat 1.3; Phos 3.5 Ca 8.5
Mg 2.1, alk phos 130; U/A neg
R Hip film unremarkable

INFECTIOUS DISEASE 2020 BOARD REVIEW

PREVIEW QUESTION

1.16

Which if the following is the most likely underlying cause of his hip pain?

A) Osteonecrosis of Femoral Head

B) Fanconi's syndrome

C) Vitamin D deficiency

D) Tenofovir bone disease

E) Hypogonadism

INFECTIOUS DISEASE 2020 BOARD REVIEW

PREVIEW QUESTION

1.17

A 55-year-old man presents with complaints of crushing chest pain

HIV diagnosed 10 years ago
Initial HIV RNA 340,000; CD4 43 cells/ul
Now HIV RNA < 50 c/ml; CD4 385 cells/ul

Initally Rx with ZDV/3TC / EFV;
Now on ABC/3TC/ EFV

On no other medications / smoker
ECG shows acute myocardial infarction

INFECTIOUS DISEASE 2020 BOARD REVIEW

PREVIEW QUESTION

1.17

Which of the following is the highest relative risk for his Acute MI?

A) Cigarette smoking

B) Lipid levels (LDL level of 180 / HDL 30)

C) Abacavir use

D) Lack of use of aspirin
E) HIV infection

INFECTIOUS DISEASE 2020 BOARD REVIEW

PREVIEW QUESTION

1.18

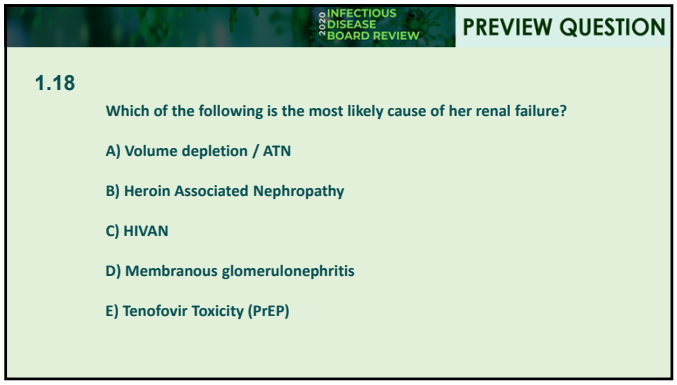
A 25-year-old black woman presents with fatigue

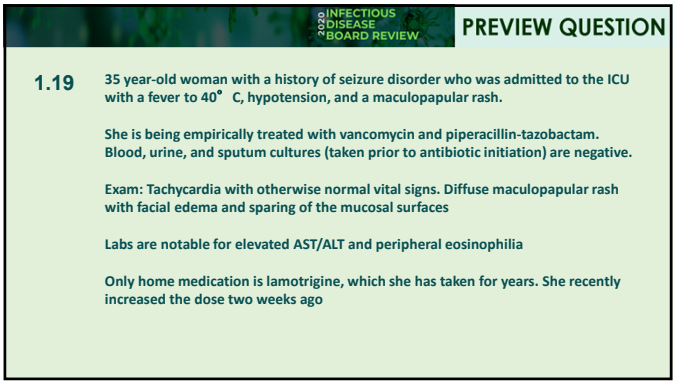
History of IV Heroin use; intermittently takes TDF/FTC PreP
Exam no edema
Work up in ER shows creatinine 8.4
BUN 79; mild anemia; mild acidemia

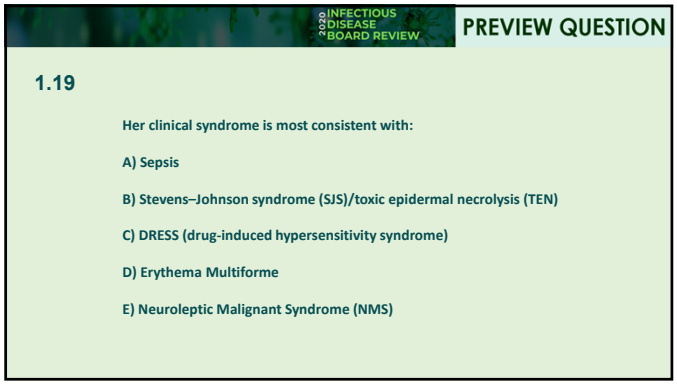
In ER 10 weeks earlier; normal renal function
U/A high grade proteinuria
US of kidneys: Normal to increase size; no obstruction
Rapid HIV test positive

26 – Daily Question Preview 3

Speaker: John Bennett, MD







27

Upper Gastrointestinal Infections

Dr. Herbert L. DuPont

27 – Upper Gastrointestinal Disease

Speaker: Herbert L. DuPont, MD

2020 INFECTIOUS DISEASE BOARD REVIEW

Upper Gastrointestinal Infections

Herbert L. DuPont, MD
Professor, Infectious Diseases, Epidemiology
The University of Texas McGovern Medical School and School of Public Health
Clinical Professor, Infectious Diseases Baylor College of Medicine and MD
Anderson Cancer Center

Disclosures of Financial Relationships with Relevant Commercial Interests

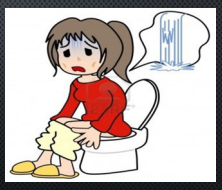
- None

OBJECTIVES

- List the most communicable and most lethal enteric pathogens
- Provide a review of the new developments for enteric pathogens including travelers' diarrhea treatment
- Indicate differences between the seafood neurotoxin disorders
- Critique PCR methods to establish enteric infection diagnosis

THE IMPORTANCE OF DIARRHEA IN THE UNITED STATES

- Prevalence 3-7% for adults and 8% for children ≤ 5 years of age
- 0.6 cases/person/year
- 48 million cases of foodborne disease (half due to noroviruses)



DEATH FROM DIARRHEA IN U.S.

- 11,255 deaths/year: 83% of deaths occur in adults ≥ 65 years of age; Pediatric deaths 369/year
- *C. difficile* infection (CDI) the most common cause of death 7,903* year (70% of total)
- Noroviruses (797/year) often in elderly in hospitals or nursing homes
- *Salmonella* (378) and
- *Listeria* (260)

*CDC data 29,000 deaths annually

Hall, AJ et al. Clin Infect Dis 2011;55:216-23
CDC http://www.cdc.gov/foodborneburden/2011-foodborne-estimates.html

PATHOGEN COMMUNICABILITY
ALL INFECTIOUS DISEASES SHOW A DOSE THRESHOLD FOR ILLNESS

Pathogen Group	Expected Inoculum Size
Highest rate of transmissibility*: *Shigella*, Noroviruses	10 to 100 organisms
High rate of transmissibility: *Giardia*, *Cryptosporidium*, *Salmonella* (infants only)	80-500 organisms
Low communicability: Shiga toxin-producing *E. coli*, *Salmonella* (older children/adults), *Campylobacter*	500 to 100,000 organisms
Absence of communicability: enteroinvasive and enterotoxigenic *E. coli* (EIEC, ETEC) and *Vibrio cholerae*	100,000 to > 1,000,000 organisms

*low inoculum requirement, stability in environment, reservoir in children
Immunocompromised/elderly people, infants, those on proton pump inhibitors may be susceptible to lower inoculum sizes

QUESTION #1

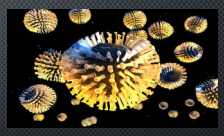
LOW DOSE PATHOGENS COMMONLY CAUSE DIARRHEA OUTBREAKS IN DAY CARE CENTER WHICH OF THE FOLLOWING DOESN'T FIT?

A. *SHIGELLA*
B. *CRYPTOSPORIDIUM*
C. *GIARDIA*
D. *CAMPYLOBACTER JEJUNI*
E. NOROVIRUS

VIRAL GASTROENTERITIS

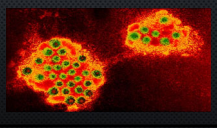
ROTAVIRUS

- KILLER OF 215,000 INFANTS GLOBALLY
- DECREASED RATES WORLDWIDE THANKS TO INEXPENSIVE VACCINES



NOROVIRUSES

- SAME MORTALITY ESTIMATES AS ROTAVIRUS FOR DEVELOPING WORLD
- > 20 MILLION CASES FOODBORNE DISEASE IN U.S. (HALF OF ALL CASES); 26% OF CASES PRESENTING TO ED
- 20% OF U.S. POPULATION NOT SUSCEPTIBLE RELATED TO ANTIGENS THAT DETERMINE BLOOD TYPES
- MAJOR PATHOGEN GENO GROUP II GENOTYPE 4 (GII.4)
- SECONDARY ATTACK COMMON (17%)
- A PROPORTION OF PEOPLE ARE NOT SUSCEPTIBLE
- INCREASING IN CHILDREN AS ROTAVIRUS DECREASING



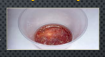
SHIGA TOXIN-PRODUCING *E. COLI* INFECTION (~300,000 CASES IN U.S.)

***E. coli* O157**
SORBITOL-NEGATIVE
SORBITOL-MACCONKEY AGAR & O157 SEROTYPING

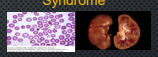
***E. coli* non-O157**
Sorbitol-positive, test stools, broth or culture plate for *Stx* 1 and 2 by EIA and if positive send *E. coli* to Health Lab

Hemorrhagic colitis

Dysentery — 85%



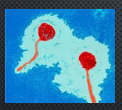
Hemolytic Uremic Syndrome — 9%



13% — 9%

STEC strains are threatening our food supply

SHIGA TOXIN PRODUCTION UNDER PHAGE CONTROL



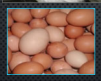
- SOME ANTIBIOTICS MOBILIZE PHAGE (E.G. FLOUROQUINOLONES, TMP-SMX),
  AZITHROMYCIN AND RIFAXIMIN DO NOT
- ANTIBIOTICS ARE NOT INDICATED IN THIS INFECTION BUT STAY TUNED
- IV ECULIZUMAB, A MONOCLONAL ANTIBODY CAN IMPROVED RENAL INSUFFICIENCY

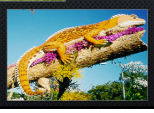
QUESTION # 2

WHAT OF THE FOLLOWING IS TRUE ABOUT ECULIZUMAB TREATMENT OF HUS?

A. ECULIZUMAB IS NOT APPROVED FOR OTHER INDICATIONS
B. TREATED PATIENTS ARE SUSCEPTIBLE TO MENINGOCOCCAL INFECTIONS
C. RED CELL DESTRUCTION IS NOT PREVENTED
D. COST OF THE DRUG HAS DECREASED WITH INCREASED USE
E. TREATMENT DOES NOT DECREASE NEED FOR BLOOD TRANSFUSIONS

NON-TYPHOID SALMONELLOSIS





- HIGHEST RATE <1 YEAR AGE
- ANTIBIOTICS ARE NOT HELPFUL IN NON-BACTEREMIC FORMS
- BECAUSE OF DEEP MUCOSAL PENETRATION BACTEREMIA RATE IN HEALTHY OCCURS IN 8% OF HEALTHY PEOPLE, HIGH-RISK GROUPS: ELDERLY, INFANTS 1-3 MONTHS, SS DISEASE, INFLAMMATORY BOWEL DISEASE, IMMUNOCOMPETENCE OR ON STEROIDS) RATE UP TO 50%

27 – Upper Gastrointestinal Disease

Speaker: Herbert L. DuPont, MD

NON-TYPHOID SALMONELLOSIS

- Current epidemic of bacteremic disease all age groups in Sub Saharan Africa which relates to host & Microbial factors: Co-existent malaria and HIV infection
- Israeli study showing that strains showing persistent infection show changes in composition of mobile genetic elements (plasmids and phages) and amino acid substitutions changing SNPs altering virulence and secondary transmission
-

Marzel, A et al. Clin Infect Dis 2016;62:879-86

PROTOZOAL PATHOGENS CAUSE PROTRACTED DIARRHEA

- Persistent diarrhea (≥ 14 days)
- Diagnostic challenges

Negative test Giardia, EIA/PCR for E. histolytica, acid fast staining not routine, multiplex PCR solves

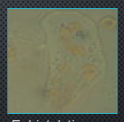
- Sporulation required for *Cyclospora* for infectivity
- *Cryptosporidium*

Animals reservoir, water vehicle of transmission

- *E. histolytica* produces liver abscess most importantly in males

Serology helpful in hepatic abscess as stools often negative

Giardia



E. histolytica

Cryptosporidium

Cyclospora

SEAFOOD FOODBORNE DISEASES

Dinoflagellates (DF) in water are the Source of toxin

Neurotoxigenic Illnesses:

- Paralytic Shellfish: toxin from different DF concentrated in in mollusks producing numbness and tingling after 30-60 minutes; serious cases may need respiratory support
- Ciguatera: toxin from DF (*Gambierdiscus toxicus*) growing around coral reefs 35°N and 35°S latitudes, that are ingested by large reef fish ~50,000 each year in world, many in travelers, GI symptoms, cold hot reversal and numbness & paresthesias
- Neurotoxin Inhalation or Shellfish poisoning: toxin from DF *Karenia brevis* inhaled during algal blooms, biggest problem in asthmatics or the toxin is ingested with mild form of paralytic shellfish poisoning
- Pufferfish: toxin from DF in pufferfish (Japanese delicacy)

SEAFOOD FOODBORNE DISEASES

Toxin concentrates in fish or mollusks (histamine-like substances from spoiled fish)

Chemical Illness:

- Scrombroid (histamine-like histidine) from improperly refrigerated or preserved tuna, mackerel, mahi-mahi, sardine, anchovy, herring, bluefish, amberjack and marlin causing a histamine reaction: flushing (like sunburn), headache, palpitations, itching, diarrhea within 10-60 minutes with resolution in 12 hours
- People report a peppery, sharp and salty taste
- Heat stable histamine

WHAT'S NEW TRAVELERS' DIARRHEA

ESBL or MDR Enterobacteriaceae

Risk Factor: Travel to tropical and semitropical areas, especially Asia (highest for travel to India)

- Diarrhea increases rate and receipt of antibiotics further increases risk

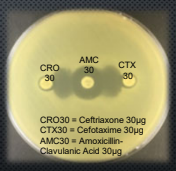
Can spread to family member

Duration of colonization after returning home is < 3 months to 12 months

Colonization by resistant organisms in traveler's diarrhea is shorter in duration than when it is acquired in a hospital

- Treat only more severe Travelers' diarrhea

Extended spectrum beta lactamase-producing Enterobacteriaceae



CRO30 = Ceftriaxone 30µg
CTX30 = Cefotaxime 30µg
AMC30 = Amoxicillin-Clavulanic Acid 30µg

Jiang Z-D, DuPont HL

DIAGNOSTIC APPROACHES IN INFECTIOUS DISEASES MOVING TO PCR

The Positives

- Syndromic approach detects organisms that clinicians may have not thought about/ordered or are difficult to isolate in the lab
- Rapid diagnosis may allow earlier initiation of therapy
- For larger centers, is cost effective
- Has potential to re-define epidemiology and treatment

CHALLENGES MULTIPLEX PCR DIAGNOSIS

The Negatives

- PATHOGENS ARE NOT ISOLATED FOR SUSCEPTIBILITY TESTING AND EPIDEMIOLOGY PURPOSES
- IN POSITIVES, CULTURE OF STOOL YIELDS PATHOGEN IN <60%
- COLONIZING *C. DIFFICILE* IN PATIENTS ASSOCIATED WITH FALSE (+), REQUIRE CONFIRMATION WITH SECOND STEP
- INTERPRETATION FOR SOME PATHOGENS IS DIFFICULT (E.G. ENTEROPATHOGENIC *E. COLI* (EPEC) & ENTEROAGGREGATIVE *E. COLI* (EAEC)
- EXPENSIVE FOR SMALLER HOSPITALS

Requires clinical judgement & correlation

CHALLENGES MULTIPLEX PCR DIAGNOSIS

MULTIPLEX PCR PLATFORMS: BIOFIRE (22 PATHOGENS), LUMINEX (19 PATHOGENS), BIOCODE (17 PATHOGENS)

TWO REASONS NOT APPROPRIATE FOR ROUTINE STUDY OF DIARRHEA: TOO EXPENSIVE AND LOW CLINICAL YIELD (IDENTIFICATION OF TREATABLE PATHOGENS*)

QUANTITATIVE (QPCR OR TAQMAN ARRAY CARD) CAN DETERMINE INFECTION FROM COLONIZATION BUT AT GREAT COST

*Clark SD et al. Open Forum Infect Dis 2019;6(4).doi:10.1093/ofid/ofz162

2017 INFECTIOUS DIARRHEA GUIDELINES (HIGHLIGHTS)

- EXERCISE CLINICAL JUDGMENT WHEN INTERPRETING PCR-BASED RESULTS
- PERFORM REFLEX CULTURES WHEN AN ORGANISM IS IDENTIFIED BY PCR FOR EPIDEMIOLOGY AND SUSCEPTIBILITY TESTING
- FECAL LEUKOCYTE, LACTOFERRIN, CALPROTECTIN ARE NOT ROUTINELY INDICATED
- DIAGNOSTIC TESTING IS NOT INDICATED FOR TRAVELERS' DIARRHEA UNLESS DIARRHEA PERSISTS >14 DAYS, CONSIDER *C. DIFFICILE* IF ANTIBIOTIC EXPOSURE. TD CAN TRIGGER INFLAMMATORY BOWEL DISEASE OR IRRITABLE BOWEL SYNDROME
- MONITOR CR/HB IN PATIENTS WITH STEC IDENTIFIED IN STOOLS AT RISK FOR HUS, EXAMINE PERIPHERAL SMEAR FOR SCHISTOCYTES
- PERFORM ENDOSCOPY FOR PERSISTENT, UNEXPLAINED DIARRHEA. EVALUATE HIV AND LYMPHOPENIC PATIENTS FOR CMV AND MAC

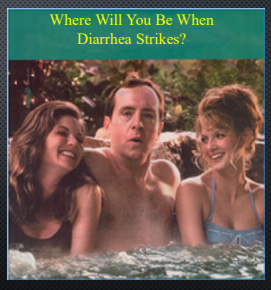
Shane, et. al. CID 2017:65 e45-80

ORGANISM-SPECIFIC THERAPY

- Shigellosis – Fluoroquinolone or azithromycin
- Non-typhoid salmonellosis – only with sepsis - fluoroquinolone or 3rd generation cephalosporin
- Campylobacteriosis – Azithromycin or erythromycin
- STEC diarrhea – none
- Non-cholera *Vibrio* diarrhea – as shigellosis
- Cholera – doxycyline
- Viral gastroenteritis – ORT, ? Bismuth subsalicylate
- Giardiasis – Tinidazole or nitazoxanide
- Cryptosporidiosis - nitazoxanide
- Cyclosporiasis or Cystoisosporiasis – TMP/SMX
- Enterocytozoon diarrhea – Albendazole
- Intestinal amoebiasis – metronidazole plus diloxanide furoate or paromomycin

CONCLUSIONS

- INFECTIOUS DOSE INFLUENCES ATTACK RATE AND INCUBATION PERIOD
- NOROVIRUSES - MOST COMMUNICABLE PATHOGEN, CAUSES HALF OF THE CASES OF FOODBORNE DISEASE, REPLACING ROTAVIRUS AS THE MAJOR PEDIATRIC ENTEROPATHOGEN
- IT IS IMPORTANT TO UNDERSTAND STEC AS A PATHOGEN, PATHOGENESIS AND DIAGNOSIS
- NON-TYPHOID SALMONELLA IS CAUSING EPIDEMIC BACTEREMIA IN ALL AGE GROUPS IN SUB SAHARAN AFRICA DUE TO HOST AND MICROBIAL FACTORS
- ANTIBIOTICS TAKEN WHILE IN A DEVELOPING REGIONS WILL ENCOURAGE COLONIZATION OF ESBL COLIFORMS
- MULTIPLEX PCR DIAGNOSTICS HAVE THE POTENTIAL TO REVOLUTIONIZE DIAGNOSIS AND EPIDEMIOLOGY OF INFECTIOUS DIARRHEA



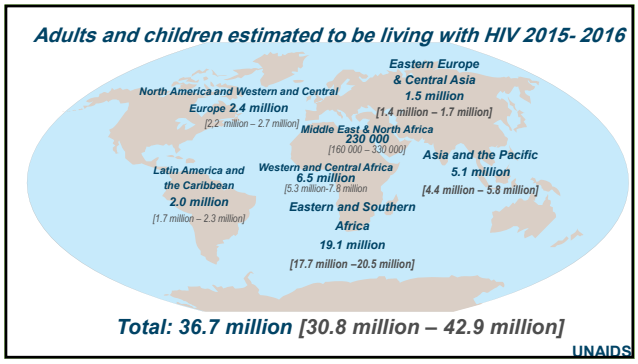
28

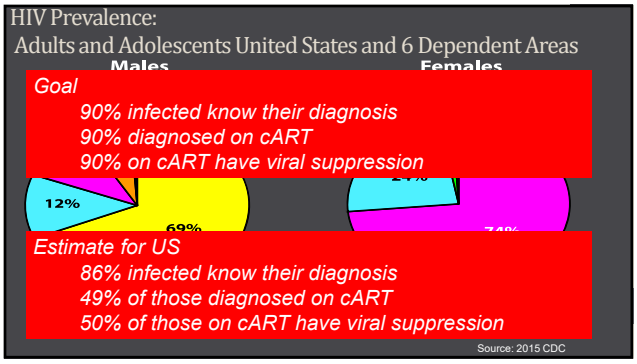
Clinical Manifestations of Human Retroviral Diseases and Slow Viruses

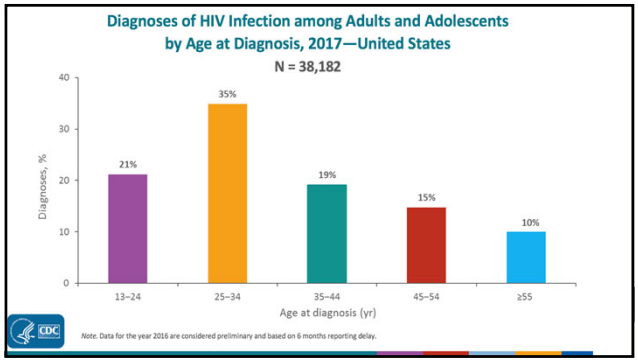
Dr. Frank Maldarelli

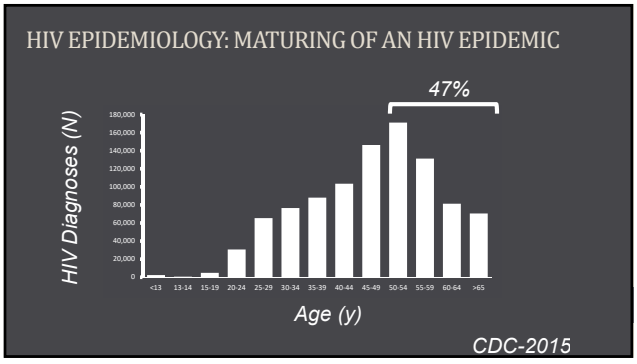
28 - Clinical Manifestations of Human Retroviral Diseases and Slow Viruses

Speaker: Frank Maldarelli, MD







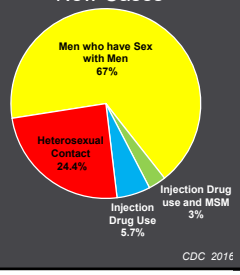


28 - Clinical Manifestations of Human Retroviral Diseases and Slow Viruses

Speaker: Frank Maldarelli, MD

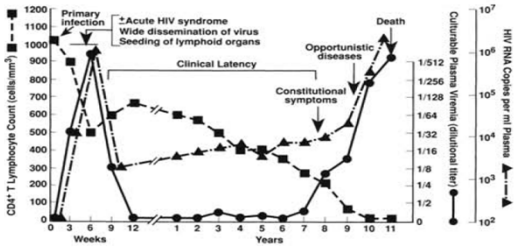
Trends in US HIV Epidemic (CDC)

- Race/ethnicity
  - African Americans exceed white/not hispanic as most common patients with AIDS
- Geography
  - ~12% of cases in locations with population <50,000
  - Outbreaks in rural US
- Gender
  - Females comprise > 25% of all AIDS cases
- Age
  - Nearly 50 of persons living with HIV is ≥ 50 yo
  - MSM most common risk



CDC 2016

HIV INFECTION COURSE

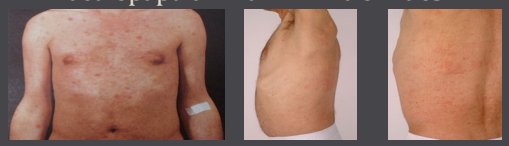


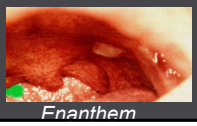
Acute HIV Syndrome

Sign/symptom	Percent Reporting NEJM Review	Kenyan sex workers	HIVNET
Fever	>80-90	53	55
Fatigue	>70-90	26	56
Rash	>40-80	9	16
Headache	32-70	44	33
Lymphadenopathy	40-70	7	35
Pharyngitis	50-70	15	43
Myalgia or arthralgia	50-70	24	39
Nausea, vomiting or diarrhea	30-60	18	12-2
Night sweats	50	nd	nd
Aseptic meningitis	24	nd	nd
Oral ulcers	10-20	nd	6
Genital ulcers	5-15	3	nd
Thrombocytopenia	45	nd	nd
Leukopenia	40	nd	nd
Elevated LFTs	21	nd	nd
Too ill to work	nd	44	58

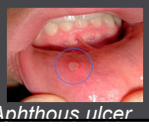
Primary HIV-1 Infection Syndrome

Maculopapular Trunk > Extremities





Enanthem



Aphthous ulcer

HIV Diagnosis: Question #1

A 23 year old man presents with a history of unprotected receptive anal sex with known HIV-infected man, and one week of fever, adenopathy.

HIV-1/2 ELISA is reactive, viral RNA level 500,000 c/ml.

He is started immediately on antiretrovirals.

His confirmatory assay is negative, and repeat assays sent 3 weeks, 3 months, and one year after starting antiretrovirals are also negative.

ELISA remains reactive. HIV-2 assay is negative.

Viral RNA on therapy is <40 c/ml.

HIV Diagnosis: Question #1 continued

Which of the following is correct:

A. The patient was infected with a strain of HIV-1 that was not detected by the confirmatory assay
B. The patient is HIV-infected but did not develop a positive confirmatory assay because of the early antiretroviral therapy intervention
C. The patient never had HIV infection.
D. The patient had HIV but is now cured of HIV and antiretrovirals can safely be stopped

Early Antiretroviral Therapy

- Prompt reduction in HIV-1 RNA
- Potential blunting of humoral immune response
- Confirmatory assay may become unreliable
- HIV-1 DNA PCR has been useful in documenting infection

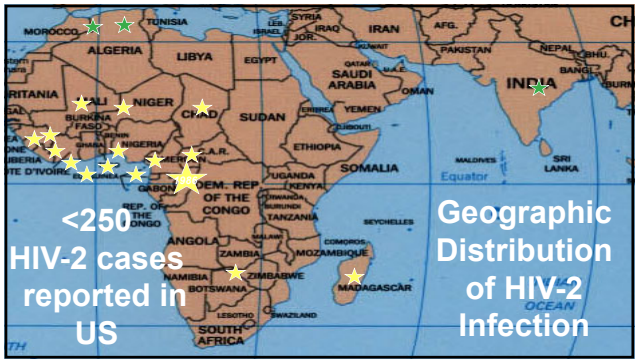
HIV Clinical Presentation: Question #2

A 49 year old woman from Guinea-Bissau has a reactive HIV-1/2 ELISA and a HIV multispot positive for HIV-2 and negative for HIV-1.

CD4 cell count is 350 cells/µl.

Which of the following is correct?

A. HIV-2 is less pathogenic than HIV-1 so she only needs therapy with one antiretroviral drug
B. She should not be treated with protease inhibitors because HIV-2 is naturally resistant to PIs.
C. She should not be treated with NNRTI therapy because HIV-2 is naturally resistant to NNRTIs.
D. Use of routine HIV-1 viral load assays is useful in patient management



HIV-1 and HIV-2 Contrasting Retroviral Infections

Characteristic	HIV-2	HIV-1
Epidemiology		
Geography	West Africa +	Worldwide
Local Distribution	Urban=rural	Urban>rural
Prevalence	Stable or Decreasing	Increasing
Pathogenesis		
Average age at diagnosis	45-55	20-34
Maternal-fetal (without RX)	0-4%	20-35%
Kaposi Sarcoma	Less common (10X)	More common
Therapy	NRTI, PI, INSTI, Corec	NRTI, PI, NNRTI
	NOT NNRTI NOT Fusion	INSTI, Corec, Fusion
Diagnosis		
Screening	HIV1/2 ELISA	HIV1/2 ELISA
Confirmatory	Supplemental (e.g., Geenius)	Supplemental Qual. HIV RNA)
Monitoring	HIV-2 RNA Assay	HIV-1 RNA assay

Question #3

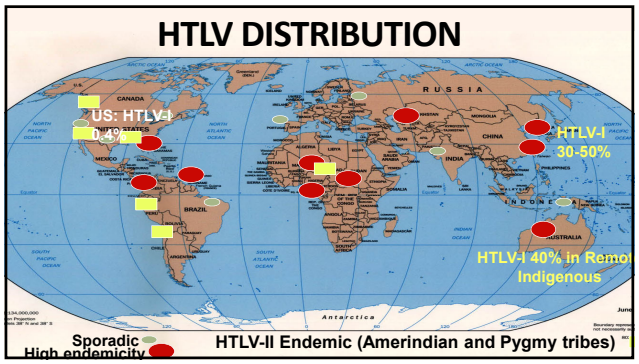
A 42 year old man from the Haiti presents with fever, moderate respiratory distress, and nonproductive cough. HIV-1/2 ELISA is reactive and discriminatory test is positive for HIV-1. A PCR test of the induced sputum is positive for *Pneumocystis jiroveci.* On evaluation the lymphocyte count is 2,000 cells/µl; the CD4 count is 750 cells/µl and th hematology technician remarks that some of the lymphocytes are "flower cells". Which of the following is most correct in explaining the hematology findings:

A. The patient has B cell lymphoma
B. The patient has HIV infection and the elevated CD4 count is due to steroids used in the treatment of the *Pneumocystis* pneumonia
C. The patient has HTLV-1 infection only the HIV test is a false positive
D. The patient has both HIV infection and HTLV-1 infection

Question #4

A 25 year old pregnant woman immigrant from southern Japan was referred to you for evaluation of a positive HTLV-I western blot. Which of the following statements is true:

A. The risk of HTLV-I transmission can be entirely eliminated by caesarean section.
B. The risk of HTLV-I transmission will be entirely eliminated by not breastfeeding.
C. Breastfeeding will provide sufficient immunity to prevent infection with HTLV-I.
D. The risk of HTLV-I transmission will be significantly decreased but not entirely eliminated by avoiding breastfeeding.
E. There is no risk of HTLV-I disease. In this ethnic group, the HTLV-I test was likely a false positive.

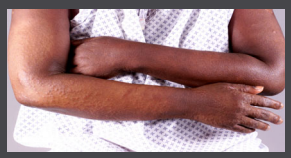


HTLV-I Transmission

- Breastfeeding
  - Prolonged duration: 20-30% seroconvert if breastfed >12 mos
  - High maternal HTLV proviral load in breastmilk: 28.7 infections/1000 person months with 1.5% HTLV+ lymphs
- Sexual
- Transfusion
  - Risk of seroconversion: 40-60%
- Testing Sequential ELISA/Western blot

Question #5

37 year old Jamaican female with diffuse pruritic rash (right), bone pain with lytic bone lesions.
WBC: 50,000, 90% lymphocytes



Which is most likely cause of her presentation?

A. HTLV-I
B. HTLV-II
C. HIV-1
D. HTLV-IV

HTLV-I Acute T cell Leukemia (ATL)

- Long Latency (>30 years)
  - Small pediatric series in SA
- Epidemiology
  - Approximately 1% of HTLV- I infected adults
  - M>F (Japan); M=F (Jamaica)
- Associated syndromes
  - Infectious
    - TB, MAC, Leprosy
    - PCP
    - Recurrent Strongyloides
    - Scabies esp. Norwegian scabies
  - Noninfectious-hypercalcemia+lytic bone lesions
- Therapy
  - Cytotoxic chemotherapy
  - AZT+Ifn
  - Transplant
  - Mogamulizumab (Poteligeo, anti CCR4 monoclonal) APPROVED in Japan for ATL
  - Lenalidamide

Question #6

38 year old woman from Jamaica presents with weakness, unsteadiness of several months duration and has recently developed incontinence. Neurologic exam notes hyperreflexia ankle clonus, and positive Babinski reflex

WBC = 7500 cells/ul

CD4 T cell = 1000 cells/ul

CSF cell count: 10 cells/mm^3 (lymphocytes)

CSF protein: 75 mg/dl

Question #6 Continued

The etiologic agent associated with this illness is also associated with

A. Acute T cell leukemia
B. Multiple sclerosis
C. Variant Creutzfeldt-Jacob
D. Hemorrhagic cystitis

HTLV-I Tropical Spastic Paraparesis /HTLV-1 Associated Myelopathy

- Epidemiology
  - <1% of HTLV-I develop HAM/TSP
  - The second most common neurologic syndrome in Jamaica after stroke
  - Latency may be short--several years
  - Female predominance

HTLV-I TSP/HAM

- Presentation
  - Spastic paraparesis
    - Lower>upper
    - Proximal>distal
  - Bladder disturbance
  - Hyperreflexia
  - Positive Babinski reflex
- Differential Diagnosis
  - Cord compression
  - B12 deficiency
  - Syphilis
  - HIV-1 myelopathy
  - Multiple sclerosis

Therapy of HTLV-I TSP/HAM

- No randomized trials
- Corticosteroids
  - May slow progression and reduce disability
- Antiretroviral therapy is NOT effective

Question #7

You are asked to see a 62 year old male smoker, former IV drug user for evaluation of recurrent cough and weight loss. Evaluation reveals metastatic non-small cell lung cancer. Serologic testing notes he is HIV negative, HTLV-1 negative, but HTLV-2 positive . The oncology team calls regarding your advice about HTLV-2 and treating the patient with the checkpoint inhibitor durvalumab (blocking PDL-1 interactions with PD-1) in addition to chemotherapy. Which of the following is most correct:

A. **He should not be treated with durvalumab**
B. **He can be treated with durvalumab, but will also require therapy for HTLV-2 infection**
C. **He can be treated with durvalumab, but is at increased risk for other infectious complications, like *Pneumocystis jiroveci* compared with HTLV-2 uninfected individuals.**
D. **He can be treated with durvalumab and does not require additional therapy for HTLV-2 infection**

Summary

HTLV-1 Infection

- **Asymptomatic -95%**
- **Acute T cell Leukemia**
- **HAM/TSP**
- **But also**
  - **Bronchiectasis**
  - **Uveitis**
  - **Rheumatologic syndromes**
  - **Lymphocytic pneumonitis**
  - **Infective Dermatitis (pediatric)**
- **"Flower" cells**
  - **Lymphocytes with HTLV provirus present**
  - **Frequency in HIGHER in ATL and HAM/TSP**
  - **NOT an indication for specific therapy**

Associated Infections

- **Strongyloides hyperinfection**
- **Norwegian Scabies**
- **Pneumocystis**
- **MAC**

HTLV-2 is a distractor

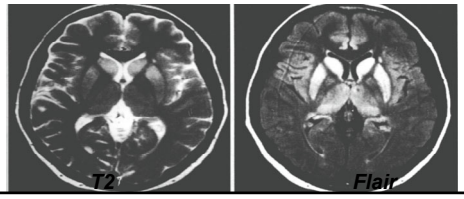
SLOW VIRUSES

Prion Disease Question #1

68 y. o. butcher who is an avid hunter presents with dementia progressing over 4 months, myoclonus, MRI below, periodic sharp waves on EEG.

Acquisition of this illness was most likely due to:

A. Contact with elk brains
B. Contact with sheep brains
C. Contact with pork brains
D. A spontaneous event

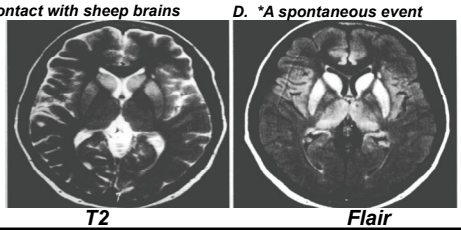


Prion Disease Question #1

68 y. o. butcher who is an avid hunter presents with dementia progressing over 4 months, myoclonus, MRI below, periodic sharp waves on EEG.

Acquisition of this illness was most likely due to:

A. Contact with elk brains
B. Contact with sheep brains
C. Contact with pork brains
*D. *A spontaneous event*

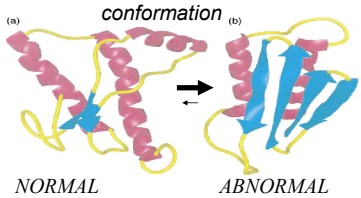


Prion Diseases: Transmissible Spongiform Encephalopathies

- **Spontaneous (N=~6000 worldwide per year)**
  - Sporadic Creutzfeldt-Jakob disease (sCJD)
- **Associated with specific ingestion**
  - Beef from cows with Bovine Spongiform Encephalopathy
    - Denoted "Variant CJD", "vCJD" (N ~ 220 total cases)
  - Human brains
    - Kuru (N= ~2700 total cases)
- **Associated with a medical procedure (N ~ 450 total cases)**
  - Iatrogenic
  - Denoted "iCJD"
- **Hereditary (N ~600-900 worldwide per year)**
  - Familial (fCJD)
  - Gerstmann-Straussler-Sheinker (GSS)
  - Fatal Familial Insomnia (FFI)
  - Fatal Sporadic Insomnia (FSI)

Prion Disease Pathogenesis A. Initiation

The prion protein is a host protein with a normal and abnormal conformation



NORMAL *ABNORMAL*

Transition to abnormal conformation is rare but essentially irreversible

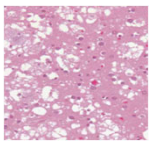
Naturally occurring mutations favor interconversion

Prion Disease Pathogenesis B. Propagation

Protein-Protein Contacts recruit normal proteins into abnormal conformation

Direct contact

Prion Protein Mutant conformation



Prion Protein Mutant conformation

Spontaneous Creutzfeldt-Jacob Disease (sCJD) Epidemiology

- Most common human Transmissible Spongiform Encephalopathy (TSE)
  - 95% cases
- Incidence estimated 1 per million
  - US: 0.1/million in <55 yo, 5.3/million >55 yo
  - Mean age of onset is 60 years

Dementia Comparison

Type	Protein	Clinical	Course	Path	MRI
sCJD	Prion	Myoclonus	<2 y	Spongif. Degen.	Caudate Striatum Thalamus
Alzheimer	Apo E4, Tau	Memory Language	>4 y	Neurofib. tangles	Hippocampus White matter
Lewy Body	α- Synuclein	Parkinsonian Visual hallucin.	>4 y	Lewy Bodies	Less common
Multi-infarct	Atheroma	Focal	Incremental	Vascular	Caudate,Pons Thalamus Ovoid Nuc

Prion Disease Question #2

A 68 year old man with dementia progressing over the last 6 months undergoes evaluation. Which of the following CSF results is most consistent with Creutzfeld Jakob Disease: .

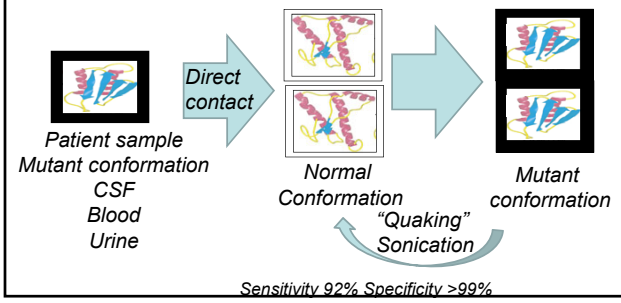
A. 14-3-3 protein: Positive
B. RT-QuIC: Positive
C. T-tau protein: 3000 pg/ml (normal 0-1150 pg/mL)
D. Abeta42: 1250 (normal >1026 pg/mL

Spontaneous Creutzfeldt-Jacob Disease

Typical Clinical Presentation

- Rapid progression
- Classic Clinical Triad
  - – Dementia
  - – Myoclonus
  - – EEG: periodic sharp waves
- RT-QuIC elevated abnormal prion protein
- 14-3-3 not specific for CJD

Abnormal Prion Detection RT-QuIC

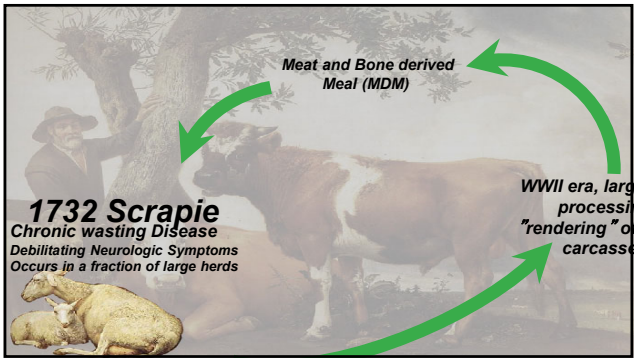


Prion Disease Question #2

A 30 year old man presents with dementia progressing over the last year. He was born in rural Indonesia, lived in London from 1990 – 2010, then moved to Philadelphia.

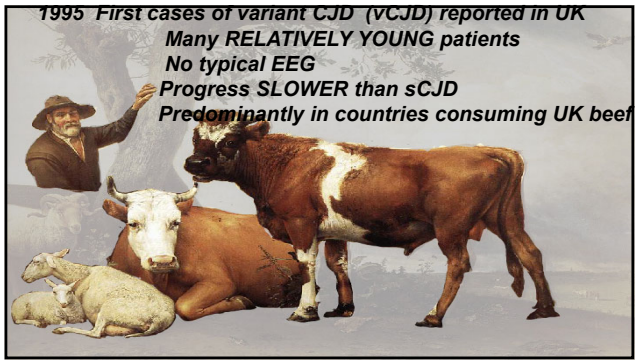
Which of the following diseases is most likely the cause of his symptoms:

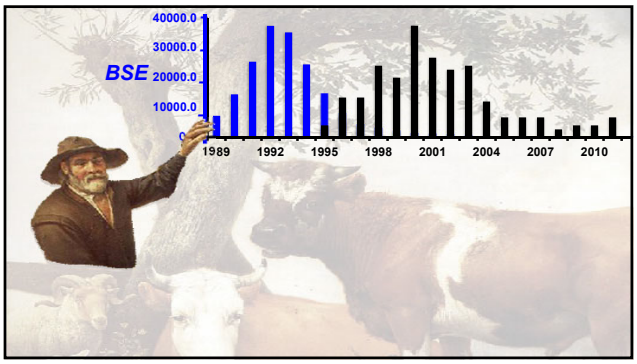
A. Kuru
B. variant Creutzfeldt-Jacob Disease
C. Familial Creutzfeldt-Jacob Disease
D. Rabies



28 - Clinical Manifestations of Human Retroviral Diseases and Slow Viruses

Speaker: Frank Maldarelli, MD





Question #4 vCJD Geographic Distribution

Residence in which of the following countries after 1980 represents the highest risk for acquiring variant CJD (vCJD):

A. *France*
B. *Borneo*
C. *United States*
D. *Australia*
E. *Argentina*

Numbers of vCJD Cases Worldwide

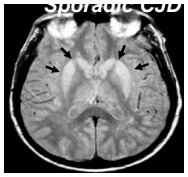
- United Kingdom: 178
- France: 28
- Spain: 5
- **US: 4**
  - **(ALL infections acquired OUTSIDE of US)**
- Ireland: 4
- Netherlands, Italy: 3
- Portugal, Canada: 2 each
- Saudi Arabia, Japan, Taiwan: 1 each

(Nat'l CJD Res. Surv. Unit, U. Edinburgh, www.cjd.ed.ac.uk 2019)

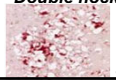
vCJD vs. sCJD

	sCJD	vCJD
Source	Spontaneous event	Ingested beef
Distribution	Worldwide	Linked to Beef originating largely in UK
Median Age (y)	68	28
Progression	SHORTER	LONGER
EEG	Typically abnormal	NOT Typically abnormal
MRI Basal ganglia	"Double Hockey Stick"	"Pulvinar sign"
Pathology	Abnormal Prion Protein deposits	"Florid Plaques"

sCJD

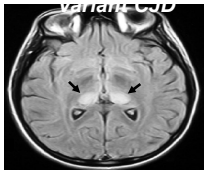


T2 axial proton weighted Putamen and caudate head "Double hockey stick sign"

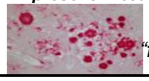


"Abnormal Prion accumulation"

vCJD



T2 axial proton weighted "Pulvinar Sign" present >75% cases



"florid plaques"

Prion Diseases Question #5

A 49 year old man recently emigrated from Japan presents with rapidly progressing dementia.

He underwent a meningioma resection with dura mater graft in Japan 35 years ago.

He is an avid deer hunter and consumes venison.

What is the most likely cause of his dementia:

A. **Iatrogenic CJD from the dura mater graft**
B. **Iatrogenic CJD from eating deer.**
C. **HTLV-I**
D. **Spontaneous CJD**

Iatrogenic CJD ~450 cases

Definite Causes

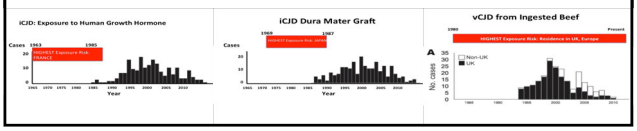
- **Pituitary extracts**
  - **Human Growth Hormone**
  - **Gonadotrophin**
  - **Delay may be >30 y**
  - **(Role in AD as well?)**
- **Dura mater grafts**
  - **Mostly Lyodura brand**
- **Transplants**
  - **Corneal**
  - **Pericardium**
  - **Liver**
- **Instrumentation**
  - **Implantable Neurosurgical-EEG, stereotactic**

No Link

- **Vaccines**
- **Feces**
- **Saliva**
- **Sputum**
- **Bovine insulin**
- **Semen, vaginal secretions**

Transmissible Spongiform Encephalopathy:Time and Place

Mode of transmission	Geographic Region	Risk Window
Beef ingestion	UK, France, Europe	1980-present
Human growth hormone	France	1963-1985
Dura mater graft	Japan	1969-1987



Zoonotic Transmission CJD

Documented Risk

- Ingestion of Beef
  - Geographically limited
  - Emphasis on UK, France

No Documented Risk

- Mink:
  - Transmissible Mink Encephalopathy
- Elk, Mule deer:
  - Chronic Wasting Disease
- Sheep, goats
  - Scrapie
- Cat:
  - Feline Spongiform Encephalopathy

CJD and Blood Supply

- Transfusion-associated vCJD rarely documented (N=4, UK)
- NO documented transfusion-associated sCJD
- No FDA approved tests to detect transmission
- Deferred from blood donation
  - Dura mater graft or human growth hormone
  - Donors with CJD or family history of CJD
  - Residence in Europe after 1980
  - Transfusion in Europe after 1980
  - Bovine insulin after 1980 unless certain that insulin was not from UK

Transmissible Spongiform Encephalopathy

Infection Control Issues

- **Universal precautions**
- **No confirmed occupational transmissions**
  - CJD in health care workers occurs, occupational links have been suggested
- **Incinerate single use instruments**
- **Inactivate other instruments and materials**
  - 1N NaOH
  - autoclave 121º C, 15 psi 30 min
  - Formic acid for tissue sections
  - Alternatives include hypochlorite (20,000 ppm chlorine) + autoclave
  - REMEMBER: Infectivity is STABLIZED by alcohol, formalin, or glutaraldehyde
- **WHO infection control guidelines**
  - **http://www.who.int/csr/resources/publications/bse/whocdscsraph2003.pdf?ua=1**

Transmissible Spongiform Encephalopathy

Therapy

- **None**
  - **uniformly fatal**

Kuru "shivering,trembling"

- Fore tribe Papua New Guinea
- Ritual mourning w/cannibalism
- Older females, children (especially female)
- Progressive Ataxia w/dementia
  - Ambulant, leaning (pictured)
  - Sedentary
  - Terminal "laughing death"
  - "Florid plaques" (inset) on H+E
- No maternal/fetal transmission
- New cases would have been infected as children
- No cases <40 y.o. since 1991

Resources

- **RT-QuIC: Case Western**
  - https://case.edu/medicine/pathology/divisions/national-prion-disease-pathology-surveillance-center/resources-professionals/contact-and-shipping-information
- **Epidemiology**
  - https://www.cdc.gov/prions/cjd/resources.html
- **Patient support**
  - https://cjdfoundation.org/other-resources
- Fmalli@mail.nih.gov

29

Lower Gastrointestinal Infections

Dr. Herbert L. DuPont

29 – Lower Gastrointestinal Disease

Speaker: Herbert L. DuPont, MD

2020 INFECTIOUS DISEASE BOARD REVIEW

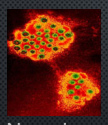
Lower Gastrointestinal Disease

Herbert L. DuPont, MD
Professor, Infectious Diseases, Epidemiology
The University of Texas McGovern Medical School and School of Public Health
Clinical Professor, Infectious Diseases Baylor College of Medicine and MD
Anderson Cancer Center

Disclosures of Financial Relationships with Relevant Commercial Interests

- None

OBJECTIVES


Noroviruses


E. coli


Shigella


Cyclospora

- Describe clinical characteristics of various forms of Enteric infection syndromes and seafood-associated illnesses
- Outline methods employed in foodborne outbreak investigation
- Define the current status of therapy of dysenteric travelers' diarrhea
- Explain the important post-diarrhea chronic complications
- Explain principles of workup of persistent diarrhea

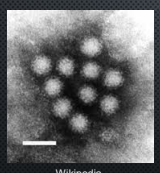
EVALUATION OF CASES OF DIARRHEA
KEYS CLINICAL FEATURES SPECIAL SETTINGS

VOMITING AS THE PRIMARY SYMPTOM

- Viral gastroenteritis with incubation period: 24 – 48 hours
- Food poisoning Performed toxin* of *Staphylococcus aureus* or *Bacillus cereus* with incubation period: 2-7 hours

**Clostridium perfringens* food Poisoning preformed toxin causes watery diarrhea without vomiting, incubation period of 8-14 hours*

CLINICAL/EPIDEMIOLOGIC CRITERIA FOR DIAGNOSING NOROVIRUS GASTROENTERITIS


Wikipedia

1. No bacterial causes identified
2. Incubation period 24-48 hours
3. Duration of illness 12-60 hours
4. Vomiting in ≥ 50%

QUESTION #1

WHAT IS NAME OF THESE CRITERIA FOR DIAGNOSING NOROVIRUS INFECTION?

A. Smidt's syndrome
B. Kaplan criteria
C. Enteric virus criteria
D. Non-bacterial gastroenteritis Criteria
E. Winter vomiting disease Criteria

1. No bacterial causes identified
2. Incubation period 24-48 hours
3. Duration of illness 12-60 hours
4. Vomiting in ≥ 50%

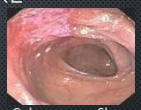
https://www.cdc.gov/norovirus/trends-outbreaks/responding.html

INDIVIDUAL CASES KEYS TO ESTABLISH CAUSE

CLINICAL FEATURES
SETTING (EPIDEMIOLOGY)
LABORATORY TESTING

83-YEAR-OLD MAN WITH BLOODY DIARRHEA DEVELOPS RENAL FAILURE

- He has a one week history of diarrhea with stools containing blood; he undergoes colonoscopy which looks like ischemic colitis
- As his diarrhea improves his urine output decreases
- Serum creatinine is 9, platelet count of 50,000, hematocrit 20 and LDH 1,000.
- Stool culture on Sorbitol MacConkey Agar grows no sorbitol-negative *E. coli* and stool sample is positive for Shiga toxin 2 by EIA
- He is treated with Eculizumab, a humanized monoclonal antibody inhibits the terminal sequence of complement



Colonoscopy Shows "Ischemic Colitis"

Peripheral Smear Shows Red Cell Fragments

QUESTION #2

What is the likely cause of dysentery and renal failure in the elderly man?

A. Ischemic bowel disease
B. Non-O157 Shigatoxin producing *E. coli* (STEC)
C. O157:H7 strain of STEC
D. *Shigella dysenteriae* 1 (Shiga bacillus)
E. *Campylobacter jejuni*

QUESTION #3

A patient develops numbness of lips, burning and tingling of his extremities, and abdominal pain and vomiting 30 minutes after a meal in Jamaica, progressing to respiratory failure.

What is the likely diagnosis?

A. Scombroid
B. Paralytic shellfish poisoning
C. Ciguatera
D. Neurotoxic shellfish poisoning
E. Monosodium glutamate toxicity

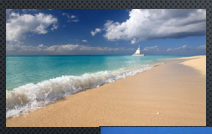
QUESTION #4

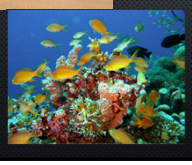
- A 65-year old chairman of medicine at a medical school with 15 days of diarrhea, passing 4-8 watery stools per day without fever or passage of bloody stools. He has not traveled and had an initial workup for diarrhea: standard stool culture and an order for parasites that includes a screen for Giardia, *Cryptosporidium* and *Entamoeba*.

Which of the following is the best next approach?

A. Collect 3 stools for parasites by EIA
B. Collect 3 stools for parasites by PCR
C. Perform multiplex PCR for enteric viral, bacterial and parasitic pathogens
D. Ask the laboratory to perform acid-fast staining of stool for parasites
E. Give the patient 1,000 mg azithromycin in single dose

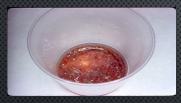
COMPLICATED CASE OF TRAVELERS' DIARRHEA





A 35-YEAR OLD WOMAN DEVELOPS DIARRHEA, CRAMPS AND IS PASSING BLOODY STOOLS WITH FEVER WHILE SNORKELING WITH HER FAMILY IN COZUMEL, MEXICO

QUESTION 5



Grossly bloody stool

Many leukocytes of stool microscopically indicate diffuse colonic inflammation

What is the preferred treatment for this patient With dysenteric traveler's diarrhea?

A. AZITHROMYCIN 1,000 MG
B. CIPROFLOXACIN 500 MG TWICE DAILY X 3 DAYS
C. LEVOFLOXACIN 500 MG
D. RIFAXIMIN 200 MG THREE TIMES/D FOR 3 DAYS
E. ORAL FLUIDS ONLY

QUESTION 6

She takes three days of ciprofloxacin, a drug she has with her for recurrent urinary tract infection.

Which of the following concerns you the most about this treatment?

A. COLONIZATION BY ESBL-PRODUCING COLIFORMS
B. ACHILLES TENDON DAMAGE
C. C. *DIFFICILE* INFECTION
D. INSOMNIA AND IRRITABILITY
E. SHE WILL RUN OUT OF DRUGS FOR FUTURE UTI

POST-ENTERIC INFECTION DISORDER

THE PATIENT EXPERIENCES A PROTRACTED COURSE

ABDOMINAL DISCOMFORT AND PAIN & BLOATING ARE NEAR CONSTANT PROBLEMS PRESENT 6 MONTHS LATER – SHE HAS NEVER BECOME WELL, ALTHOUGH THE ILLNESS HAS CHANGED IN CHARACTER FROM DIARRHEA TO ABDOMINAL DISCOMFORT WITH CHANGE IN BOWEL PATTERN (EATING INCREASES PAIN AND DECREASES STOOL FORM)

POST-INFECTIOUS IRRITABLE BOWEL SYNDROME 5-10% AFTER BACTERIAL DIARRHEA

PATHOGENESIS OF POST-INFECTIOUS IBS

Inflammatory Enteric Bacterial Infection

Diarrheal Illness

Non-susceptible host: Complete Recovery

Genetically Susceptible host with an abnormal host response related to microbe virulence

Post-Infectious IBS

POST-ENTERIC INFECTION DISORDER 2

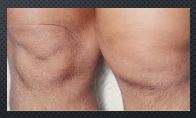
QUESTION 7

Which one of the following represents an antibody-Mediated post- enteric autoimmune complication?

A. CROHN'S DISEASE
B. FUNCTIONAL CONSTIPATION
C. REACTIVE ARTHRITIS
D. CELIAC DISEASE
E. WHIPPLE'S DISEASE

Post-Enteric Infection Disorder 2

- Reactive arthritis after infection by *Salmonella*, *Shigella* or *Yersinia* due to autoimmune responses targeting epitopes common to pathogen and joint tissues



What is another antibody-mediated post enteric infection Syndrome?

POST-ENTERIC INFECTION DISORDER 3

- Guillain-Barré Syndrome after *Campylobacter* infection due to cross reactivity between organism and neural ganglioside epitopes seen in 1-2/10,000 cases of campylobacteriosis

OUTBREAK INVESTIGATIONS

KEYS
EPIDEMIC CURVE
CLINICAL FEATURES
INCUBATION PERIOD
CASE-CONTROL STUDIES OF CAUSE

QUESTION 8

Three non-family members begin vomiting 2 hours after eating at a local Italian restaurant.

What is the likely cause?

A. Shigella spp. from restaurant
B. Staphylococcal enterotoxin from restaurant
C. Clostridium perfringens enterotoxin from restaurant
D. Norovirus from restaurant
E. Forget the restaurant

QUESTION 9

A foodborne outbreak occurred among 100 school children and teachers after a special luncheon.

- Median incubation period – 28 hours
- Vomiting seen in 70%
- Diarrhea in 50%
- Objective Fever in 30%
- Recovery occurred in 12 – 60 hours

What is the likely cause of the outbreak?

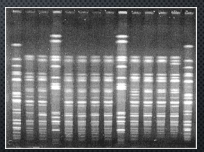
A. Norovirus
B. *Shigella sonnei*
C. Enterotoxin from *Staphylococus aureus*
D. *Clostridium perfringens*
E. *Bacillus cereus*

AN EPIDEMIC OF SHIGA-TOXIN (STX) PRODUCING *E. COLI* (STEC) O157:H7

- On May 19, 2009, the PulseNet national molecular subtyping network for foodborne disease surveillance identified a cluster of 17 cases of *E. coli* infection from 13 states with identical PFGE pattern
- Cases occurred between March 1 and July 31, 2009

PFGE being combined with WGS

PulseNet*



- Developed in 1996, two enzymes cut bacterial DNA, with an electrical
- Current moves DNA according to size showing unique banding patterns

EPIDEMIC CURVE - CASES BY DAY OF THE EPIDEMIC

Step 1: Outbreak Investigation

- 77 CASES WERE IDENTIFIED FROM 30 STATES WERE IDENTIFIED
- THE MEDIAN AGE WAS 15 YEARS, 71% WERE FEMALES
- 55% WERE HOSPITALIZED, 18% DEVELOPED HUS AND NONE DIED

*

CASE CONTROL STUDY PERFORMED TO IDENTIFY THE SOURCE

STEP 2: OUTBREAK INVESTIGATION

- CONTROLS WERE FOUND FROM CORRESPONDING HEALTH DEPARTMENTS WITH NON-STEC ENTERIC INFECTION
- CONVENTIONAL STEC RISK FACTORS* WERE NOT FOUND

**Ground beef, raw dairy products, leafy green vegetables, wading pools and animal contact*

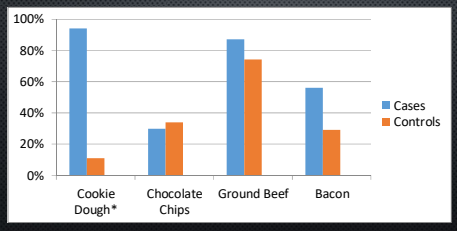
A CASE CONTROL STUDY WAS PERFORMED TO IDENTIFY THE SOURCE

STEP 2: OUTBREAK INVESTIGATION

- OPENED QUESTIONS IN ONE HEALTH REGION FOUND 5/5 ATE READY-TO-BAKE COOKIE DOUGH

A CASE CONTROL STUDY WAS PERFORMED TO IDENTIFY THE SOURCE

STEP 2: OUTBREAK INVESTIGATION



53% of college student reported eating unbaked homemade cookie dough Byrd-Bredbenner C et al. J Am Diet Assoc 2008;108:549-52

QUESTION 10

A FOODBORNE OUTBREAK OCCURRED AMONG 100 SCHOOL CHILDREN AND TEACHERS AFTER A SPECIAL LUNCHEON.

- MEDIAN INCUBATION PERIOD – 28 HOURS
- VOMITING SEEN IN 70%
- DIARRHEA IN 50%
- OBJECTIVE FEVER IN 30%
- RECOVERY OCCURRED IN 12 – 60 HOURS

WHAT IS THE LIKELY CAUSE OF THE OUTBREAK?

A. NOROVIRUS
B. *SHIGELLA SONNEI*
C. ENTEROTOXIN FROM *STAPHYLOCOCUS AUREUS*
D. *CLOSTRIDIUM PERFRINGENS*
E. *BACILLUS CEREUS*

CONCLUSIONS

1. THE CLINICAL FEATURES AND INCUBATION PERIOD PROVIDE CLUES TO THE CAUSE OF ILLNESS
2. KNOW HOW TO DIAGNOSE STEC INFECTION (O157 & NON-O157)
3. MOLECULAR CHARACTERIZATION (PULSENET), THE EPIDEMIC CURVE AND CASE CONTROL STUDY ARE KEYS TO FOODBORNE OUTBREAK INVESTIGATION
4. OUTBREAKS REQUIRE PRESENCE OF MULTIPLE NON-FAMILY MEMBERS
5. CONSIDER PI-IBS IN PERSONS WITH PERSISTENT ABDOMINAL PAIN AFTER DIARRHEA BOUTS
6. LEARN SEAFOOD SYNDROMES
7. MULTIPLEX PCR WILL HELP DEFINE THE CAUSES OF DIARRHEA AND IS MOST VALUABLE IN WORKUP OF PERSISTENT DIARRHEA

30

HIV Diagnosis

Dr. Frank Maldarelli

2020 INFECTIOUS DISEASE BOARD REVIEW

HIV Diagnosis

Frank Maldarelli, MD, PhD *
Bethesda, Maryland

Disclosures of Financial Relationships with Relevant Commercial Interests

- None

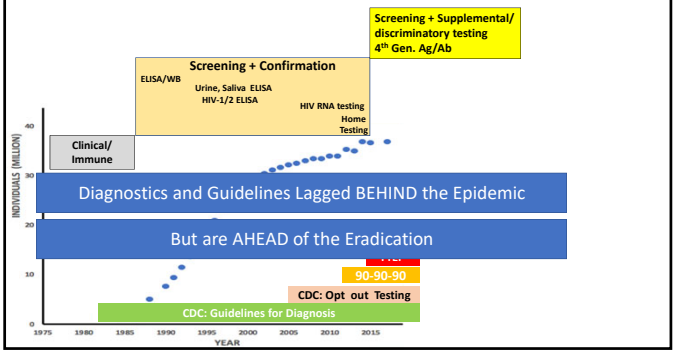
A 26 year old otherwise healthy gay white man has his first HIV test as part of a new health plan. The fourth generation test is antibody reactive and antigen non-reactive. A supplemental third generation HIV-1/2 ELISA is non reactive, and an HIV RNA test does not detect HIV RNA. The most likely explanation for these results is

- **This person HIV infected and is an elite non-controller**
- **This person is HIV infected but is in the window period for HIV infection**
- **This person is infected with an HIV variant that is not detected by the supplemental test**
- **This person is not HIV infected**

HIV Diagnosis: New Modalities and New Terminology Old Limitations Persist

- HIV Diagnosis
  - History
  - Physical
  - Laboratory testing
- Two Step Diagnostic Approach
- No Laboratory Test is Perfect
- False positive results require resolution

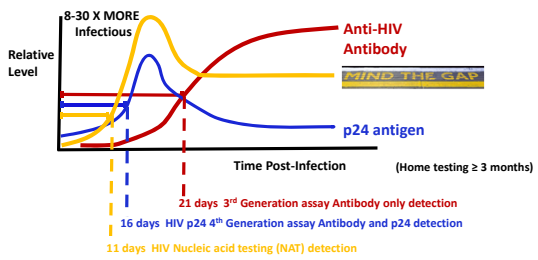
Evolution of the HIV Diagnostic Approach



27 year old female commercial sex worker working in Washington DC visits your clinic and requests PrEP. She shows you her home HIV test, which she took yesterday, and which is non-reactive. She has normal laboratory results and a negative pregnancy test. Which of the following is most appropriate next step

A. **She can immediately initiate PrEP with tenofovir-FTC with no additional testing**
B. **She requires additional testing with fourth generation Ag/Ab HIV test to determine whether she is infected with a non-B subtype of HIV-1 that is not detected by the home HIV test.**
C. **She requires additional testing with fourth generation HIV test to determine whether she has early HIV infection not detected by the home HIV test.**
D. **She should not initiate PrEP because PrEP does not work well in women**

HIV Detection: There is always a Window Period



Detecting HIV Infection TWO STEPS

- Screening - Highest Sensitivity
  - 4th gen ELISA for HIV antibody + p24 antigen detection
  - Qualitative HIV RNA
- Supplemental/Discriminatory - Highest Specificity
  - MULTISPOT/GEENIUS
    - Confirms HIV-1 or HIV-2

NO Test is Perfect

Diagnosis of Early HIV Infection

- HISTORY, PHYSICAL, LABORATORY TESTING
- Most sensitive Modalities
  - 4th Generation
  - HIV RNA: APTIMA
- Less Sensitive Modalities
  - Oral or urine testing
  - Home testing (3 month window)
  - GEENIUS is LESS sensitive for EARLY infection
- FOLLOW UP and REPEAT testing
- Antiretroviral therapy may blunt serologic immune response from maturing

Evaluation for HIV Infection during PrEP

- Every three months
- Includes detailed history and physical examination
- Ag/Ab (4th generation) testing preferred
- Viral RNA
  - Qualitative assay – FDA approved
  - Quantitative assay
    - >3000 copies/ml plasma cutoff

You are following a couple who have had a planned pregnancy. The man is HIV positive and 100% adherent with first line therapy with Tenofovir+3TC+Dolutegravir; The woman has had monthly fourth generation HIV testing, which has been non-reactive throughout the first two trimesters; on the most recent visit the man has an HIV RNA was <20 c/ml, but the woman has shows HIV antigen negative and HIV antibody positive. The most appropriate next step is

- Obtain a viral RNA level but begin antiretroviral therapy immediately
- Consider laboratory error, repeat the same 4th generation test
- Perform supplemental testing with Third generation discriminatory testing
- Reassure the couple that the woman is not infected and the test is just a false positive

HIV Testing During Pregnancy

- False positive results with antibody testing are possible
- May be specific for individuals tests and persist during pregnancy
- Testing with viral RNA testing can resolve most issues
  - Qualitative tests (e.g., APTIMA) are FDA APPROVED for testing
    - Expensive and generally longer turn around
  - Quantitative testing are not FDA APPROVED
    - Rapid but low level results are possible
- Rapid screening reactive during labor in previously untested
  - Initiate therapy
  - Do not wait for supplemental results

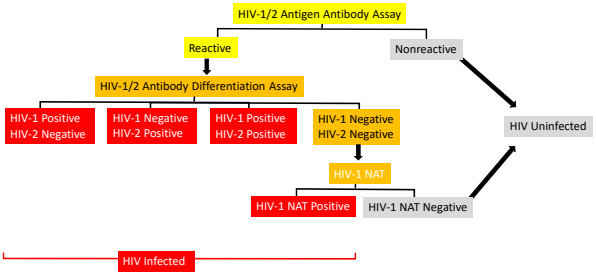
A 65 yo American male has had unprotected sex with men for many years. The HIV-1/2 ELISA is reactive and supplemental testing is positive for HIV-1. Viral RNA level is <50 copies/ml and CD4 count is 700 cells/µl. He has no history of travel outside the US. Which of the following is most likely:

A. The patient is in the window period of HIV-1 infection.
B. The patient is chronically infected with HIV-1 and has a low viral load because he is a long term non progressor.
D. The patient is not infected with HIV-1 or -2, all tests are false positive.
E. The patient is infected with non-B subtype of HIV-1

HIV-1 Long Term Non-Progressors

- Represents authentic HIV infection
- ELISA REACTIVE
- SUPPLEMENTAL POSITIVE
- HIV RNA may not be detectable
- Slow disease progression
- Associated with specific HLA subtypes

HIV Diagnostic Algorithm



You are the new head of ID at your hospital and the administration asks your input regarding HIV testing in the emergency room. Based on IDSA and CDC guidelines which of the following is correct:

A. Testing for HIV should be opt-in
B. Testing for HIV should be opt-out
C. Specific signed testing is required
D. Consent for HIV testing is not required

HIV Testing

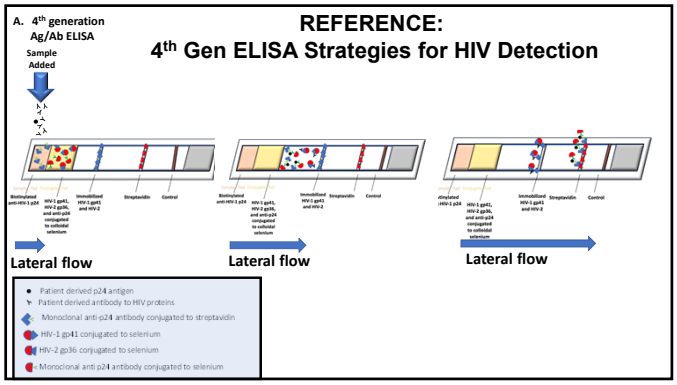
- Opt-out testing is Recommended by IDSA and CDC
  - Patients are informed that an HIV test will be conducted unless they explicitly decline to be tested.
  - Written consent in this setting is incorporated into intake
  - Counseling is available
- Opt-in: NOT Recommended by IDSA and CDC
  - Patients need to initiate the request for HIV infection
- Requirements for testing:FIVE C's:
  - Counseling
  - Consent
  - Confidentiality
  - Correct test results
  - Connection to prevention care and treatment

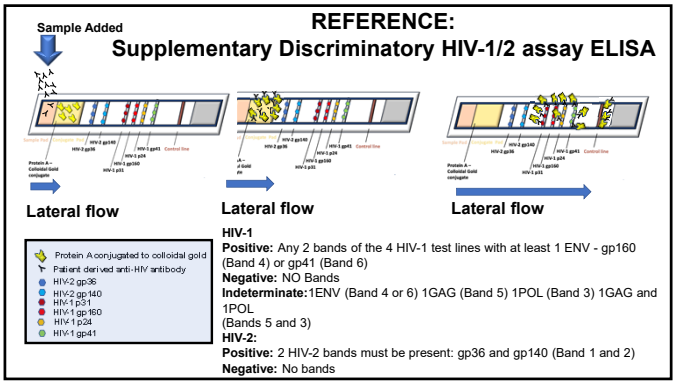
Pearls for Board Exam

- HIV Testing is Comprehensive
  - Non-B Subtypes are all detectable
  - HIV-2 has an approved diagnosis
  - Long term Non-Progressor
    - ELISA reactive / Supplemental Positive
- Resources:
  - https://www.cdc.gov/hiv/guidelines/testing.html
  - Fmalli@mail.nih.gov
- No test is perfect
  - 4th Gen less sensitive
    - Acute
    - PEP/PrEP
    - Early Antiretroviral therapy
  - False Positives
    - Pregnancy
  - Mind the gap
    - Home testing
- Board exam isn't perfect either So don't overthink it

30 - HIV Diagnosis

Speaker: Frank Maldarelli, MD

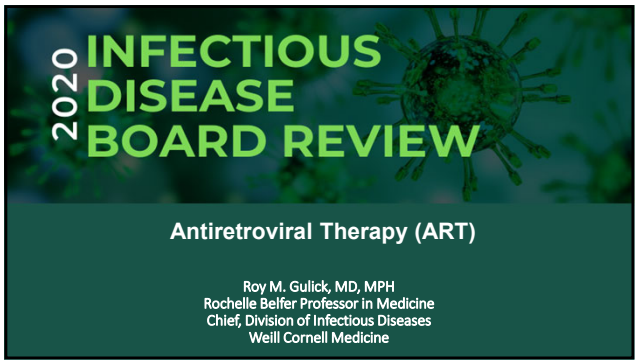


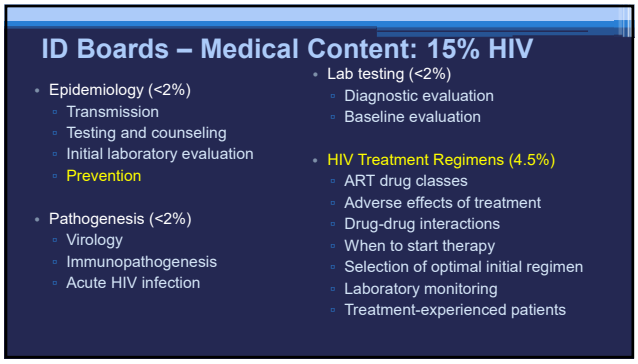


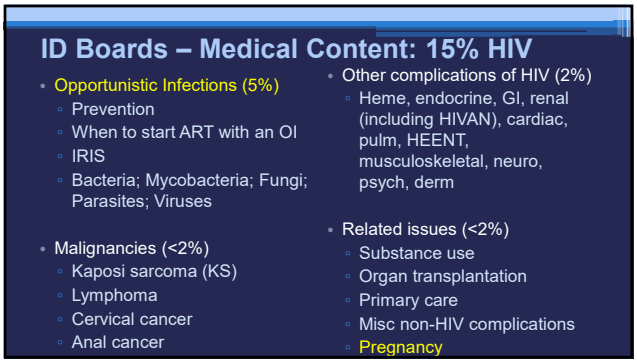
31

Antiretroviral Therapies

Dr. Roy Gulick







Question #1

A 43-year-old HIV+ man has CD4 900-1200 and HIV RNA consistently <200 copies over the last 11 years. Do you recommend starting ART?

A. Yes, all current guidelines recommend starting.
B. No, he's a long-term non-progresser and doesn't need ART.
C. No, he should wait until his viral load level is confirmed >200 copies/ml.
D. No, he should wait until CD4 is confirmed <500.

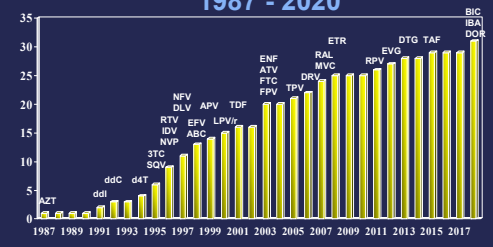
When to Start?: Chronic Infection

	AIDS/ symptoms	Asymptomatic			
		CD4 <200	CD4 200-350	CD4 350-500	CD4 >500
US DHHS 2019 www.aidsinfo.nih.gov	recommended				
IAS-USA 2018 JAMA 2018;320:379-396	recommended				

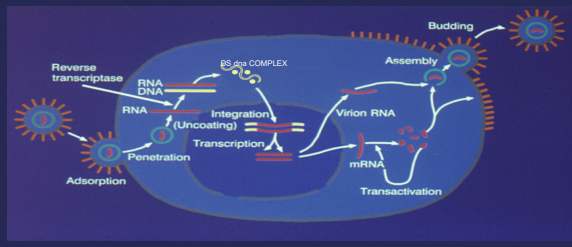
Goal of Antiretroviral Therapy

- To suppress HIV RNA (viral load level) as low as possible, for as long as possible
- To preserve or enhance immune function
- To delay clinical progression of HIV disease (and prolong healthy life)

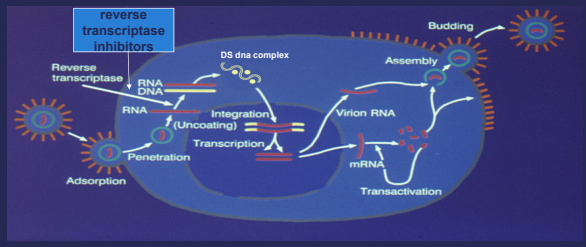
Antiretroviral Drug Approval: 1987 - 2020

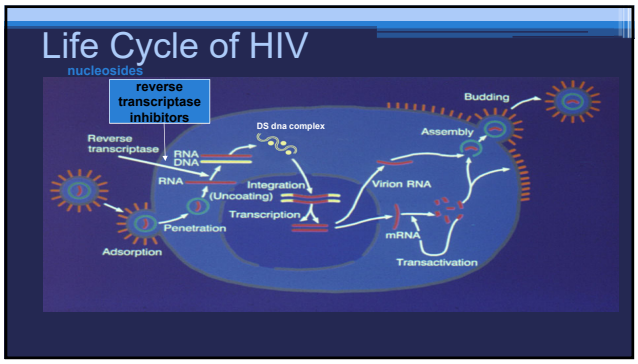


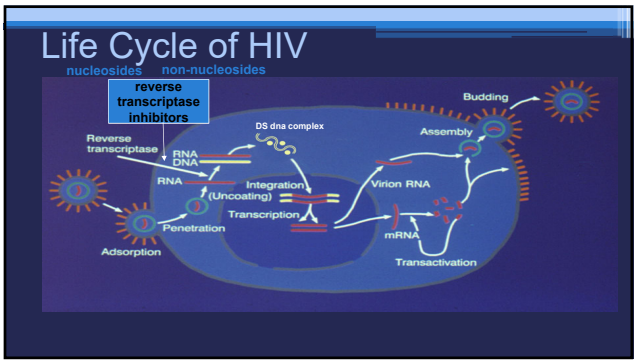
Life Cycle of HIV

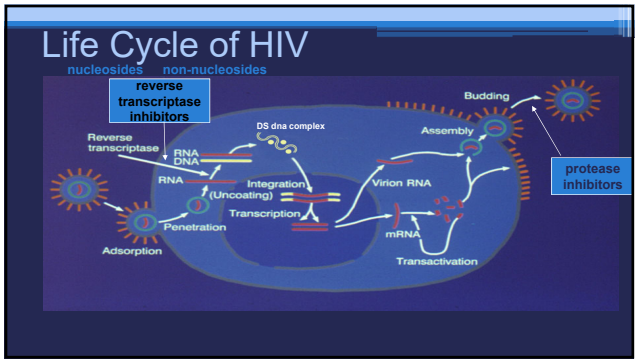


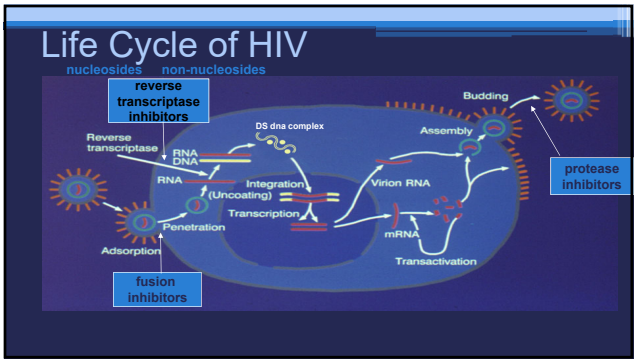
Life Cycle of HIV

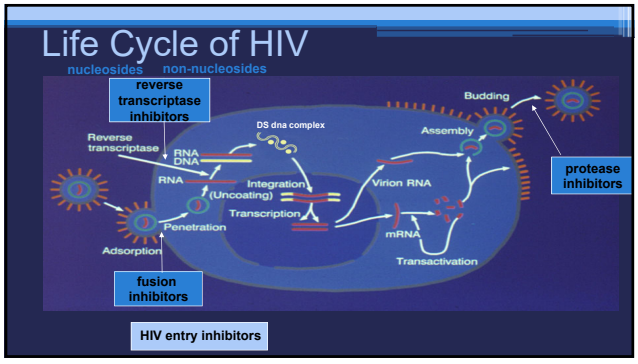


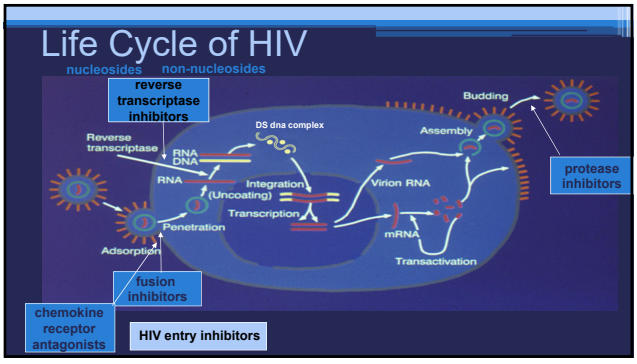


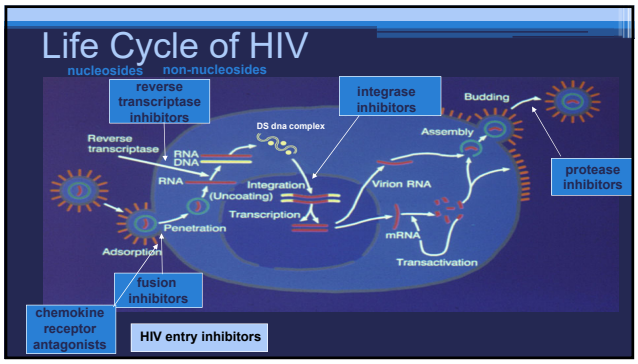


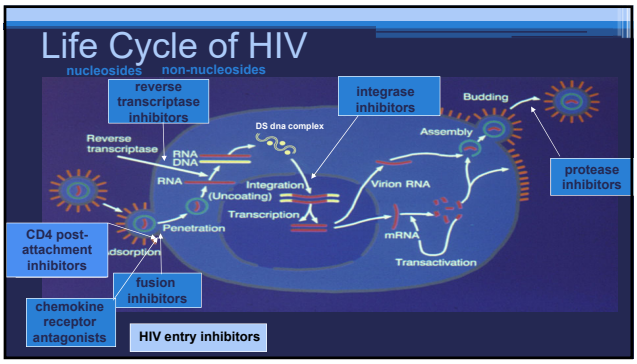












Approved ART: 2020

nucleoside/tide RTIs (NRTIs)
- zidovudine (ZDV, AZT)
- didanosine (ddI)**
- stavudine (d4T)**
- lamivudine (3TC)
- abacavir (ABC)
- emtricitabine (FTC)
- tenofovir (TAF, TDF)

NNRTIs
- nevirapine (NVP)
- delavirdine (DLV)**
- efavirenz (EFV)
- etravirine (ETR)
- rilpivirine (RPV)
- doravirine (DOR)

protease inhibitors (PIs)
- saquinavir (SQV)
- ritonavir (RTV)
- indinavir (IDV)
- nelfinavir (NFV)
- lopinavir/r (LPV/r)
- atazanavir (ATV)
- fosamprenavir (FPV)
- tipranavir (TPV)
- darunavir (DRV)

*ddC and APV withdrawn from market
**withdrawal from market planned

entry inhibitors (EIs)
- enfuvirtide (T-20, fusion inhibitor)
- maraviroc (MVC, CCR5 antagonist)
- ibalizumab (CD4 post-attachment inhibitor)

integrase inhibitors (IIs)
- raltegravir (RAL)
- elvitegravir (EVG)
- dolutegravir (DTG)
- bictegravir (BIC)

What to start?

Question #2

You have been monitoring a 36 year old HIV+ man with CD4 ~350, VL 636,000 who is now ready to start ART, but wants the "simplest regimen possible." Which of these regimens do you recommend?

A. zidovudine/lamivudine + darunavir (boosted)
B. tenofovir/emtricitabine/rilpivirine
C. abacavir/lamivudine + efavirenz
D. lamivudine/dolutegravir
E. tenofovir/emtricitabine + dolutegravir

First ART Regimen: Individual Factors

- antiretroviral activity (VL, CD4, clinical responses)
- durability of responses
- baseline drug resistance
- tolerability
  - acute side effects
  - chronic side effects
- convenience (number of pills, dosing interval, food/fasting requirements)
- preserving future treatment options
- stage of HIV disease, concomitant illnesses and medications (drug-drug interactions)
- access and cost

Recommended Regimens (for most people) (2 NRTI + integrase inhibitor)

- Integrase inhibitor-based
  - bictegravir/TAF/emtricitabine
  - dolutegravir/abacavir/lamivudine (if HLA-B*5701 negative)
  - dolutegravir + tenofovir (TAF or TDF) + (emtricitabine or lamivudine)
  - dolutegravir/lamivudine (except HIV RNA >500,000 cps/ml, HBV surface antigen +, or no resistance results)
  - raltegravir + tenofovir (TAF or TDF) + (emtricitabine or lamivudine)

U.S. DHHS Guidelines 12/18/19 www.aidsinfo.nih.gov

Alternative Regimens (Certain Situations) (1)

- Integrase inhibitor-based (INSTI + 2 NRTI)
  - elvitegravir/cobicistat/tenofovir (TAF or TDF)/emtricitabine
- Protease inhibitor-based (Boosted PI + 2 NRTI)
  - In general, boosted darunavir preferred over boosted atazanavir
  - darunavir/(ritonavir or cobicistat) + tenofovir (TDF or TAF) + (lamivudine or emtricitabine)
  - atazanavir/(ritonavir or cobicistat) + tenofovir (TDF or TAF) + (lamivudine or emtricitabine)
  - darunavir/(ritonavir or cobicistat) + abacavir*/lamivudine

U.S. DHHS Guidelines 12/18/19 www.aidsinfo.nih.gov

Alternative Regimens (Certain Situations) (2)

- NNRTI-based (NNRTI + 2 NRTI)
  - doravirine/TDF/lamivudine or doravirine + TAF/emtricitabine
  - efavirenz + tenofovir (TAF or TDF) + (emtricitabine or lamivudine)
    - efavirenz 600 + TDF + (emtricitabine or lamivudine)
    - efavirenz 400/TDF/lamivudine
    - efavirenz 600 + TAF/emtricitabine
  - rilpivirine + tenofovir (TAF or TDF)/emtricitabine (if VL <100,000 cps/ml and CD4 >200)

U.S. DHHS Guidelines 12/18/19 www.aidsinfo.nih.gov

Alternative Regimens (Certain Situations) (3)

- Consider when ABC, TAF, and TDF cannot be used
  - dolutegravir + lamivudine (except HIV RNA >500,000 cps/ml, HBV surface antigen +, or no resistance results)
  - darunavir/ritonavir + raltegravir BID (if HIV RNA <100,000 cps/ml and CD4 >200)
  - darunavir/ritonavir + lamivudine

U.S. DHHS Guidelines 12/18/19 www.aidsinfo.nih.gov

Choice of NRTIs

Combination	DHHS	Dosing	Toxicities	Considerations
tenofovir (TAF or TDF)/ emtricitabine	recommended	1 tab qd	renal, bone (with TDF); ↓ tox with TAF	1-pill, once-daily formulations available
abacavir/ lamivudine	recommended (with dolutegravir only) / alternative	1 tab qd	HSR (5-8%) (do HLA-B*5701 test)	ABC/3TC/DTG available; ?less effective; ??↑MI
zidovudine/ lamivudine	no longer recommended	1 tab bid	GI, anemia, lipoatrophy	toxicity

DHHS Guidelines 12/18/19

Choice of NNRTIs

Drug	DHHS	Dose	Toxicities	Considerations
doravirine	alternative	qd	↓ CNS toxicity than EFV; ↓ lipid abnor.	TDF/FTC/DOR (1 pill, once-daily)
efavirenz	alternative	qd (600 or 400 mg)	CNS toxicity (50%), rash (10%), suicidality (rare)	TDF/FTC/EFV (1 pill, once-daily)
rilpivirine	alternative	qd	not well absorbed with PPI	(TAF or TDF)/FTC/RPV (1 pill, once-daily with a meal); NOT for HIV RNA >100K or CD4 <200
nevirapine	no longer recommend	qd or bid	hepatotoxicity, hypersensitivity	toxicity

DHHS Guidelines 12/18/19

Choice of PIs

Drug	DHHS	Dose	Toxicities	Considerations
darunavir /(ritonavir or cobicistat)	alternative; in general, prefer-red over ATV	qd (if no prior PI resistance) or bid	skin rash (rare);	activity against PI-resistant viral strains
atazanavir /(ritonavir or cobicistat)	alternative	qd	↑ indirect bilirubin, GI	avoid PPI; kidney stones (uncommon)
lopinavir/ ritonavir	other	bid or qd	diarrhea, ↑lipids	co-formulated

DHHS Guidelines 12/18/19

Choice of Integrase Inhibitors (II)

Drug	DHHS	Dosing	Toxicities	Considerations
bictegravir	recommended with TAF/FTC	1 coform-ulated pill	few, ↑creat, wt gain(?)	TAF/FTC/BIC (1 pill, qd) ↑ barrier to resistance
dolutegravir	recommended with (TAF or TDF)/(FTC or 3TC) or ABC/3TC	50 mg qd (bid with II resistance)	few, ↑creat, CNS, neural tube defects, wt gain	ABC/3TC/DTG (1 pill, qd) ↑ barrier to resistance
elvitegravir	alternative with (TAF or TDF) /FTC/cobicistat	1 coform-ulated pill	mild GI	(TAF or TDF)/FTC/ EVG/cobicistat (1 pill, qd); drug interactions
raltegravir	recommended with (TAF or TDF)/FTC	400 mg bid; 600 mg X 2 qd	few	twice-daily dosing; no co-formulation

DHHS Guidelines 12/18/19

Selected Drug Interactions (1)

- Cytochrome P450 3A4 effects
- Most NNRTI (EFV, ETR, NVP, RPV – NOT DOR) are inducers
  - In general, ↓ levels of other metabolized drugs
- Concern with: rifampin/(rifabutin), ketoconazole/itraconazole, anticonvulsants, simvastatin/lovastatin, midazolam/triazolam, ergotamines
- HIV protease inhibitors
- maraviroc
- Some HCV drugs

Selected Drug Interactions (2)

- Cytochrome P450 3A4 effects
- PIs are inhibitors; ritonavir is the most potent inhibitor ever described; cobicistat is an inhibitor
  - In general, ↑ levels of other metabolized drugs
- Concern with: rifampin – cannot be used/(rifabutin), ketoconazole/itraconazole, anticonvulsants, simvastatin/lovastatin, midazolam/triazolam, ergotamines, St. John's Wort
- HIV NNRTI
- maraviroc
- HCV drugs

ART: What NOT to use as Initial therapy

- Nucleosides (NRTI)
  - 3 or 4 all-NRTI combination regimens
  - older drugs (didanosine, stavudine, zidovudine)
- Non-nucleosides (NNRTI)
  - older drugs (delavirdine, nevirapine)
  - etravirine in initial regimens
- Protease Inhibitors (PI)
  - unboosted PIs
  - older drugs (fosamprenavir, indinavir, lopinavir, nelfinavir, ritonavir [except as booster], saquinavir tipranavir)
- Entry inhibitors (EI)
  - enfuvirtide, maraviroc, ibalizumab

Based on DHHS Guidelines 12/18/19

ART: Side Effects (1)

- **Life threatening**
  - hepatitis (NNRTIs, PIs)
    - nevirapine – women with CD4 >250; men with CD4 >400;
  - hypersensitivity reaction (HSR) (abacavir, nevirapine, etravirine)
    - abacavir HSR greatly reduced with HLA-B*5701 screening
    - stop nevirapine or etravirine for rash + constitutional symptoms
  - lactic acidosis (older nucleoside analogues: didanosine, stavudine)
  - pancreatitis (older nucleoside analogues: didanosine, stavudine)
  - Stevens-Johnson syndrome (nevirapine, etravirine)
  - teratogenicity (efavirenz = pregnancy category D; dolutegravir during conception/very early pregnancy → neural tube defects)

ART Side Effects (2)

- **Acute/early**
  - gastrointestinal (zidovudine, didanosine, TDF, PIs, ?all ART)
  - anemia, neutropenia (zidovudine)
  - bone mineral density ↓ (TDF)
  - central nervous system (efavirenz; integrase inhibitors[?])
  - fatigue (zidovudine)
  - indirect hyperbilirubinemia (atazanavir, indinavir)
  - injection site reactions (enfuvirtide)
  - rash (NNRTIs)

ART Side Effects (3)

- **Chronic/longer term**
  - cardiovascular (abacavir??, PIs except atazanavir)
  - kidney stones (indinavir > atazanavir)
  - metabolic – glucose, lactate, lipids (older PIs, stavudine)
  - morphologic –
    - fat loss – lipoatrophy (stavudine, zidovudine)
    - fat gain – lipohypertrophy (older PIs)
  - peripheral neuropathy (stavudine, didanosine)
  - proximal renal tubular dysfunction (TDF)
  - weight gain (bictegravir, dolutegravir)

ART Switch

- Reasons: adverse events, drug-drug or drug-food interactions, pill burden, pregnancy, cost, simplification
- Fundamental principle: Maintain virologic suppression.
- Review ART history, prior ART-associated toxicities, cumulative drug resistance testing results.
- Within-class or between-class Δ usually works if no resistance.
- Specific regimens:
  - DTG+RPV; DTG+3TC; Boosted PI (ATV, DRV, LPV) + [3TC or FTC]; Boosted PI + II (e.g. DRV/r + DTG)
  - Not recommended: monotherapy, boosted ATV + RAL, MVC-based
- Consideration: concomitant HBV infection

DHHS Guidelines 12/18/19

Why Does Treatment Fail Patients?

- ADHERENCE
- Baseline resistance or cross-resistance
- Prior use of antiretroviral therapy
- Less potent antiretroviral regimens
- Drug levels and drug interactions
- Tissue reservoir penetration
- Provider inexperience
- Other, unknown reasons

Question #3

28 year old HIV+ man on TDF/emtricitabine + atazanavir/ritonavir for 2 years with HIV RNA <50 cps/ml and CD4 200s→300s presents for routine follow-up; labs reveal HIV RNA 102 cps/ml and CD4 352.

What do you recommend?

A. Obtain genotype.
B. Obtain genotype and phenotype.
C. Repeat HIV RNA at next visit.
D. Change regimen to abacavir/lamivudine/dolutegravir to improve adherence.

When to change therapy?

Virologic failure

- VL undetectable – drug resistance unlikely
- VL <200 cps/ml – controversial; one large retrospective analysis found no increased risk of failure
- VL persistently >200 cps/ml – drug resistance often associated (particularly >500 cps/ml)
- Caution with change to newer VL assays and blips

Immunologic failure

- Associated factors:
  - CD4 <200 at ART initiation
  - older age
  - co-infections
  - meds
  - persistent immune activation
  - loss of regenerative potential
  - other reasons
- No consensus on definition or treatment

DHHS Guidelines 12/18/19

What to change to?: U.S. DHHS Guidelines

- Review goal of therapy:
  - Maximal virologic suppression (HIV RNA below detection)
- Review ART history
- Assess adherence, tolerability, and PK
- Perform resistance testing while on drugs (or within 4 weeks of d/c of ART)
- Identify susceptible drugs/drug classes
- Consider newer agents (expanded access or clinical trials)
- Goal:
  Design a regimen with 2 (preferably 3) fully active agents

DHHS Guidelines 12/18/19

Treatment = Prevention

Treatment = Prevention

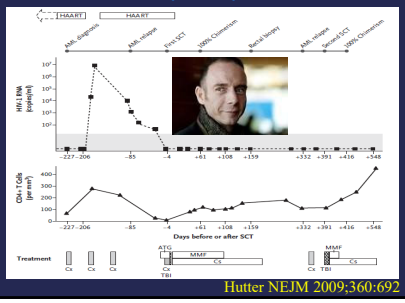
- HIV+ pregnant women
  - 3-drug ART decreases transmission risk to child to 0.5%
    Fowler NEJM 2016
- HIV+ men and women
  - Suppressive ART decreases transmission to sexual partners by 93% *Cohen NEJM 2016;375:830*
- HIV- men and women
  - 2-drug ART (PrEP) decreases HIV acquisition by sex ~99%
    Baeten NEJM 2012, Molina NEJM 2015, McCormack Lancet 2016
- HIV- post-exposure prophylaxis (PEP)
  - 3-drug integrase-inhibitor based ART recommended for 4 weeks *CDC Guidelines*

Cure

HIV Cure (N=2)

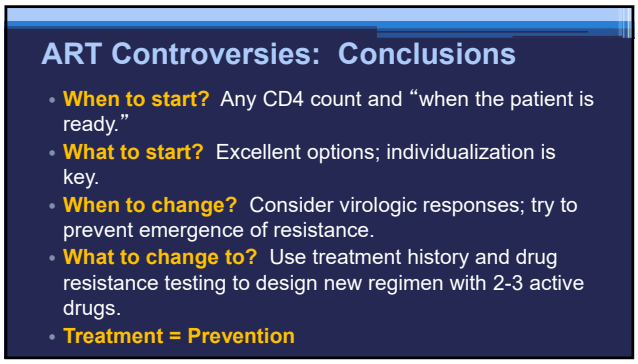
HIV-1 RNA

CD4 cell count



Cure #2 Gupta Nature 2019;568: 244-248.

Hutter NEJM 2009;360:692



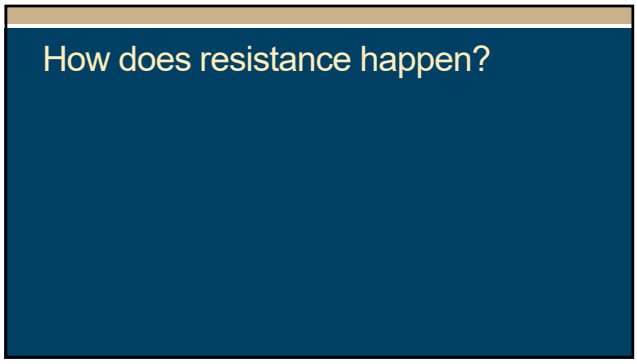
32

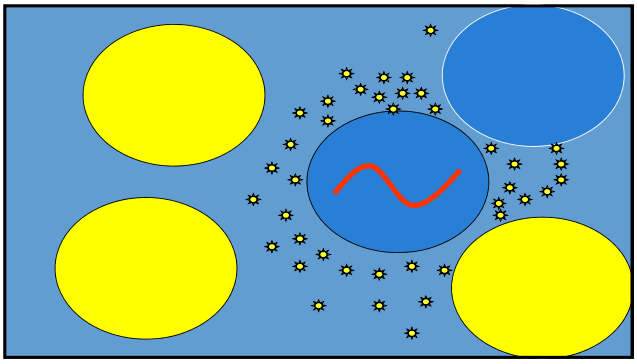
HIV Drug Resistance

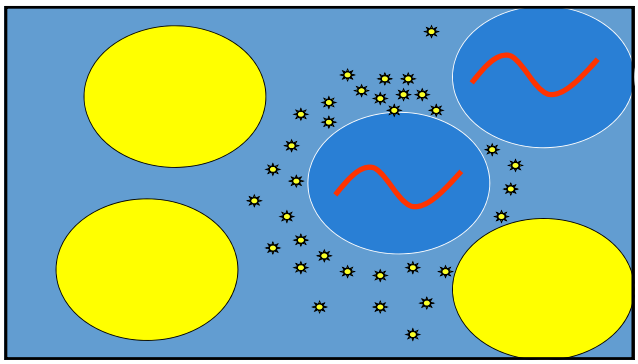
Dr. Michael Saag

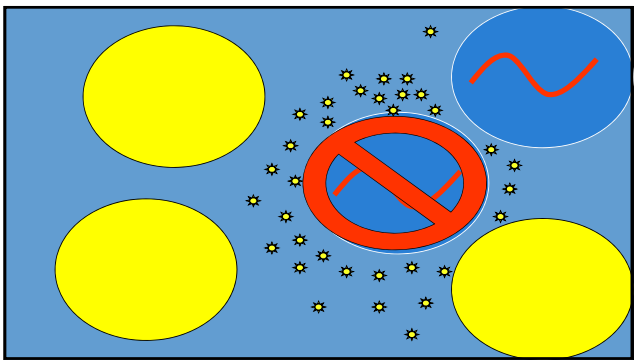
32 – HIV Drug Resistance

Speaker: Michael Saag, MD



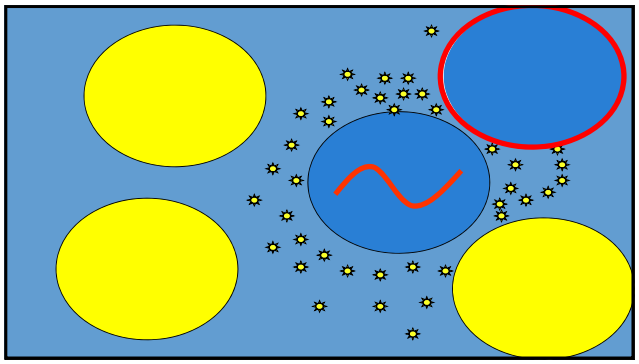


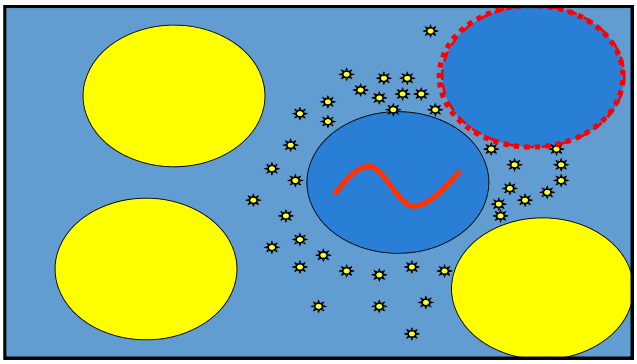


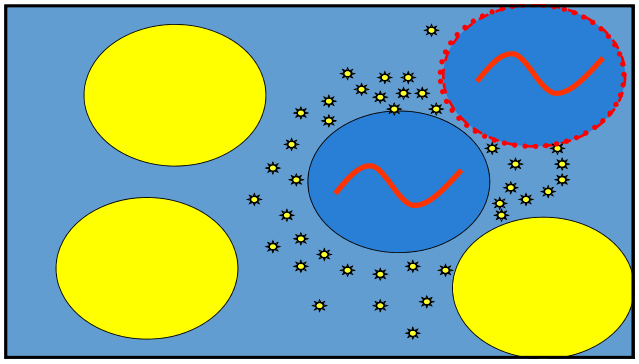


32 – HIV Drug Resistance

Speaker: Michael Saag, MD



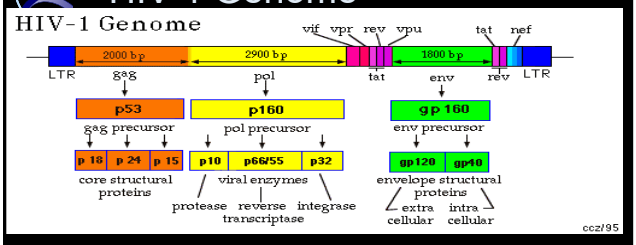




Resistance Testing

- Genotypic resistance test
  - Perform test that gives mutations in viral genes
- Phenotypic resistance test
  - Perform test that describes growth of virus in the presence of anti-HIV drugs
- Limitations:
  - Cannot detect minority species (< 10% of viral population)

HIV-1 Genome



Mutation Nomenclature

Codon (position)
PR = 1-99 amino acids
RT = 1-560 amino acids

M184V

32 – HIV Drug Resistance

Speaker: Michael Saag, MD

Mutation Nomenclature

Codon (position)
PR = 1-99 amino acids
RT = 1-560 amino acids

M184V

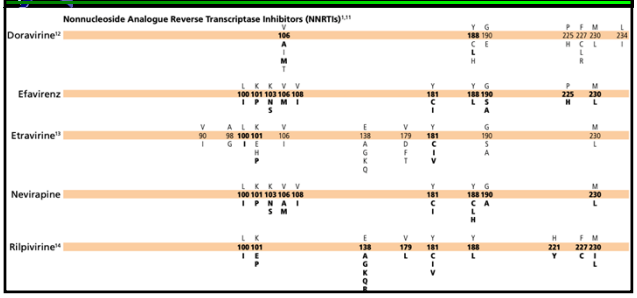
Wild-type amino acid (consensus)

Mutant amino acid

Table 1. Amino acids and their abbreviations.

Alanine	A
Cysteine	C
Aspartate	D
Glutamate	E
Phenylalanine	F
Glycine	G
Histidine	H
Isoleucine	I
Lysine	K
Leucine	L
Methionine	M
Asparagine	N
Proline	P
Glutamine	Q
Arginine	R
Serine	S
Threonine	T
Valine	V
Tryptophan	W
Tyrosine	Y

Mutations Selected by NNRTIs



Key Issues in HIV Resistance

Easily Tested

- Specific Mutations
- Cross – resistance
- Prevalence of resistance at baseline

Tough to Test

- Definition of Phenotypes
- Complex resistance patterns
- Genetic Barrier
- Nuances of Resistance
- Relationship between Pk and Pd

15

HIV Drug Resistance Testing

- Current guidelines recommend an HIV genotype as part of screening BEFORE ART is started.
- Following failure of 1st or 2nd regimens, HIV genotype is recommended to use with the history to choose the optimal next regimen.
- Following failure of 3rd and subsequent regimens, both HIV genotype AND HIV phenotype should be sent.
- If there is discordance between genotype and phenotype results, use the geno result (more sensitive).
- NOTE WELL: Resistance mutations accrued from an earlier regimen MAY NOT be detected by tests obtained at the time of the current failing regimen

Everything You Need to Know About Nucleoside Analog Resistance in One Slide!

Mutation	Selected by	Effects on other NRTIs
184V	3TC, FTC	- Loss of susceptibility to 3TC, FTC - ↓ susceptibility to ABC, ddI (clinically insignificant) - Delayed TAMS and ↑ susceptibility to AZT, d4T, TDF
TAMs	AZT, d4T	- ↓ susceptibility to all NRTIs based on number of TAMs - More resistance with 41/210/215 than 67/70/219 pathway
151M, 69ins	AZT/ddI, ddI/d4T	- Resistance to all NRTIs - T69ins: TDF resistance
65R	TDF, ABC, ddI	- Variable ↓ susceptibility to TDF, ABC, ddI (and 3TC, FTC) - ↑ susceptibility to AZT
74V	ABC, ddI	- ↓ susceptibility to ABC, ddI - ↑ susceptibility to AZT, TDF
44D, 118I	AZT, d4T	-Increase NRTI resistance (with 41/210/215 pathway)

CASE 1

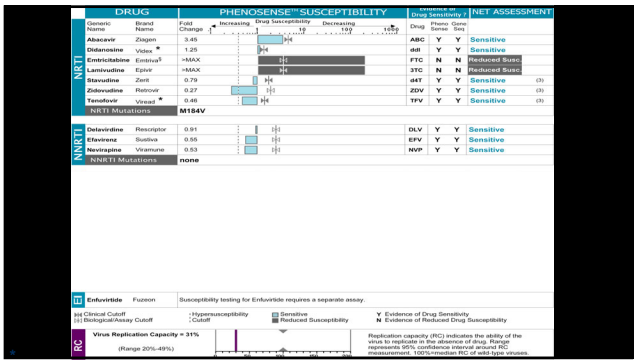
- 25 year old man presents with newly diagnosed HIV
- Had an episode c/w acute seroconversion syndrome 4 months ago
- Initial HIV RNA 40,000; CD4 443 cells/ul
- He wants to start ARV therapy

18

Question #1

A baseline genotype is ordered that shows an M184V mutation. Which of the following drugs will have reduced susceptibility with this mutation?

A. Efavirenz
B. Zidovudine
C. Tenofovir
D. Etravirene
E. Emtricitabine



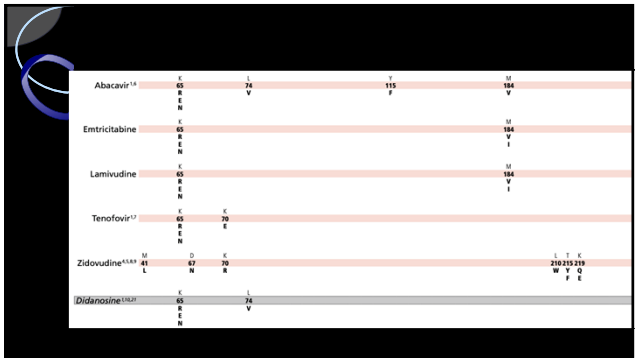
CASE 2

- 34 yo woman diagnosed with HIV 10 years ago
- Initially presented with PJP
- Initial Lab values
  - CD4 82 cells/uL
  - VL 106,000 c/mL
- Started on TDF / FTC / EFV (FDC)
- Did well for a while, then the regimen failed

Question #2

The genotype shows an M184V and K65R mutations. Which nRTI drugs would you include?

A. ZDV
B. TDF
C. ddI
D. ABC



CASE 3

- 34 yo woman diagnosed with HIV three years ago
- Initially presented with PJP
- Initial Lab values
  - CD4 82 cells/uL
  - VL 106,000 c/mL
- A Genotype was ordered.

Question #3

Which of the following mutations indicate high level resistance to efavirenz ?

A. M184V
B. K65R
C. K219Q
D. K67N
E. K103N

Non-nucleoside Reverse Transcriptase (NNRTI) Mutations

- K103N is the signature mutation for efavirenz (EFV).
- Y181C is the signature mutation for nevirapine (NVP).
- Older NNRTIs, efavirenz and nevirapine, have low genetic barriers (require only 1 mutation for resistance) and are **COMPLETELY** cross-resistant to one another.
- Newer NNRTIs, etravirine (ETR), rilpivirine (RPV), and doravirine (DOR) have higher barriers to resistance (require >1 mutation for resistance).
- K103N has no effect on etravirine susceptibility.
- Rilpivirine failure is associated with E138K, K101E, and/or Y181C and consequently, resistance to ALL NNRTIs.

HIV Resistance – Protease inhibitors (PI)

- In general, currently used protease inhibitors require multiple mutations for resistance (i.e. have a high genetic barrier).
  - Exception: I50L alone confers resistance to atazanavir (ATV).
- Patients experiencing failure on a 2 NRTI + boosted PI regimen most often have NO PI mutations.
- With significant prior protease inhibitor use, because of multiple mutations, a phenotype is

CASE 4

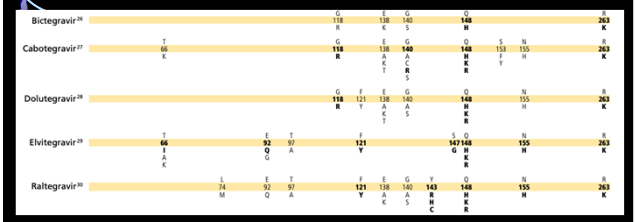
- 34 yo woman diagnosed with HIV three years ago
- Initially presented with PJP
- Initial Lab values
  - CD4 82 cells/uL
  - VL 106,000 c/mL
- She was treated with TDF / FTC / ELV/ Cobi (FDC)
- The regimen failed after 12 months

Question #4

Which of the following mutations indicate high level resistance to elvategravir ?

A. Q148R
B. L68I
C. L68V
D. K67N
E. K65R

InSTI Resistance Mutations



CASE 5

- 34 yo woman diagnosed with HIV three years ago
- Initially presented with PJP
- Initial Lab values
  - CD4 82 cells/uL
  - VL 106,000 c/mL
- A Tropism test was ordered.

Question #5

Which of the following results would indicate the highest likelihood of maraviroc activity in the regimen?

A. Pure R5 virus
B. Pure X4 virus
C. Mixture of R5 and X4 viruses
D. Dual Tropic (R5/X4) virus

CASE 6

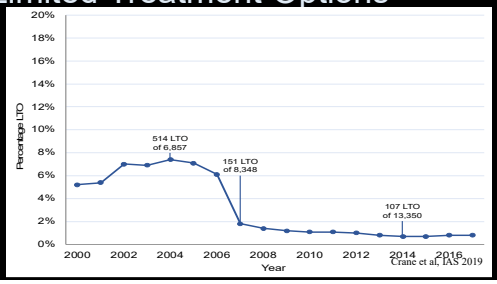
- 34 yo woman diagnosed with HIV 22 years ago
- Initially presented with PJP
- Initial Lab values
  - CD4 82 cells/uL
  - VL 106,000 c/mL
- Has been on multiple regimens over the years

Question #6

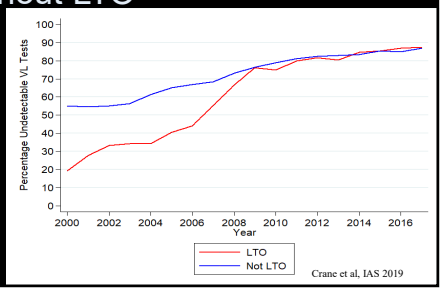
What is the likelihood she has high level resistance (< 2 active drugs available) ?

A. < 1 %
B. 1 - 5 %
C. 5 -10%
D. 10 - 20%
E. > 20%

Prevalence of Patients with Limited Treatment Options



Virologic Success in Those with or without LTO



Common Mutations To Memorize

- M184V/I — 3TC and FTC
- M41L, D67N, K70R,L210W, T215Y, K219Q — "TAMS"
  - 4 or more thymidine-analog mutations (TAMS) affect all approved nucleosides
- K65R — tenofovir
- Q151M, 69SSS — multi-NRTI
- K103N — EFV (and NVP)
  - retains susceptibility to etravirine
- Y181C — NVP and other NNRTI
- E138K, K101E — RPV and other NNRTI
- I50L — ATV
- N155H, Q148H/R/K — RAL and EVG
- Y143C — RAL
- R263K — DTG

Summary

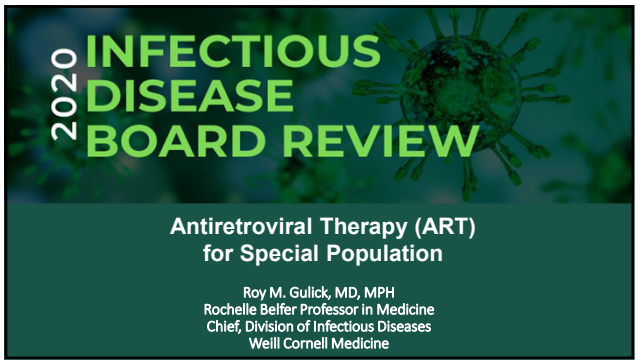
- High concern about resistance testing on Board Exams
- Difficult to create test questions that do not require complex interpretation, have a single best answer, or are not 'multiple true-false'
- Knowing common mutations and their role is a good way to prepare for the exam

39

33

Antiretroviral Therapy for Special Populations

Dr. Roy Gulick



Disclosures of Financial Relationships with Relevant Commercial Interests

- None

Special Populations

- acute/recent HIV infection
- acute opportunistic infection
- tuberculosis
- HIV-HBV co-infection
- HIV-HCV co-infection
- pregnancy
- post-HIV exposure (PEP)
  - occupational
  - non-occupational
- pre-HIV exposure (PrEP)

Question #1

A 22-year-old man presents with fever, mouth pain, and skin rash. PE reveals 3 small oral ulcers and diffuse macular rash. Labs show WBC 3K, platelets 89K, monospot negative, RPR NR, HIV antibody negative, HIV RNA 1,876,000 cps/ml.

Which statement is correct?

A. ART should not be offered.
B. ART would decrease his symptoms.
C. ART has long-term virologic benefits in this setting.
D. ART has long-term clinical benefits in this setting.

Acute or Recent HIV

- ART is RECOMMENDED.
- ART reduces symptoms and signs and reduces transmission.
- No long-term virologic, immunologic, or clinical data available.
- If ART is started, use standard regimens with goal of full virologic suppression.
- Obtain genotype prior to ART.
- If ART is started prior to genotype results, use bictegravir, boosted darunavir, or dolutegravir together with tenofovir (TAF or TDF) + emtricitabine.

DHHS Guidelines 12/18/19

Question #2

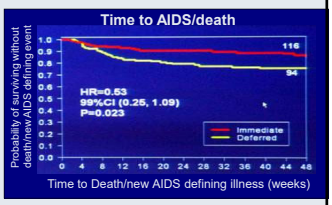
A 52-year-old woman is admitted for progressive SOB, is intubated, undergoes BAL and is found to have PCP. HIV Ab test is positive, CD4 103, HIV RNA 135,000 copies/ml. She is day 4 of IV trimethoprim-sulfa and corticosteroids and still intubated.

When should she start ART?

A. Immediately
B. In the next 2 weeks
C. After completing 21 days of trimethoprim-sulfa
D. At her first outpatient clinic visit

ACTG 5164: Immediate vs Delayed ART with an Acute OI

- 282 patients with treatable OI diagnosed within 14 days randomized to start ART within 48 hours vs. after 4 weeks
  - most common OI: PCP (63%)
- AIDS progression/death: immediate rx (14%) vs **delayed rx (24%)**
- No differences in safety/toxicity, IRIS, or week 48 responses



Zolopa PLoS One 2009;4:e5575

Acute Cryptococcal Meningitis

- Randomized clinical trial at Parirenyatwa Hospital in Harare, Zimbabwe
- Study population: 54 patients with CM treated with 800 mg fluconazole daily; median CD4 37
- Study Treatment: early ART (within 72 hours of diagnosis) or delayed ART (10 weeks after fluconazole)
- Results (through 3 years): 73% mortality rate overall
  - 88% (early ART) vs. **54% (late ART)**
  - HR of death 2.85 (95% CI 1.1, 7.2)
- Conclusion: Early ART led to ↑ mortality

Makadzange CID 2010;50:1532

HIV-TB Co-infection

- Treat active TB the same with or without HIV.
- All HIV+ pts with TB should start TB meds immediately.
- In HIV+ patients with TB, timing of starting ART depends on CD4 count:
  - For CD4 <50, start ART ASAP, within 2 weeks of TB rx
  - For CD4 ≥50, start ART within 8 weeks of TB rx
- Start HIV+ pregnant women with TB on ART as early as feasible.

DHHS Guidelines 12/18/19

Question #3

A 39-year-old man with HIV disease, CD4 298, HIV RNA 23,000 cps/ml, never on ART is diagnosed with pulmonary TB. The plan is to start INH, RIF, PZA, and ETH pending susceptibilities. He agrees to start ART and genotype is wild-type.

Which ART regimen do you recommend?

A. tenofovir/emtricitabine/efavirenz
B. tenofovir/emtricitabine + atazanavir (boosted)
C. tenofovir/emtricitabine + atazanavir (unboosted)
D. tenofovir/emtricitabine + darunavir (boosted)

HIV-TB Co-infection (2)

- Include a rifamycin in the regimen.
  - rifampin
    - significantly ↓ ALL PIs – cannot use together
    - ↓ DTG concentrations (need to ↑ DTG to 50 mg bid)
    - ↓ NNRTI concentrations: EFV 600 mg daily is recommended
  - rifabutin: preferred; more manageable drug interactions with protease inhibitors
- For IRIS, continue both ART and TB meds while managing the syndrome.
- Treatment support, including DOT of TB rx is strongly recommended.

DHHS Guidelines 12/18/19

Question #4

A 55-year-old treatment-naïve man with HIV disease, CD4 320 and HIV RNA 67,000 cps/ml

Lab testing reveals: toxoplasma Ab+; CMV Ab+; HAV total Ab+; HBV surface Ag+, core Ab+, surface Ab-; HCV Ab-; RPR NR

Of the following, which ART regimen would you recommend?

A. abacavir/lamivudine/dolutegravir
B. abacavir/lamivudine + atazanavir (boosted)
C. tenofovir (TAF or TDF)/emtricitabine + zidovudine
D. tenofovir (TAF or TDF)/emtricitabine + darunavir (boosted)

HIV-HBV Co-infection

- Some ART has activity against HBV
  - lamivudine (3TC), emtricitabine (FTC), tenofovir (TDF and TAF)
- Some HBV drugs have activity against HIV
  - entecavir *McMahon NEJM 2007;356:2614*
- If treatment started, treat both optimally
  - 2 active agents for HBV
  - 3 active agents for HIV
  - e.g. [TDF or TAF] + [FTC or 3TC] + 3rd drug

DHHS Guidelines 12/18/19

HIV-HCV Co-Infection

- Anyone with HCV should be screened for HIV.
- High-risk HIV+ patients should be screened for HCV annually.
- ART should be started in those with concomitant HCV.
  - Same initial regimens recommended, but caution with drug-drug interactions and overlapping toxicities.
- Patients with HIV and HCV should be evaluated for HCV therapy.
  - Also evaluate for HBV co-infection.
- New direct-acting antiviral regimens

DHHS Guidelines 12/18/19

Question #5

A 26-year-old woman with HIV disease on abacavir/lamivudine + efavirenz with CD4 630 and VL suppressed below detection becomes pregnant.

What do you recommend regarding ART?

A. Discontinue ART until 2nd trimester.
B. Change abacavir to zidovudine.
C. Change efavirenz to bictegravir.
D. Continue current regimen.

Antiretrovirals in Pregnancy

- ART recommended for prevention of MTCT for all pregnant women, as early as possible, regardless of CD4 or VL level
  - Perform drug-resistance testing if VL >500-1000 cps/ml and adjust regimen, based on results
  - ART does NOT increase the risk of birth defects
  - Start (or continue) standard ART:
    - 2 NRTIs + a 3rd drug (PI, II, or NNRTI)
    - NO 2-drug regimens
- Near delivery, if HIV RNA >1000 (or unknown), use intravenous zidovudine, and recommend Cesarean section at 38 weeks

DHHS Perinatal Guidelines 4/14/20 <www.aidsinfo.nih.gov>

ART in Pregnancy: NRTI

- Preferred:
  - abacavir/lamivudine
  - tenofovir (TDF)/(emtricitabine or lamivudine)
- Alternative:
  - zidovudine/lamivudine
- Insufficient data: tenofovir (TAF)
- Not recommended:
  - zidovudine/lamivudine/abacavir (3 NRTIs) (insufficient virologic activity)
  - didanosine (toxicity)
  - stavudine (toxicity)
- IV zidovudine recommended close to delivery if HIV RNA >1000

DHHS Perinatal Guidelines 4/14/20 <www.aidsinfo.nih.gov>

ART in Pregnancy: NNRTI

- Alternative:
  - efavirenz (birth defects in primate studies were NOT borne out in human studies or extensive experience in pregnancy; screen for depression)
  - rilpivirine (not with baseline VL >100K or CD4 <200)
- Insufficient data: doravirine
- Not recommended:
  - etravirine (not for treatment-naïve)
  - nevirapine (toxicity, need for lead-in dosing, low barrier to resistance)

DHHS Perinatal Guidelines 4/14/20 <www.aidsinfo.nih.gov>

ART in Pregnancy: PI

- Preferred:
  - atazanavir/ritonavir
  - darunavir/ritonavir (use bid)
- Alternative:
  - lopinavir/ritonavir (use bid)
- Not recommended: (pill counts and toxicity)
  - cobicistat
  - fosamprenavir
  - indinavir (boosted)
  - nelfinavir
  - ritonavir (as a single drug)
  - saqunavir/ritonavir
  - tipranavir (not for treatment-naïve)

DHHS Perinatal Guidelines 4/14/20 <www.aidsinfo.nih.gov>

ART in Pregnancy: II

- Preferred:
  - dolutegravir (neural tube defects described if taken during conception or very early, but not later in pregnancy)
  - raltegravir
- Insufficient data: bictegravir
- Not recommended:
  - elvitegravir combinations

DHHS Perinatal Guidelines 4/14/20 <www.aidsinfo.nih.gov>

ART in Pregnancy: Other

- Not recommended:
  - 2-drug regimens (e.g. with dolutegravir/rilpivirine)
  - enfuvirtide (not for treatment-naïve)
  - maraviroc (tropism testing; not recommended in treatment-naïve)
- Insufficient data: ibalizumab

DHHS Perinatal Guidelines 4/14/20 <www.aidsinfo.nih.gov>

Question #6

A 34-year-old HIV-negative nurse sustains a needlestick from an HIV-positive patient who has not taken ART for 2 years.

Which of these post-exposure (PEP) regimens do you recommend?

A. tenofovir (TDF)/emtricitabine
B. tenofovir (TDF)/emtricitabine + integrase inhibitor
C. tenofovir (TAF)/emtricitabine + integrase inhibitor
D. tenofovir (TDF)/emtricitabine + protease inhibitor

Antiretrovirals for PEP (1)

Postexposure prophylaxis (PEP) for occupational exposure:

- Assess nature of exposure:
  source fluid, volume of fluid, type of exposure, timing
- Assess exposure source; HIV and hepatitis testing
- Testing (baseline, 6 + 12 wks + 6 months with standard HIV Ab or 6 wks + 4 months if new HIV Ab/p24 test used) and counseling
- Offer 4 weeks of rx for recognized transmission risk
  - start ASAP (within 72 hours)
  - tenofovir (TDF)/emtricitabine + dolutegravir (not in women in early pregnancy or sexually active and not on birth control) or raltegravir
  - adjust regimen for possibility of resistance in source patient
  - f/u within 72 hours

PHS Guidelines updated 5/23/18

Antiretrovirals for PEP (2)

PEP for non-occupational exposure:

- Presentation ≤72 hours with substantial risk exposure from HIV+ source – recommended
- Presentation ≤72 hours with substantial risk exposure from source with unknown HIV status – case-by-case basis
- Presentation >72 hours or no substantial risk of exposure – not recommended

- Testing: rapid HIV (Ag)/Ab test; if results not available, start PEP
- Treatment: 4 weeks of
  - Preferred: TDF/FTC + dolutegravir (not in women in early pregnancy or sexually active and not on birth control) or raltegravir
  - Alternative: TDF/FTC + darunavir/ritonavir

PHS Guidelines update 5/23/18 <www.aidsinfo.nih.gov>

Question #7

23 year old HIV-negative man with an HIV+ partner on ART with HIV RNA suppressed below detection asks about starting pre-exposure prophylaxis (PrEP).

In addition to safer sex counseling, which of these do you recommend?

A. Nothing – PrEP is not indicated.
B. PrEP with tenofovir (TDF)/emtricitabine daily.
C. PrEP with tenofovir (TAF)/emtricitabine "on demand".
D. PrEP with bictegravir/tenofovir (TAF)/emtricitabine daily.

CDC Guidance for PrEP:

https://www.cdc.gov/hiv/pdf/risk/prep/cdc-hiv-prep-guidelines-2017.pdf

- Before starting:
  - document HIV Ab negative and r/o acute infection within a week of starting
  - document CrCl ≥60, screen for STIs and HBV infection
- Prescribe tenofovir (TDF)/emtricitabine 1 po daily X 90 days
  - provide risk reduction, adherence counseling, condoms
- On treatment:
  - HIV testing every 3 months
  - check CrCl every 6 months
  - risk reduction, condoms, STI assessments/rx
  - evaluate the need to continue PrEP
- 10/19 FDA approved TAF/FTC for PrEP, based on DISCOVER Studies

Conclusions

1. Acute (and recent) HIV – ART recommended.
2. Acute OI – ART within 2 weeks of diagnosis reduces mortality; caution with CNS opportunistic infections.
3. TB – Early ART prolongs survival; caution with rifamycin drug interactions.
4. Hepatitis B and C co-infection – Consider antiviral activity, drug-drug interactions, drug toxicities.
5. Pregnancy – Treat to reduce MTCT; modify ART recommendations based on safety and experience.
6. Post-exposure prophylaxis (PEP) – ART within 72 hours; give for 4 weeks; adjust for known drug resistance.
7. Pre-exposure prophylaxis (PrEP) – tenofovir (TDF)/emtricitabine qd

Acknowledgments

- **Cornell HIV Clinical Trials Unit (CCTU)**
- Division of Infectious Diseases
- Weill Cornell medicine
- AIDS Clinical Trials Group (ACTG)
- HIV Prevention Trials Network
- Division of AIDS/NIAID/NIH
- The patient volunteers!

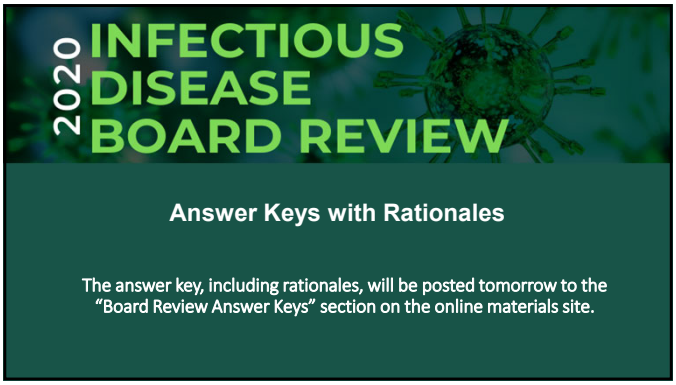
34

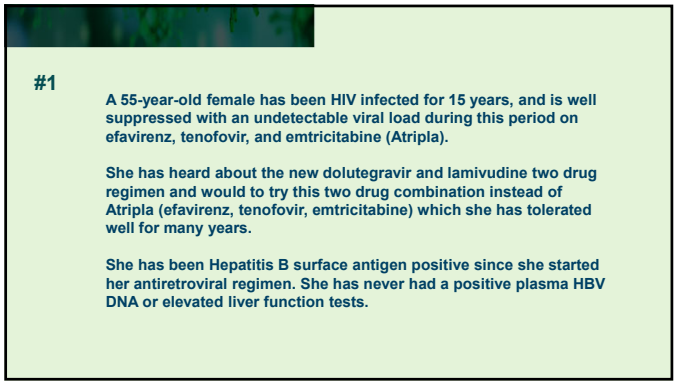
Board Review Session 3

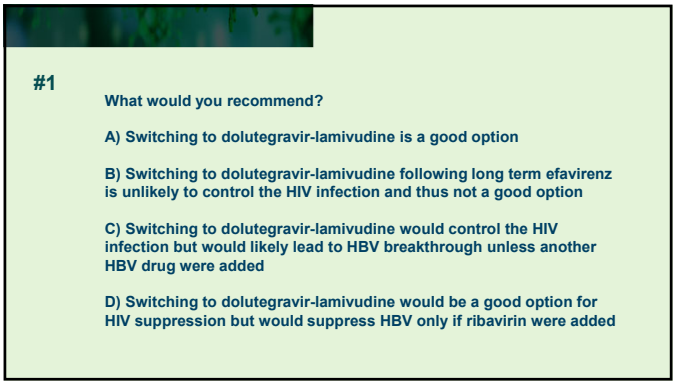
Drs. Gulick (Moderator), Bell, DuPont, Maldarelli, Saag, and Weinstein

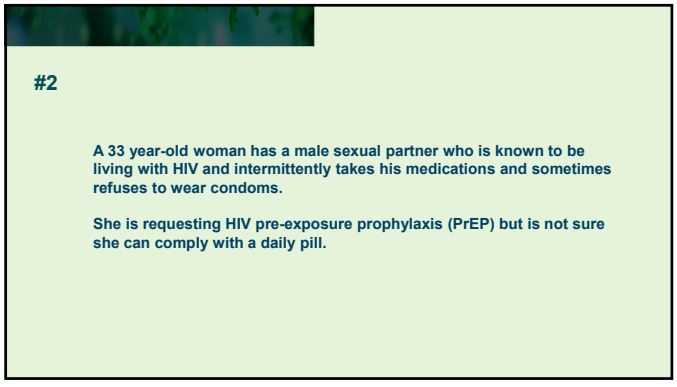
34 – Board Review Session 3

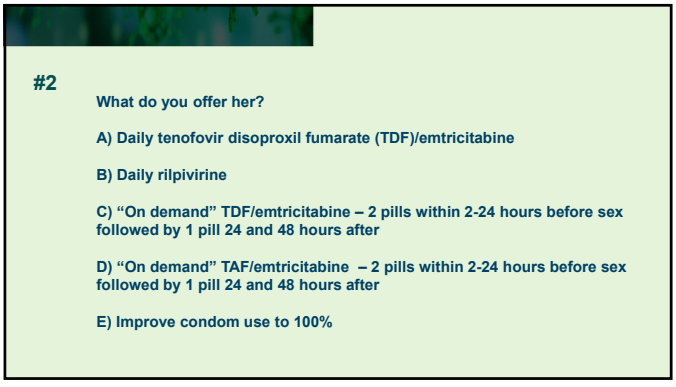
Drs. Gulick (Moderator), Bell, DuPont, Maldarelli, Saag, and Weinstein











#3

A 37-year-old man with no past medical history except HBV surface antibody positive after vaccination presents the morning after an episode of receptive anal intercourse with another man where the condom broke.

He is unaware of his sexual partner's medical history or whether he takes medications.

In addition to offering testing for HIV, hepatitis C, and bacterial STIs.

#3

What do you advise?

A) No specific prophylaxis

B) 2-drug prophylaxis with tenofovir disoproxil fumarate (TDF)/emtricitabine.

C) 2-drug prophylaxis with tenofovir alafenamide (TAF)/emtricitabine

D) 3-drug prophylaxis with TDF/emtricitabine + dolutegravir

E) 3-drug prophylaxis with TAF/emtricitabine + efavirenz

#4

A 34 year old gay man presents requesting HIV pre-exposure prophylaxis (PrEP).

His past medical history is notable only for gonorrhea two months ago that was treated with IM ceftriaxone; he has had repeated negative HIV tests.

He notes "a few days of feeling feverish" but has not taken his temperature. On physical exam his temperature is 38.6 C. (101.5 F.), he has a non-tender 1 cm oral ulcer and a faint macular red rash, the remainder of the exam in normal.

#4

A rapid HIV oral test in the office is negative.
In addition to routine blood work and HIV testing, what do you recommend?

A) Start PrEP with tenofovir disoproxil fumarate (TDF)/emtricitabine

B) Start PrEP with tenofovir alafenamide (TAF)/emtricitabine

C) Start PrEP with generic tenofovir disoproxil fumarate (TDF)/lamivudine

D) Start PrEP with tenofovir disoproxil fumarate (TDF)

E) Hold PrEP until laboratory results return

#5

You are asked to see a 62 year old female admitted for acute myocardial infarction.

1 of 2 blood cultures drawn from a central venous catheter for a new fever on hospital day 3 was positive on day 4 for Gram-positive cocci in clusters, later identified as Staphylococcus epidermidis.

The aerobic bottle was positive at 33 hours but the anerobic bottle remained negative Two peripheral blood cultures were obtained on day 4, the central venous catheter was replaced, and she was started empirically on vancomycin.

#5

The Staph.

Epidermidis from hospital day 3 (before the line was removed and before antibiotics were started) is growing coagulase-negative staphylococcus with the following MICs in mcg/ml:

- vancomycin 2 mcg/ml
- daptomycin MIC 0.5
- linezolid 2
- clindamycin 1
- TMP/SMX 0.5/5

#5

The other 3 blood cultures prior to starting vancomycin have no growth at 48 hours.

Since removing the line and starting vancomycin, the patient is afebrile with no localizing signs or symptoms.

White blood count remains normal.

#5

What would you recommend?

A) Continue vancomycin for 5 days

B) Switch to IV daptomycin and complete 5 days of therapy

C) Switch to oral linezolid to complete 5 days of therapy

D) Discontinue vancomycin and start daptomycin

E) Discontinue vancomycin

#6

A 56-year-old alcoholic woman with adult onset diabetes mellitus and depression fractured her right hip falling down the stairs.

She had an open reduction and internal fixation repair one week ago, but developed redness and drainage of the wound secondary to a vancomycin resistant E. faecium (VRE) infection of the operative site.
She was started on linezolid. You are called to see her on day 10 of hospitalization (day 8 of linezolid) because of anxiety, tremulousness, fever to 39.6°C, agitation and confusion.

The patient takes metformin (Glucophage) and glipizide for her diabetes mellitus and citalopram (Celexa) for her depression.

#6

If this is a drug reaction, which one of the following is most likely?

A) Delirium tremors

B) IgE mediated allergic reaction

C) IgG mediated allergic reaction

D) Hyper-serotonin syndrome

E) Malignant hyperthermia

#7

A 40-year-old businessman develops diarrhea while traveling to Thailand.

The illness progresses to passage of grossly bloody stools. He has been ill three days when he returns home.

He is still passing bloody stools and is weak, febrile and tachycardic when you see him.

#7

What treatment do you recommend while you are awaiting culture results?

A) a single dose of ciprofloxacin (500 mg)

B) a single dose of tinidazole (2 grams)

C) rifaximin 200 mg three times a day for three days

D) only oral rehydration therapy

E) single dose of azithromycin (1,000 mg)

#8

Six months after an otherwise healthy young international traveler returns home to the United States from India, she presents for medical evaluation.

She has been sick since she visited India although her symptoms have changed. She initially had a bout of diarrhea, passing grossly bloody stools that responded to three days of ciprofloxacin.

During the next six months, she experienced recurrent bouts of abdominal pain, abdominal bloating and loose stools without frank diarrhea. The abdominal pain is cramping and exacerbated by eating.

#8

What do you suspect is the diagnosis?

A) Post-infectious irritable bowel syndrome (IBS)

B) Chronic Cyclospora infection

C) Chronic norovirus infection

D) Clostridium difficile diarrhea

E) Celiac disease

#9

A 22 year-old woman recently underwent HIV testing done as part of a routine annual check-up. She's had 3 prior male sexual partners and used condoms "most of the time"; her last episode of intercourse was 3 months ago.

Testing reveals:

HIV antigen/antibody screening test: positive
HIV-1 Supplemental immunoassay: negative
HIV-2 Supplemental immunoassay: negative
HIV-1 RNA: 12 copies/ml

#9

What's the correct interpretation?

A) She has chronic HIV-1 infection

B) She has chronic HIV-2 infection

C) She has acute HIV-1 infection

D) She has HIV, but is a long-term non-progressor

E) She does not have HIV

#10

A 26-year-old man who had a negative HIV test 6 months ago presents to urgent care following unprotected sex with another man 10 days ago.

He feels "flu-ish" and has a fever of 101.2 F; the rest of his physical examination is normal. A rapid test for HIV is positive.

He is willing to start antiretroviral therapy if you recommend it.

#10

While awaiting further lab testing, you would recommend:

A) Start tenofovir disoproxil fumarate/lamivudine/doravirine

B) Start tenofovir alafenamide/emtriticitabine/elvitegravir/cobicistat

C) Start abacavir/lamivudine/dolutegravir

D) Start tenofovir alafenamide/emtricitabine/bictegravir

E) Hold ART until testing returns.

#11

A 23 year old man with HIV and pre-treatment HIV RNA 2.2 million copies/ml started tenofovir alafenamide (TAF)/emtricitabine + raltegravir and suppressed his HIV RNA to <20 copies/ml by 6 months; subsequent HIV RNA levels were <20 copies/ml at 9 months and 12 months, but 1507 copies/ml at 15 months, repeated at 5440 copies/ml.

When questioned, the patient admitted to missing occasional doses but vows to improve his adherence.

Genotype shows RT: M184V, PR: L63P, Integrase: Y143R and N155H.

#11

Which of the following regimens would you recommend?

A) TAF/FTC + dolutegravir (double-dose)

B) TDF/FTC/doravirine

C) TDF/FTC/efavirenz

D) TAF/FTC/elvitegravir/cobicistat

#12

A 59-year-old MSM with hypertension controlled on an ACE inhibitor takes PrEP with daily tenofovir disoproxil fumarate (TDF)/emtricitabine. His pre-PrEP creatinine was 1.1 mg/dL (creatinine clearance ~75 cc/min).

On routine follow-up testing, his creatinine is now 1.4 mg/dL (creatinine clearance ~55 cc/min).

A urinalysis is negative for protein, glucose, or cells.

#12

What do you advice?

A) Stop PrEP, use condoms

B) Repeat labs in 3 months

C) Change to every other day TDF/emtricitabine

D) Change to daily tenofovir alafenamide (TAF)/emtricitabine

E) Change to “on demand” TAF/emtricitabine

#13

A 25-year-old woman is 3 months pregnant and is found to be HIV+, HIV RNA is 96,000 copies/ml and CD4 cell count is 625 cells/μL. She is willing to start ART if you recommend it.

What is the most appropriate strategy?

A) Hold ART until the 3rd trimester

B) Start tenofovir alafenamide/emtricitabine/bictegravir

C) Start tenofovir disoproxil fumarate/emtricitabine + dolutegravir

D) Start tenofovir disoproxil fumarate/lamivudine/doravirine

#14

A 21-year-old college student is seen in the University Health Service for symptoms of abrupt onset, including headache, myalgia, fever (T 102.2°F) and cough. Some of her friends have been ill with similar symptoms. The student has just returned from winter break in the last week from her home in state. She has had symptoms for three days. Her roommate, who is otherwise in good health, does not have respiratory symptoms.

She is a non-smoker and has no significant past medical history. She is on an oral contraceptive as her only prescription medicine, but she has taken some of her roommate's guaifenesin. Her last influenza immunization was while in high school.

#14

On exam, she has a temperature of T 100.0ºF, unlabored respirations with a rate of 16, BP 100/70 and pulse of 88.

Her lung fields are clear.

According to the CDC and state Health Department reports, seasonal influenza is circulating in the state, and there is a high incidence of influenza-like illness.

#14

Which of the following is the best recommendation?

A) Perform a rapid influenza diagnostic test (RIDT)

B) Perform a rapid point-of-care molecular test for influenza

C) Prescribe either oseltamivir or baloxivir

D) Recommend student stay in her room until at least 24 hours after resolution of fever (and not using antipyretics)

E) Recommend her roommate receive oseltamivir chemoprophylaxis for influenza

#15

You are asked to examine a person under investigation (PUI) for COVID-19. Your gown and garb should be which of the following?

A) Cover gown, surgical mask, and gloves

B) Cover gown, N-95 respirator, and gloves

C) Cover gown, N-95 respirator, gloves, and disposable shoe covers

D) Cover gown, N-95 respirator, gloves, and googles

E) Cover gown, N-95 respirator, gloves, disposable shoe covers, and goggles

35

Hospital Epidemiology

Dr. Robert Weinstein

35 - Hospital Epidemiology

Speaker: Robert Weinstein, MD

2020 INFECTIOUS DISEASE BOARD REVIEW

Hospital Epidemiology

Robert A. Weinstein, MD
The C. Anderson Hedberg, MD Professor of Medicine
Rush University Medical Center
Chairman Emeritus
Department of Medicine, Cook County Hospital

Disclosures of Financial Relationships with Relevant Commercial Interests

- None

TOPICS

1. Healthcare-associated Infection (HAI) Pathogens
2. Isolation Precautions
3. Device- and Procedure-related Infections
4. Antimicrobial Stewardship
5. Outbreaks
6. Occupational Health

TOPIC 1: PATHOGENS

Question #1

A 50 y.o. previously healthy man developed urinary retention followed by urosepsis during admission for acute myocardial infarction. Initial antibiotic therapy appears to be failing. The most likely antimicrobial-resistant pathogen is:

A. Carbapenem-resistant *K. pneumoniae*
B. ESBL-producing *E. coli*
C. Multi-drug resistant *P. aeruginosa*
D. Vancomycin-resistant Enterococcus
E. Candida auris

CAUSATIVE PATHOGENS & TYPES OF INFECTION — KEY POINTS

Most Common Pathogens (% of HAIs) -- 10 states, 2011 & 2015

- *C. difficile* (12-15)
- *S. aureus* (11)
- *E. coli* (9-10)
- Candida (6)
- Klebsiella (5-10)
- Enterococcus (5-9)
- *P. aeruginosa* (5-7)
- Enterobacter (3-5)

MDR U.S. Case #s 2012-17 (hospital and community); % change

• Methicillin-R *S. aureus*	400K-320K	21% decrease
• Vancomycin-R Enterococci	85K-54K	39% decrease
• ESBL-producing Enterobacteriaceae	130K-200K	53% increase
• Carbapenem-R Enterobacteriaceae	12K-13K	no trend
• Carbapenem-R *Acinetobacter spp*	12K-9K	32% decrease
• MDR *P. aeruginosa*	46K-33K	30% decrease

N Engl J Med **2014**; 370:1198-1208 **2018**; 379:1732-44 **2020**; 382:1309-19

National Data for Acute Care Hospitals, Year 2017

Card View | Table

National Data by HAI Type

HAI Type	# OF FACILITIES THAT REPORTED DATA TO CDC'S NHSN, 2017*	2017 NATIONAL SIR VS. 2016 NATIONAL SIR	2017 NATIONAL SIR VS. NATIONAL BASELINE
CLABSI	3,576	↓ -9%	↓ -19%
CAUTI	3,679	↓ -5%	↓ -12%
VAE	2,046	↓ -3%	↓ -5%
C. difficile Events	3,669	↓ -13%	↓ -20%
MRSA Bacteremia	3,662	↓ -8%	↓ -14%
SSI: Abdominal Hysterectomy	2,970	= 2%	↓ -11%
SSI: Colon Surgery	3,158	= 3%	↓ -9%

SIR, Standardized Infection Ratios; National Baseline is 2015
https://www.cdc.gov/hai/data/portal/progress-report.html
https://www.cdc.gov/HAI/pdfs/progress-report/hai-progress-report.pdf
Magill et al, *N Engl J Med* 2018; 379:1732-44

Question #2

An 25 y.o. man with a recent renal transplant was admitted via the Emergency Room with gross hematuria. Three days after admission he developed fever and flu-like symptoms. An NP PCR test is positive for SARS-CoV-2. The most likely source of infection is:

A. Community exposure before admission
B. Food-borne illness in the community
C. Emergency Department exposure
D. In-hospital exposure to visitors or personnel
E. In-hospital exposure to contaminated respiratory therapy equipment

Incubation Periods for Selected Pathogens

• Influenza	1-4 days
• Parainfluenza	2-7 days
• Norovirus	12-48 hrs
• Rotavirus	<2 days
• RSV	2-8 days
• SARS-CoV-2	mean 5-6 (up to 14) days
• Wound Infection	
• Clostridia	24-48 hrs
• Group A Strep	24-48 hrs
• *S. aureus*	5-7 days
• Gram-negative bacilli	>7 days (variable)

Characteristics of COVID-19, SARS, MERS and Influenza

Characteristic	COVID-19	SARS-CoV/MERS-CoV	Influenza
Clinical severity	Asymptomatic to severe	Mostly severe	Mostly mild
Infection fatality risk	0.5% to 1%	10% (to 30%)	Seasonal: ≤0.1% 1918/1919 pandemic: 2%
Incubation period	Mean 5-6 (up to 14) days	Mean 3-5 (up to 14) days	Mean 1 (up to 3) days
Basic reproductive number	1.5 to 3.0	SARS: 1.5 to 4 MERS: 0.5 to 1	1.5 to 2.0
Modes of transmission	Respiratory droplets > aerosols Possible spread via fomites and fecal-oral	Respiratory droplets and aerosols Possible fomites	Respiratory droplets, some aerosols & fomites
Infectiousness profile	Most infectious before illness onset	Most infectious 7-10 days after illness onset	Most infectious around time of illness onset
Location of person-to-person transmission	Mainly community and long-term care facilities	Mainly hospitals	Mainly community; also can spread in hospitals
Importance of children in transmission dynamics	Unclear	Not important	Very important
Possible to avoid widespread transmission?	Unlikely	Yes	Maybe

Adapted from Cowling & Aiello, *J Infect Dis* 2020; 221:1749-51 and Weinstein, *NEJM* 2004; 350:2332-4.

Question #3

A nursing home reports that over the past 2 months 25% of its 100 residents have been diagnosed with suspected gastrointestinal infections. The symptoms — low grade fever, nausea, vomiting, and occasional diarrhea — resolved for most patients within 48-96 hours. The clinical lab's diagnostic test of choice for the most likely pathogen is:

A. MALDI-TOF of blood culture
B. Aerobic culture of vomitus
C. Aerobic culture of stool
D. EIA on stool
E. PCR on stool

Norovirus (Norwalk-like virus)

- Non-enveloped single-stranded RNA viruses that cause acute, self-limited gastroenteritis; major cause of foodborne outbreaks
- Caliciviridae family (includes sapoviruses, also a cause of gastroenteritis); multiple genotypes & reinfection possible
- Incubation 12-48 hrs; duration of illness 24-72 hrs
- Vomiting > diarrhea; low grade fever, headache, myalgia
- Highly contagious; infective inoculum – 18 viral particles; spreads indirectly, directly, common source, droplet
- Lab diagnosis: PCR>EIA; culture – a research tool (2016)

TOPIC 2: Isolation Precautions

Control & Prevention Keyed to Modes of Transmission

- Contact
  - Direct (body-to-body)
  - Indirect (e.g., fomites/environment, HCWs' hands)
- Droplet (>5 µm; travel 3-6 feet)
- Airborne (droplet nuclei ≤ 5 µm; remain aloft)
- Endogenous (auto-inoculation & device-related)
- Common source (outbreak potential)
- Vectorborne

HCW, healthcare worker

Droplet vs. Airborne Spread – Dichotomy or Continuum?

Droplet generation. A flash photo of a human sneeze, showing the expulsion of droplets that may be laden with infectious pathogens. Sneezing can produce as many as 40 000 droplets of 0.5–12 μm. These particles can be expelled at a velocity of 100 m/s, reaching distances of several metres. Smaller droplets with less mass are less influenced by gravity, and can be transported as a 'cloud' over greater distances by air flows. Larger droplets with more mass are more strongly influenced by gravity and less so by air flows, and move more 'ballistically', falling to the ground more quickly. Reproduced with the kind permission of Prof. Andrew Davidhazy, School of Photographic Arts and Sciences, Rochester Institute of Technology, Rochester NY, USA.

Tang JW et al, *J Hosp Infect* 2006; 64:100-14.

Isolation Categories & Precautions are Based on Three Modes of Transmission

		Healthcare Worker		
Category	**Private Room**	**Gloves**	**Gown**	**Mask**
Contact (Touch)	**Yes***	**Yes**	**Yes**	PRN
Droplet (3-6 ft)	**Yes***	PRN	PRN	**W/in 3-6 ft**
Airborne (Same air space)	**All**	PRN	PRN	**N95**

* When possible; cohort if not possible. Avoid rooming with immunosuppressed or high risk patients.
AII = Airborne Infection Isolation: negative pressure with no air recirculation (unless HEPA-filtered); 6-12 ACH (air changes per hour).
Hand hygiene – yes for all; eye protection – PRN for all.

Question #4

A hospitalized patient with nosocomial Influenza A was treated promptly with oseltamivir.
She should be placed on:

A. Standard Precautions in any room
B. Standard Precautions in a private room
C. Contact Precautions
D. Droplet Precautions
E. Airborne Precautions

Isolation Precautions — Examples of Indications

- Standard – All patients
- Contact – Multidrug resistant bacteria, infectious diarrhea, Ebola, chickenpox
- Droplet – Bacterial meningitis, pertussis, mumps, seasonal influenza
- Airborne – Tuberculosis, measles, chickenpox
- "Opportunistic" Airborne* – SARS, MERS-CoV, SARS-CoV-2, Pandemic flu, Ebola, Some BT agents

*e.g., increased transmission risk during aerosol generating procedures (such as intubation)

TABLE
Two Perspectives on Occupational Infections

	Infection Control	Occupational Medicine
Tradition	Nosocomial infection	Occupational exposure
Focus	Patients	Workers
Setting	Hospitals	Industries
Goal	Disease transmission	Exposure prevention
Authority	CDC	OSHA
Approach	Infection control policy	Exposure control plan
Enforcement	Voluntary guidelines	Mandatory regulations
Prevention	Isolation Behaviors Barrier precautions	Hierarchy of controls Engineering Work practices Personal protective gear

Gerberding JL, *Infect Control Hosp Epidemiol* 1993; 14:686-8.

Question #5

A 30 y.o. landscaper in Martha's Vineyard is admitted with fever and pneumonia. Blood cultures are growing gram-negative coccobacilli in the aerobic bottle. The appropriate patient placement and specimen lab containment, respectively, are:

A. Standard precautions for patient and lab containment for specimen
B. Contact precautions for patient and no lab containment for specimen
C. Droplet precautions for patient and no lab containment for specimen
D. Respiratory isolation for patient and lab containment for specimen
E. Strict (Respiratory & Contact) isolation for patient and lab containment for specimen

CDC Category A Bioterrorism Agent Infection Control

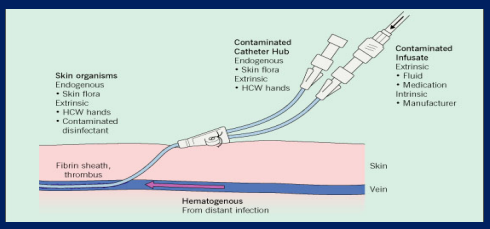
Disease	Patient Isolation	Laboratory Containment
Smallpox	AII & CP	Y
Plague	AII or DP	Y
Viral Hemorrhagic Fever	AII & CP	Y
Anthrax	SP*	N
Botulism	SP	N
Tularemia	SP	Y

AII = Airborne Infection Isolation, CP = Contact Precautions, DP = Droplet Precautions, SP = Standard Precautions

*Exception: CP if cutaneous anthrax has uncontained drainage

Topic 3: Devices & Procedures – Outcomes, Better

Potential Sources of Infection of a Percutaneous Intravascular Device (IVD)



Potential sources of infection of a percutaneous intravascular device (IVD). These include contiguous skin flora, contamination of the catheter hub and lumen, contamination of infusate and hematogenous colonization of the IVD from distant, unrelated sites of infection. HCW, health care worker. Adapted from Crnich and Maki, *Clin Infect Dis* 2002; 34:1232-4.

Question #6

You are revising your ICU's CVC-infection prevention guidelines. Which one of the following measures should not be included?

A. Maximum barrier precautions for CVC insertion
B. Removal of idle CVCs
C. Education of personnel
D. Preference for chlorhexidine for CVC site preparation
E. Regular guidewire-facilitated replacement of CVCs during prolonged use

CDC/HICPAC IV Catheter Infection Prevention Guidelines
Use this "Bundle" for a "Checklist"

- Education of personnel
- Is catheter needed?
- Avoid routine central line replacement as an infection control strategy
- Chlorhexidine skin prep (other uses of chlorhexidine?)
- Maximum barrier precautions
- Use of coated catheters (if after full implementation of above, goals are not met)

http://www.cdc.gov/hicpac/pdf/guidelines/bsi-guidelines-2011.pdf
HICPAC = Healthcare Infection Control Practices Advisory Committee

Catheter Infection Don'ts

- Don't culture catheter tips unless removed for suspected infection
- Don't order qualitative catheter tip cultures (e.g., don't stick catheter in broth)
- Don't under-fill blood culture bottles (because positivity rates are proportional to amount sampled)
- Don't start antibiotics without (re)culturing blood (peripheral & through catheter)
- Don't use thrombolytics routinely (usually case-by-case decision)
- Don't ignore infection control of peripheral IVs (PIVs)

Question #7

Which of the following patient care measures is least likely to be effective for preventing the ventilator-associated infection complication of pneumonia (VAP)?

A. Subglottic suction ports on ET tube
B. Elevation of the heads of beds to 30-45 degrees
C. Regularly scheduled changes of the ventilator tubing
D. Assessing extubation readiness daily
E. Non-invasive ventilation

Ventilator Complication Prevention Bundle – Update

DO When Possible
- Non-invasive ventilation
- Avoid sedation/ "Sedation Vacation" daily
- Assess extubation readiness daily/ breathing trials off sedatives
- Facilitate early mobility
- Use subglottic suction ports (if >48 hr intubation)
- Avoid ventilator circuit changes
- Elevate head of bed to 30-45°

Increased Interest in Non-ventilator Healthcare-associated Pneumonia

Klompas et al, *Infect Control Hosp Epidemiol* 2014; 35(8):915-36.

Ventilator Complication Prevention Bundle – Update

Special Approaches
- Selective decontamination
- Oral chlorhexidine
- UltraThin ET tube cuffs
- Auto-control ET tube cuff pressure
- Saline instillation pre-suctioning
- Mechanical tooth brushing

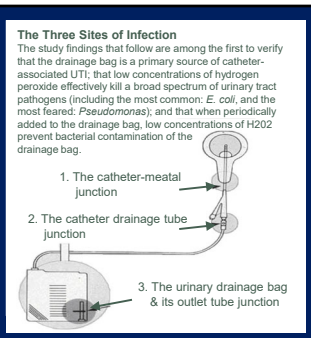
Klompas et al, *Infect Control Hosp Epidemiol* 2014; 35(8):915-36.

Ventilator Complication Prevention Bundle – Update

Don't Use (for infection prevention)
- Silver-coated ET tubes
- Kinetic beds
- Prone positioning
- Stress ulcer prophylaxis
- Early tracheotomy
- Gastric volume residual monitoring
- Early parenteral nutrition

No Recommendation
- Closed/in-line ET suctioning

Klompas et al, *Infect Control Hosp Epidemiol* 2014; 35(8):915-36.



Reduce cUTIs

- Avoid use of catheters (Key role for bladder ultrasound)
- Don't open or irrigate system
- Aseptic drainage of bag
- Bag below bladder

Reduce Surgical Site Infections

- Appropriate use of prophylactic antibiotics: start within 30-60 min of incision; stop within 24h
- Appropriate hair removal: no razors
- Surgical site skin prep – Chlorhexidine-alcohol
- Perioperative normothermia (colorectal surgery patients)*
- Post operative glucose control (major cardiac surgery patients cared for in an ICU)*
- Supplemental perioperative oxygen
- Nasal *S. aureus* decolonization
- Checklists
- Reporting of rates

* These interventions are supported by clinical trials and experimental evidence in the specified groups and may prove valuable for other surgical patients as well.

Being studied: Negative-pressure wound therapy
Not on list: Laminar air flow technologies; UV light use

Refs: *N Engl J Med* 2010; 362:18-26 and *JAMA Surg* 2017; 152:784-91 and 2020; 155:479.

What is Essential?*

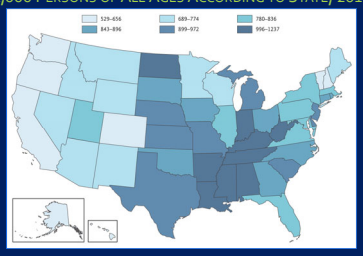
Preventing Device and Procedure Infections:

- HAND HYGIENE — Often the answer
- CVC-BSI — CHG prep, maximum barrier precautions, daily CHG bathing, CVC removal
- PIV — Observe site daily; change post ED insertion & q ≤3 days
- VAP — Oral CHG & sedation vacations (tube removal), positioning 45°
- UTI — Closed system & catheter removal
- SSI — Skin prep, antibiotic prophylaxis timing, & capable surgeon
- REPORT RATES
- As device infection rates fall, increasing attention to other HAIs

*Qualifier: RAW's views

TOPIC 4: ANTIMICROBIAL STEWARDSHIP

PROFLIGATE ANTIBACTERIAL USE: ANTIBIOTIC PRESCRIPTIONS PER 1,000 PERSONS OF ALL AGES ACCORDING TO STATE, 2010



Hicks et al, *N Engl J Med* 2013; 368:1461-2.

SEVEN CORE ELEMENTS CRITICAL TO THE SUCCESS OF HOSPITAL ANTIBIOTIC STEWARDSHIP PROGRAMS

- LEADERSHIP COMMITMENT: Dedicating necessary human, financial, and information technology resources
- ACCOUNTABILITY: Appointing a single leader responsible for program outcomes. Experience with successful programs has shown that a physician leader is effective
- DRUG EXPERTISE: Appointing a single pharmacist leader responsible for working to improve antibiotic use
- ACTION: Implementing at least one recommended action, such as systemic evaluation of ongoing treatment need after a set period of initial treatment (i.e., "antibiotic time out" after 48 hours)
- TRACKING: Monitoring antibiotic prescribing and resistance patterns
- REPORTING: Regular reporting information on antibiotic use and resistance to doctors, nurses and relevant staff members
- EDUCATION: Educating clinicians about resistance and optimal prescribing

Source: CDC. Core elements of hospital antibiotic stewardship programs. Atlanta GA: US Department of Health and Human Services, 2014.
Available at http://www.cdc.gov/getsmart/healthcare/implementation/core-elements.html

TOPIC 5: OUTBREAKS

Question #8

During a 1 week period, 5 ICU patients develop fulminant sepsis. Blood cultures from each grow *Serratia marcescens*; cultures of respiratory secretions and urine are normal flora and negative, respectively. No Serratia infections have occurred in this ICU in the past 3 months. On a general medical ward 2 months ago a patient had a Serratia cUTI.
The evaluation most likely to explain this ICU cluster of infections is a(n):

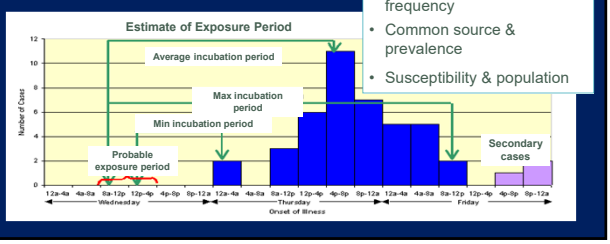
A. Assessment of ICU staff hand hygiene adherence
B. Whole genome sequence (WGS) analysis of the ICU Serratia isolates
C. Case-control study focused on IV medications
D. Rectal swab culture survey of patients in the ICU
E. Environmental cultures of the ICU rooms of the infected and control patients

STEPS IN OUTBREAK INVESTIGATION

1. Establish existence of epidemic
2. Verify diagnosis (*preceding question was an outbreak of "primary bacteremia" with Serratia*)
3. Case count
4. Orient data into time, place, person
5. Determine size of population at risk
6. Develop hypothesis regarding source & mode of spread, e.g., indirect person-to-person, common source, personnel carrier (*e.g., primary bacteremia – possibility of contaminated IV medications/infusions*)
7. Test hypothesis, refine above, plan and implement control measures. Test may be typing (such as PFGE or WGS) of epidemic isolates; case-control study (*e.g., in primary bacteremia outbreak, assess IV exposures*)

INTERPRETING EPIDEMIC CURVES

Infer from size, shape, & repetition of curves:
- Person-to-person spread & frequency
- Common source & prevalence
- Susceptibility & population



SOME OUTBREAK ASSOCIATIONS

- Unusual bug (esp. if BSI): Think common-source contamination, e.g., *Pantoea agglomerans*, Pseudomonas spp, Flavobacterium from IV fluids or propofol; extrinsic > instrinsic contamination
- *Burkholderia cepacia* – Contaminated iodophors, benzalkonium chloride
- *Cronobacter* (formerly *Enterobacter*) *sakazakii* – yellow pigment, powdered infant formula
- Listeria – foodborne (soft cheese, dairy, cabbage); miscarriages; a psychrophile
- Yersinia – blood products, pork, hot dogs; post-infectious reactive arthritis; a psychrophile

Key Emerging Outbreak Pathogens

- ***Candida auris***
  - Multi-continent emergence in "unrelated" outbreaks (different clades)
  - Heavy environmental contamination in affected nursing home and hospital wards
  - Some clades resistant to anti-fungals
- Mycobacteria (***M. chimera***) in CV surgery heater-cooler devices

Dry & Wet Environmental Contamination Increasingly Implicated in Outbreaks of Some Nosocomial Pathogens

Bacteria	*C. difficile*, VRE, MRSA, Acinetobacter, *P. aeruginosa*, "Water Bugs" (various gram-negative bacilli)
Virus	Norovirus, HBV, HCV
Fungi	Aspergillus, Mucor, Rhizopus, *Candida auris*
Mycobacterium	*M. chimera*

Topic 6: Occupational Health

Question #9

A healthy new resident has 12 mm of induration around a PPD skin test at 48 hours and a positive quantiferon gold assay. She says a PPD skin test in medical school 2 years ago, 12 weeks after a "tuberculosis exposure", was non-reactive. Her chest x-ray has no active disease. Which of the following is the most appropriate prophylaxis in this case:

A. 2 months of daily rifampin and pyrazinamide
B. 3 months of weekly isoniazid and rifapentine
C. 6 months of daily isoniazid
D. 9 months of daily isoniazid
E. Because no known exposure, not needed unless PPD ≥ 15 mm

MMWR Recomm Rep Feb 14, 2020; 69:1-11.

Classification of the Tuberculin Reaction (continued)
A reaction of ≥ 10 mm is positive in:

- Recent PPD converters (≥10mm increase within 2 years)
- Persons with medical risk factors (diabetes, silicosis, CKD, gastrectomy, j-i bypass, malnutrition, immunosuppressive therapy)
- Foreign-born persons from high prevalence countries
- Intravenous drug users or alcoholics

Classification of the Tuberculin Reaction (continued)
A reaction of ≥ 10 mm is positive in:

- Residents of long-term-care facilities, such as correctional institutions and nursing homes or homeless individuals
- Other high risk populations identified locally, e.g., healthcare workers

Employee Health – A Common Question:
Classification of the Tuberculin Reaction
A reaction of ≥ 5 mm is positive in:

- Close contacts to patients with infectious tuberculosis
- Persons with HIV infection
- Persons who have CXRs with fibrotic lesions consistent with healed TB
- Organ transplant recipients
- Persons on ≥15mg/day of prednisone for ≥1 month
- Persons on TNF-α antagonist treatment

Classification of the Tuberculin Reaction (continued)
A reaction of ≥ 15 mm is positive in:

- Persons with no additional risk factors for tuberculosis

But PPD tests now often replaced by IGRAs

IGRAs = Interferon gamma release assays

Question #10

A worried health care worker who is planning international travel gets a booster dose of MMR vaccine. His work restrictions during the 2 weeks after vaccination should be:

A. Furlough
B. Work in non-patient contact area
C. No contact with immunosuppressed patients
D. No restrictions unless there is evidence of vaccine-related fever or rash
E. No restrictions

Question #11

A 30 y.o. Neurosurgery resident was stuck with a bloody, brain-contaminated scalpel by a medical student during an OR procedure. The source patient was in the hospital for treatment of a febrile rash illness and confusion and was found to have positive tests for HIV antibody, HCV antibody, and HBs Ag; an RPR titre of 1:64; and a brain MRI that showed changes of PML. Appropriate viral load and PCR test results for the patient are not yet available. The surgeon has negative serologic tests for HBV, HCV, HIV, and syphilis.

Question #11

The infection most likely to be transmitted by this blood exposure is:

A. JC Virus infection
B. HBV
C. HIV
D. HCV
E. Syphilis

Healthcare Worker Post Exposure Prophylaxis (PEP)

Pathogen or Disease	Mode of Transmission	High-risk HCW	PEP	Modifying Factors
HIV	Percutaneous, splash — Blood or sterile body fluid or bloody fluids **Risk 0.3%**	Seronegative	ARVs for 4 weeks; serologic follow-up for 6 months	Sharp type, puncture depth, contaminating fluid, patient, VL & treatment, duration after exposure (24-36h or longer); pregnancy
Hepatitis C	Percutaneous **Risk 3%**	Seronegative	Pre-emptive therapy vs watchful waiting	Serologic follow-up
Hepatitis B	Percutaneous **Risk 30%**	Seronegative	HBIG & vaccine	Duration after exposure (24-48h)

Healthcare Worker PEP (continued)

Pathogen or Disease	Mode of Transmission	High-risk HCW	PEP	Modifying Factors
Hepatitis A	Fecal-oral	Seronegative	Vaccine; IG	Duration after exposure (14 days)
Parvovirus B19	Droplet, contact	Seronegative and pregnant, HIV, or hemoglobinopathy	No PEP	Exclude pregnant HCW from patient care
Pertussis	Droplet, contact	Seronegative or waned immunity	Macrolide	Duration after exposure (3 weeks)

HEALTHCARE WORKER PEP (CONTINUED)

Pathogen or Disease	Mode of Transmission	High-risk HCW	PEP	Modifying Factors
N. meningitidis	Droplet	Close contact	Ciprofloxacin, rifampin, ceftriaxone, or azithromycin (or sulfa if S)	Duration & proximity of contact
VZV	Contact, airborne	Negative VZV history or seronegative and immunocompromised or pregnant	VZIG or valacyclovir; VZV vaccine (Furlough day 10-21 PE; 10-28 if VZIG used)	Duration of, and after, exposure
Tuberculosis	Airborne, rarely contact	PPD- or IGRA-negative	Several regimens if PPD conversion	PPD results (baseline;12 weeks post-exposure)

Thank You

36

Antifungal Drugs

Dr. John Bennett

36 – Antifungal Drugs

Speaker: John Bennett, MD

Disclosures of Financial Relationships with Relevant Commercial Interests

- None

Plan of the talk

- 1. review of antifungals
  - Key points are underlined
- 2. questions on antifungals with answers

Mechanisms of action of antifungals

- Echinocandins (caspofungin, micafungin, anidulafungin) inhibit glucan synthase, block synthesis of 1-3 beta glucans in the fungal cell wall.
- Azoles inhibit sterol C-14 demethylase, block synthesis of sterol
- Ampho damages fungal cytoplasmic membranes
- Flucytosine converted to 5FU, inhibits DNA synthesis

Mechanisms of antifungal resistance

- Azoles:
  - mutations in CYP51A (codes for C14 demethylase) gene in Candida and Aspergillus
  - mutations in CYP51A promoter region in Aspergillus
  - increased drug efflux in Candida glabrata
- Echinocandins: mutations in FKS1 and FKS2 (code for glucan synthase)

Antifungal resistant species

- Amphotericin B resistant: Scedosporium apiospermum (Pseudallescheria boydii), Lomentospora (Sc) prolificans, Aspergillus terreus, Variable in Candida lusitaniae, C. auris +/-
- Fluconazole resistant: All moulds, Candida krusei, Candida auris, Candida haemulonii, some Candida glabrata
- Voriconazole resistant: mucormycosis, Fusarium solani, some rare Aspergillus species higher MIC's: (lentulus, ustus, calidoustus)
- Posaconazole resistance: like vori but more mucor activity
- Echinocandin resistance: Cryptococcus, Trichosporon, Histoplasma, Blastomyces, Coccidioides, moulds other than Aspergillus.

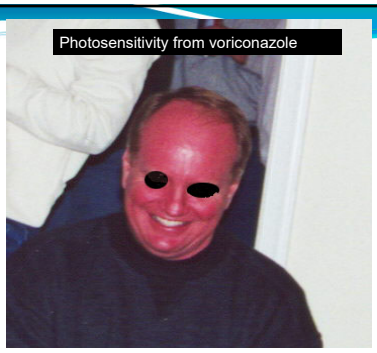
36 – Antifungal Drugs

Speaker: John Bennett, MD

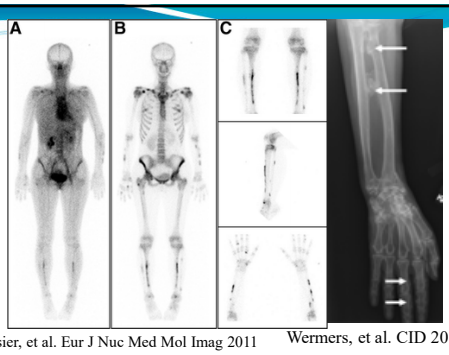
Azole antifungals

Voriconazole: the fundamentals

- Candida, Aspergillus , Scedosporium apiospermum, etc.
- Children are rapid metabolizers. Japanese 20% slow (2C19)
- Good CSF levels, none in urine.
- IV (sulfobutylcyclodextran=16x vori dose) accumulates in azotemia but not obviously toxic. Use oral in azotemia.
- Many drug interactions, Increases other drug levels: cyclosporine, tacrolimus, serolimus, steroids (budesonide, fluticasone), etc
- Side effects: hallucinations, hepatitis, photosensitivity, visual changes, peripheral neuropathy
- Many months of Rx: skin cancer, periostitis



Voriconazole Periostitis:
-Bone pain
-Months of Rx
-Alk phos high
-Plasma fluoride high (fluorosis)
-Bone scan
-Exostoses



Rossier, et al. Eur J Nuc Med Mol Imag 2011

Wermers, et al. CID 2011

Isavuconazonium/Isavuconazole

- Noninferior to vori in invasive aspergillosis.
- Use for mucor controversial
- Inferior to caspofungin for candidemia
- No good data on prophylaxis
- Pharma: like vori but long half life (5.4 days), no drug in CSF or urine. Fewer drug interactions than vori or posa. Best antimold azole for use with ibrutinib.
- Isavuconazonium 372mg=isavuconazole 200 mg
- Load with 200 mg q8h X6 than 200 mg qd, IV or PO
- No dose change for renal or moderate liver failure.
- Cost= $142/d. Fewer side effects than vori. Teratogenic.

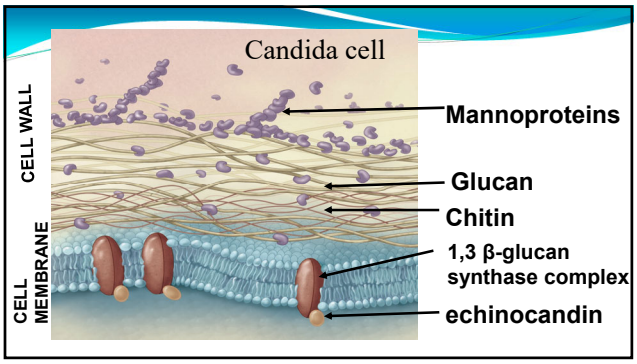
Posaconazole

- Approved for prophylaxis in GVHD or prolonged neutropenia.
- Extended release three 100 mg tablets twice first day then daily. IV same dose, has cyclodextran. 7-10 days for steady state. Check trough levels (usually 1-5 mcg/ml)
- Has been used in mucormycosis once patient has responded to amphotericin B
- Interactions with CYP3A4 increase some drug levels
- Well tolerated. Hypertension, hypokalemia

36 – Antifungal Drugs

Speaker: John Bennett, MD

Echinocandins



Caspofungin, Micafungin, Anidulafungin

- All Candida (including C. auris) susceptible but resistance can arise during long therapy. Mold activity: Aspergillus
- Cryptococcus, Trichosporon, endemic mycoses resistant
- IV once daily. Plasma half life: 10-15 hr.
- No drug in urine. Azotemia: same dose
- Protein binding high: poor penetration into CSF and vitreous humor of eye
- Drug interactions: none important

Clinical trials in deeply invasive candidiasis

- Candidiasis guidelines: an echinocandin preferred over fluconazole for initial treatment of candidemia
- Equivalent results in comparison trials of non-neutropenics
  - Micafungin 100 mg/day=Caspofungin 50 mg/day =Liposomal amphotericin B 3 mg/kg per day
  - Fluconazole 400 mg/d=ampho B 0.5-0.6 mg/kg/d
- Comparison trial with unclear result
  Anidulafungin 100 mg/day vs. Fluconazole 400 mg/day
- Isavuconazole 60% response vs caspofungin 71%

Caspofungin and Micafungin in invasive aspergillosis

- No randomized, controlled treatment trials done
- Treatment data are all from data the manufacturer collected in "salvage therapy" "failed" or "intolerant" of prior Rx and number of patients was small
- Anidulafungin: no data.
- IDSA Guidelines: "Primary therapy with an echinocandin is **NOT** recommended. Echinocandins (micafungin or caspofungin) can be used in settings in which azole and polyene antifungals are contraindicated."
- Prophylaxis for aspergillosis: Case series with micafungin

Amphotericin B formulations

- Lipid formulation: AmBisome or Ablecet
- Liposomal formulation: AmBisome
- Deoxycholate formulation: conventional amphotericin B

Pharmacology: penetrate CSF and vitreous humor poorly,

Urine concentrations low

AmBisome can cause acute back or chest pain with first infusion.

Potassium wasting in urine

Flucytosine

- Bioavailability 100%, good levels in CSF, eye, urine
- Accumulates in azotemia: bone marrow depression, hepatitis, colitis. Measure blood levels/dose adjust.
- Drug resistance arises during monotherapy.
- Used with ampho in cryptococcal meningitis

Now for a few questions

Question #1

A 47-year-old male with acute myeloid leukemia and an neutrophil count below 100/mcl for the past three weeks has been febrile for 10 days, first treated with piperacillin-tazobactam Had been on prophylactic micafungin but a blood culture is growing a yeast on Gram stain.

Question #1 Continued

The most likely echinocandin-resistant yeast is which of the following:

A. Candida parapsilosis
B. Candida glabrata
C. Candida auris
D. Trichosporon asahii
E. Candida krusei

Question #2

A 72 yr man with diabetes mellitus, renal failure and a central venous catheter developed fever and hypotension. Blood cultures grew Candida lusitaniae. On day 5 of liposomal amphotericin B 5 mg/kg he remained febrile and his creatinine rose from 4.5 to 6.0 mg/dl.

Question #2 Continued

In addition to changing his IV catheter, which of the following would be most appropriate?:

A. Itraconazole
B. Micafungin
C. Amphotericin B lipid complex
D. IV Voriconazole
E. Isavuconazole

Question #3

Echinocandin class of antifungals has which mechanism of action:

A. inhibits synthesis of membrane sterols
B. damages cytoplasmic membrane
C. interferes with synthesis of fungal cell wall glucans
D. inhibits fungal DNA synthesis
E. interfere with synthesis of fungal cell wall chitin

Question #4

A 37 yr female with diabetes mellitus is admitted for ketoacidosis, fever and sinus pain. Biopsy of a necrotic area of the middle turbinate shows wide, branching nonseptate hyphae. Serum creatinine is 2.5 mg/dl.

Question #4 Continued

Which of the following would be most appropriate?

A. Voriconazole
B. Anidulafungin
C. Fluconazole
D. Liposomal amphotericin B
E. Itraconazole

Question #5

You are asked to advise your hem-onc colleagues as to what prophylactic antifungal agent might be useful in preventing aspergillosis in their patients with acute graft-vs-host disease after allogeneic stem cell transplantation.

Question #5

According to the IDSA guidelines and literature you recommend:

A. itraconazole solution
B. posaconazole
C. micafungin
D. voriconazole
E. caspofungin

Question #6

45 yr old male 6 weeks post stem cell transplant for myelodysplasia, with a history of chronic hepatitis C was discharged home to Florida on cyclosporine, mycophenylate, prednisone , Bactrim (tmp/smz), citalopram and voriconazole. Diffuse nonpruritic erythema developed over his sun exposed skin.

Question #6 Continued

The most probable cause was:

A. porphyria cutanea tarda
B. graft versus host disease
C. drug interaction
D. voriconazole
E. Bactrim allergy

Question #7

A 66 yr old male with neutropenia following chemotherapy for lung cancer, serum creatinine 5 mg/dl, and congestive heart failure is found to have a Scedosporium apiospermum lung abscess.

Question #7 Continued

Which of the following would be preferred?

A. Anidulafungin
B. Itraconazole
C. Micafungin
D. Oral voriconazole
E. Liposomal amphotericin B

Question #8

- 65 yr wm admitted with cryptococcal meningitis, seizures, diabetes mellitus and granulomatosis with polyangiitis. Given conventional amphotericin B, flucytosine, phenytoin, glipizide, prednisone and cyclophosphamide.
- By the end of the first week of treatment, his creatinine had risen from 1.6 to 3 mg/dl.
- By the end of the second week his WBC had fallen to 1.2K, platelets 60K and diarrhea began.

Question #8 Continued

The cause of his WBC falling to 1.2K, platelets 60K and copious diarrhea is most likely which of these drugs?

A. flucytosine
B. phenytoin
C. glipizide
D. cyclophosphamide
E. cytomegalovirus

Take home messages

- Ampho: not *Scedosporium (Pseudallescheria boydii), Candida lusitaniae, Asperillus terreus*
- Only ampho for mucormycosis
- Fluconazole: not *Candida krusei , Candida auris,*
- +/- *Candida glabrata*
- Echinocandins: not Trichosporon or crypto
- Know mechanisms of action: glucan, sterol, cell membrane, DNA synthesis
- Flucytosine WBC & plt fall, diarrhea, hepatitis

Take home, continued

- Voriconazole: **phototoxicity, periostitis**, hallucinations
- Azole interactions:
  - Increases other drug levels: cyclosporine, tacrolimus, serolimus, warfarin, midazolam, steroids, etc.
  - Decrease azole level: **phenytoin**, rifampin, etc

The End

email
john_bennett@comcast.net

37

Non AIDS-Defining Complications of HIV/AIDS

Dr. Michael S. Saag

37 – Non AIDS-Defining Complications of HIV/AIDS

Speaker: Michael Saag, MD

2020 INFECTIOUS DISEASE BOARD REVIEW

Non AIDS-Defining Complications of HIV/AIDS

Michael S. Saag, MD
Director, Center for AIDS Research, University of Alabama at Birmingham
Professor of Medicine, Director of UAB CFAR, Jim Straley Chair in AIDS Research, University of Alabama at Birmingham

Disclosures of Financial Relationships with Relevant Commercial Interests

- None

CASE 1

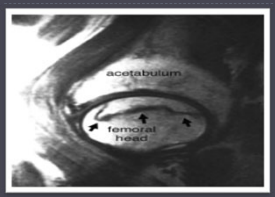
- 55 year old man presents with R hip pain
- H/o COPD requiring steroids frequently
- HIV diagnosed 17 years ago
- On TDF / FTC / EFV for 10 years; originally on IND / AZT / 3TC
- Initial HIV RNA 340,000; CD4 43 cells/ul
  - Now HIV RNA < 50 c/ml; CD4 385 cells/ul
- Electrolytes NL; Creat 1.3; Phos 3.5 Ca 8.5
- Mg 2.1, alk phos 130; U/A neg
- R Hip film unremarkable

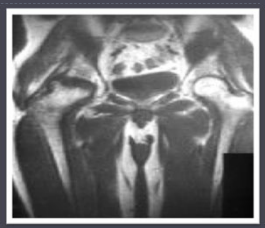
QUESTION #1

Which if the following is the most likely underlying cause of his hip pain?

A. Osetonecrosis of Femoral Head
B. Fanconi's syndrome
C. Vitamin D deficiency
D. Tenofovir bone disease
E. Hypogonadism

Osteonecrosis





This image demonstrates a classic segmental area of osteonecrosis with a dark line denoting the border between dead bone and living bone.

M. Levine. Ostoenecrosis of the hip- emedicine.com

Avascular necrosis in HIV

- Reported prior to the HAART era; increasing in HAART era.
- Rates of AVN 4.8/1000 person years >> general population.
  - Age ~ 35 yrs
  - Male predominance
  - H/o IDU
  - Increased duration of HIV
  - Low CD4
  - Elevated lipids
  - Glucocorticoid steroid use
  - Alcohol use

Monier et al, CID 2000;31:1488-92, Moore et al, AIDS 2003

CASE 2

- 46yowf c/o (CD4 582, VL <50 c/ml) c/o 1 week cramps in calves, tingling in hands, feet
- Today awoke and can't move except hands/feet
- No F/C, chest pain, SOB, incontinence
- + chronic diarrhea 4x/day
- Chronic fatigue, poor appetite
- Meds
  - TDF/FTC/EFV (2008), on TDF/FTC/Elv/cobi since 2014
  - zoloft, buproprion, norco, prilosec, trazodone, pravachol ibuprofen

CASE 2: Exam

- VS: T 98.2 P 79 BP 112/73
- RR 16, O2 sat 97%
- Pertinent findings
- Neuro: CNII-XII intact, strength 1+ all extremities except 4+ hand/wrist and ankles.
- NI reflexes. Alert, oriented.

CASE 2: Labs

137|116|5 Gluc 83
1.6 |18 |1.0 AG 3

Ca 8.3 Phos 1.8 Mg 2.1
Lactate 1.5 CK 186
UDS +cocaine/benzo/opiate
UA: 1.015 pH 6.5 2+ pro
Neg: gluc/ketones

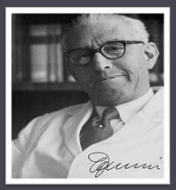
QUESTION #2

Which of the following is the most likely diagnosis?

A. Cocaine toxicity
B. Nucleoside-induced myopathy (ragged red fiber disease)
C. Serotonin Syndrome
D. Statin toxicity
E. Fanconi's syndrome

Fanconi syndrome

- Type II RTA
- Generalized proximal tubule dysfunction
- Hypophosphotemia, renal glucosuria, hypouricemia, aminoaciduria
  - Not all have present at once
- Osteomalacia can occur
- Recovery is the rule; can take months



CASE 3

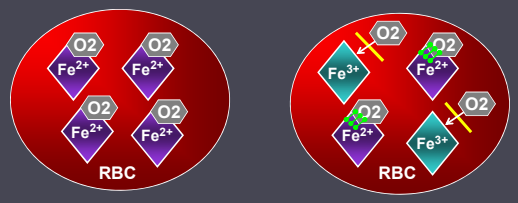
- 35 year old man presents with complaints of increasing fatigue, headache, SOB / DOE
- HIV diagnosed 4 mos ago with PCP; intolerant to TMP/SMX
- Now on TAF / FTC / BIC + PCP Prophylaxis with Dapsone
- Claims adherence to all meds;
  "Doesn't miss a dose!"
- Normal PE
- Pulse Ox 85%; CXR no abnormalities
- ABG: 7.40 / 38 / 94/ 96% (room air)

QUESTION #3

Which of the following is the most likely underlying cause of his symptoms?

A. Recurrent PCP
B. IRIS Reaction
C. Drug toxicity
D. Pulmonary Embolus
E. Patent Foramen Ovale

Hemoglobin and Methemoglobin



Methemoglobinemia: Therapy

- Discontinue offending agent
- Methylene blue
  - Action: reduces methemoglobin by NADPH-pathway
  - Indication: methemoglobin level > 30%
  - Dose: 1-2 mg/kg IV given over 5 minutes
  - Avoid: do not give to patients with G6PD deficiency (won't work)

CASE 4

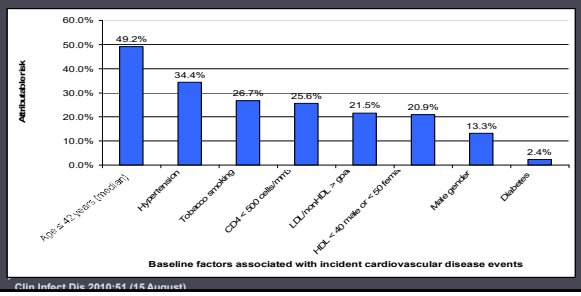
- 55 year old man presents with complaints of crushing chest pain
- HIV diagnosed 10 years ago
- Initial HIV RNA 340,000; CD4 43 cells/ul
  - Now HIV RNA < 50 c/ml; CD4 385 cells/ul
- Initally Rx with ZDV/3TC / EFV;
  now on ABC/3TC/ EFV
- On no other medications / smoker
- ECG shows acute myocardial infarction

QUESTION #4

Which of the following is the highest relative risk for his Acute MI?

A. Cigarette smoking
B. Lipid levels (LDL level of 180 / HDL 30)
C. Abacavir use
D. Lack of use of aspirin
E. HIV infection

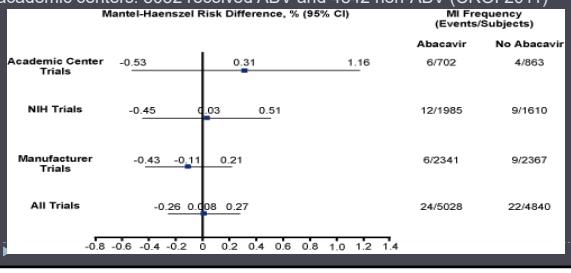
Low CD4+ T Cell Count Is a Risk Factor for Cardiovascular Disease Events in the HIV Outpatient Study



Clin Infect Dis 2010;51 (15 August)

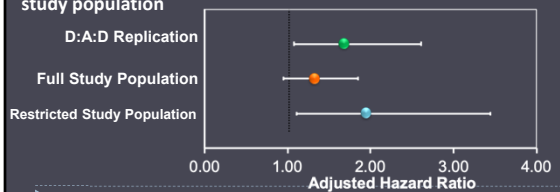
FDA meta-analysis

26 randomized, controlled ART trials of abacavir. 16 GSK studies, 5 NIH, 5 academic centers. 5032 received ABV and 4842 non-ABV (CROI 2011)



Abacavir and Risk for Myocardial Infarction- Analysis of NA-ACCORD

Adjusted hazard ratios of MI among persons with recent ABC use (vs. no recent ABC use): replication of the D:A:D model, NA-ACCORD model in the Full study population, and NA-ACCORD model in the Restricted study population



Palella FJ *et al*, Abstract 749 CROI Seattle 2015

MI Classification Protocol

Universal Definition of MI:

Primary MI (Type 1 'traditional' MI atherosclerosis)

Plaque rupture with thrombus

Secondary MI (Type 2 supply-demand mismatch)

Vasospasm

Secondary MIs common in HIV-infected individuals before age 50

Causes of Secondary MI in HIV-infected Individuals*	N (%)
Sepsis/bacteremia	100 (35%)
Cocaine induced/illicit drug	39 (14%)
Hypertensive urgency/emergency	28 (10%)
Respiratory failure	26 (9%)
Non-coronary cardiac	23 (8%)
Hypotension	15 (5%)
Procedure related	12 (4%)
GI bleed	11 (4%)
Neurologic	6 (2%)
Overdose	5 (2%)
Other/unknown	23 (8%)

*Crane et al. *Am J Epidemiol* Apr 15 2014

CASE 5

- 25 year old black woman presents with fatigue
- History of IV Heroin use; intermittently takes TDF/FTC PreP
- Exam no edema
- Work up in ER shows creatinine 8.4 BUN 79; mild anemia; mild acidemia
- In ER 10 weeks earlier; normal renal function
- U/A high grade proteinuria
- US of kidneys: Normal to increase size; no obstruction
- Rapid HIV test positive

QUESTION #5

Which of the following is the most likely cause of her renal failure?

A. Volume depletion / ATN
B. Heroin Associated Nephropathy
C. HIVAN
D. Membranous glomerulonephritis
E. Tenofovir Toxicity (PrEP)

Bonus Question:

In a patient with HIV Associated Nephropathy, which of the following is the most effective intervention to prevent progression to ESRD?

A. An ACE inhibitor
B. Corticosteroids
C. High Molecular Weight Dextran
D. Antiretroviral Therapy
E. A calcium channel blocker

CASE 6

- 55 year old man presents with complaints of fever / volume depletion
- HIV diagnosed in ER on rapid test
- Lymphadenopathy / splenomegaly / few petechiae / Oriented X 3
- HIV RNA 340,000; CD4= 3 cells/ul
- On no medications

Hb 8.2 gm/dl; Plt count 21,000; Creatinine 2.0
Rare schizocytes on peripheral blood smear

QUESTION #6

Which of the following is the most effective intervention to increase the platelet count?

A. Splenectomy
B. Corticosteroids
C. Plasmapheresis
D. Ethambutol + Azithromycin
E. Antiretroviral Therapy

CASE 7

- 45 year old recently diagnosed with HIV
- HIV RNA 140,000; CD4= 230 cells/ul
- Baseline labs:
- Hb 11.2 gm/dl; AST 310 / ALT 120

140|101 | 5 Gluc 100
4.2 | 28 |1.1 eGFR = 65 ml/min

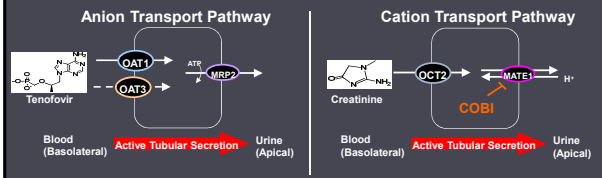
- Started on TAF/FTC+ Dolutegravir; No other medications
- Returns 4 weeks later, labs unchanged except creatinine now 1.3 mg/dl (eGFR 55)

QUESTION #7

Which of the following is the most likely cause of her increased creatinine / reduced eGFR?

A. Glomerular lesion
B. Proximal Tubule damage
C. Proximal Tubule inhibition
D. Distal Tubule damage
E. Distal Tubule inhibition

Tenofovir and COBI Interact with Distinct Renal Transport Pathways

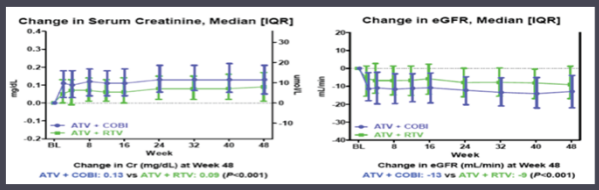


The active tubular secretion of tenofovir and the effect of COBI on creatinine are mediated by distinct transport pathways in renal proximal tubules

Ray A, et al. Antimicro Agents Chemo 2006;3297-3304
Lepist E, et al. ICAAC 2011; Chicago. #A1-1724

Changes in Serum Creatinine and eGFR Study 114

- COBI increases serum creatinine by inhibiting renal creatinine secretion[1]
- COBI does not affect actual glomerular filtration rate[2]



Gallant IAS 2012

CASE 8

- 26 year old presents with cryptococcal meningitis and newly diagnosed HIV (Rx with AMB +5FC; to fluconazole)
- HIV RNA 740,000; CD4= 23 cells/ul
- Baseline labs:
- CSF: 2 lymphocytes / protein 54 / glu 87 (serum 102)
  OP = 430 mm H_20
  Started on TAF/FTC /Bictegravir at week 2
- Returns 6 weeks later, Fever 103 and a mass in supra-clavicular region (3 x 4 cm)

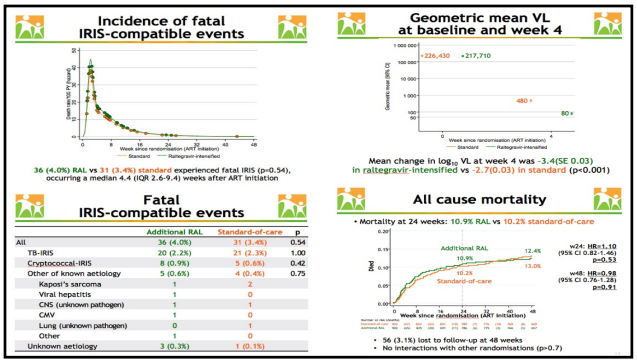
QUESTION #8

Which of the following is the most likely cause of the new mass?

A. B Cell Lymphoma
B. Multicentric Castleman's Disease
C. IRIS reaction to cryptococcus
D. Mycobacteria Avium Complex
E. Bacterial Abscess from prior PICC line

IRIS

- Immune Reconstitution Inflammatory Syndrome
- Occurs 4 – 12 weeks after initial ARV administration
- Most often in patients with advanced HIV infection
- High viral load / low CD4 count
- TB, MAC, crypto, PML, KS are most common OIs
- Is **NOT** related to type of ARV therapy



CASE 9

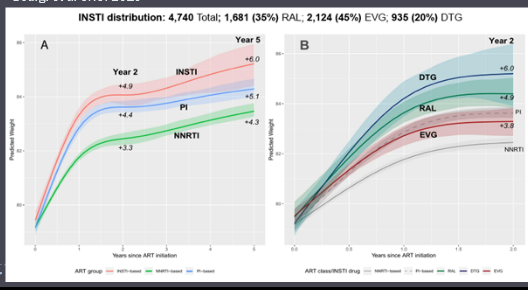
- 48 yo Male presents with newly diagnosed HIV infection
- Asymptomatic
- **Initial: HIV RNA 160,000 c/ml**
  CD4 count 221 cells/ul
- Other labs are normal; Started on ARV Rx with DTG + TAF/FTC
- Returns for a 3 month follow up visit
- **HIV RNA < 20 c/ml; CD4 390 cells/ul**

QUESTION # 9

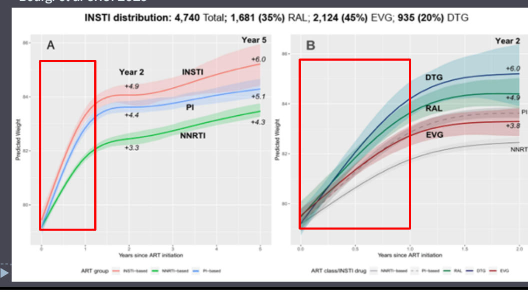
Which of the following will most likely be present on his 3 month visit from use of dolutegravir:

A. Morbilliform skin rash (extremities)
B. 3 kg weight gain
C. Mild cognitive impairment
D. Depression
E. Anemia

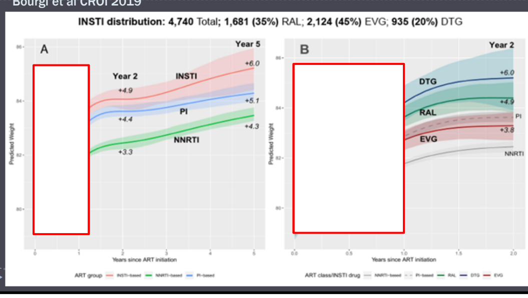
Change in Weight Overtime – NA-ACCORD
Bourgi et al CROI 2019



Change in Weight Overtime – NA-ACCORD
Bourgi et al CROI 2019



Change in Weight Overtime – NA-ACCORD
Bourgi et al CROI 2019



CASE 10

- 48 yo Male presents with newly diagnosed HIV infection
- Asymptomatic except for weight loss / fatigue
- **Initial: HIV RNA 160,000 c/ml**
  CD4 count 221 cells/ul
- Other labs are normal; Started on ARV Rx
- Returns for a 3 month follow up visit
- **HIV RNA < 20 c/ml; CD4 390 cells/ul**

QUESTION # 10

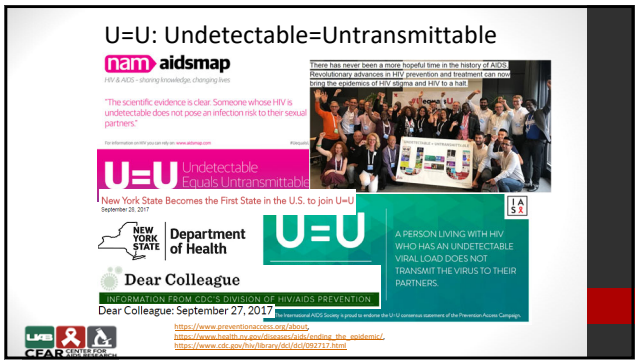
Assuming he remains undetectable, you tell him that his risk of transmitting HIV to his seroneg partner via sex is:

A. Virtually zero risk (< 0.2%)
B. Very low risk (< 2%)
C. Possible (<10 %)
D. It depends on which ARV regimen he's on

PARTNERS Study

- 548 heterosexual and 972 discordant gay couples followed up to 8 years
- Seropositive partner had VL < 200 c/ml
- 77,000 sexual acts without condoms
- Zero transmissions (from seropositive partner)
- Upper bound of 95% CI: 0.23 /100 CYFU
- **Sexual Transmission from a person with Undetectable Viral Load is Effectively Zero**

Rodger AJ, et al. Lancet 393: 2428-38, 2019



CASE 11

- 48 yo Male presents with cough, fever, loss of snese of smell, diarrhea and fatigue for 10 days
- On ARV Rx:
- **HIV RNA < 20 c/ml; CD4 590 cells/ul**
- **SARS-CoV-2 PCR test is positive**

QUESTION # 11

Which of the following is true regarding COVID-19 in PLWH vs non-HIV individuals:

COVID-19:

A. Occurs more often in PLWH and is more severe
B. Occurs less often in PLWH and is less severe
C. Occurs more often in PLWH but is less severe
D. Occurs less often in PLWH but is more severe
E. Neither occurs more often in PLWH nor is more severe

Few studies on how HIV influences COVID-19 outcomes to date

Case report of pt with HIV, HCV, and COVID-19 showed RT-PCR repeatedly negative, IgM peak prolonged (42 days) & IgG titers blunted compared to those without HIV[1]
Case series of 9 patients in Bronx COVID-19 had severe disease but all had co-morbidities[1]
Mount Sinai- PWH admitted with COVID-19 (n = 88) matched to people without HIV (n=405) by age, race/ethnicity, sex, week of COVID-19 hospitalization admission: No differences in disease severity on admission or adverse outcomes (mechanical ventilation or death)[3]

[1]Zhao CID 2020; [2]Suwanwongse K. J Med Virol 2020; [3]Sigel. JID in press;

38

Syndromes in the ICU that ID Physicians Should Know

Dr. Taison D. Bell

38 - Syndromes in the ICU that ID Physicians Should Know

Speaker: Taison Bell, MD

2020 INFECTIOUS DISEASE BOARD REVIEW

Syndromes in the ICU that Infectious Disease Physicians Should Know

Taison D. Bell, MD
Assistant Professor of Medicine
Division of Pulmonary and Critical Care Medicine
Division of Infectious Disease and International Health

Disclosures of Financial Relationships with Relevant Commercial Interests

- None

Question 1: What proportion of patients in the ICU develop fever during their stay?

A. Less then 5%

B. Between 15-25%

C. Over 50%

D. Everyone. Absolutely everyone

Exam Blueprint: Critical Care Topics ~8-10%

Critical care medicine
- Systemic inflammatory response syndrome (SIRS) and sepsis
- Ventilator-associated pneumonias
- Noninfectious pneumonias (eosinophilic and acute respiratory distress syndrome [ARDS])
- Bacterial pneumonias
- Viral pneumonias
- Hyperthermia and hypothermia
- Near-drowning and *Scedosporium* and *Pseudallescheria* infection

General internal medicine
- Malignancies
- Hemophagocytic lymphohistiocytosis (Hemophagocytic syndrome)
- Noninfectious inflammatory disorders (e.g., vasculitis, lupus, inflammatory bowel disease)
- Dermatologic disorders
- Hematologic disorders
- Noninfectious central nervous system disease
- Bites, stings, and toxins
- Drug fever
- Ethical and legal decision making

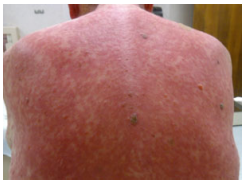
Question 2

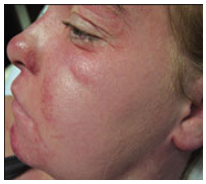
- You are asked to see a 35 year-old woman with a history of seizure disorder who was admitted to the ICU with a fever to 40°C, hypotension, and a maculopapular rash
- She is being empirically treated with vancomycin and piperacillin-tazobactam. Blood, urine, and sputum cultures (taken prior to antibiotic initiation) are negative
- Exam: Tachycardia with otherwise normal vital signs. Diffuse maculopapular rash with facial edema and sparing of the mucosal surfaces
- Labs are notable for elevated AST/ALT and peripheral eosinophilia
- Only home medication is lamotrigine, which she has taken for years. She recently increased the dose two weeks ago

Her clinical syndrome is most consistent with:

A. Sepsis
B. Stevens–Johnson syndrome (SJS)/toxic epidermal necrolysis (TEN)
C. DRESS (drug-induced hypersensitivity syndrome)
D. Erythema Multiforme
E. Neuroleptic Malignant Syndrome (NMS)

Morbilliform Rash with Facial Edema and Eosinophilia





38 - Syndromes in the ICU that ID Physicians Should Know

Speaker: Taison Bell, MD

Exanthematous drug eruptions

- T-cell-mediated, delayed type IV hypersensitivity reaction
- Diffuse maculopapular rash (morbilliform)
- Highest incidence with aromatic antiseizure medications: carbamazepine, phenytoin, and lamotrigine (1:100)

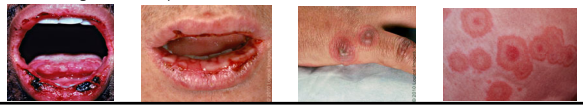
SJS/TEN	AGEP	DRESS
• Severe blistering • Mucosal involvement common • SJS: <10% BSA • TEN: >30% BSA	• Rapidly spreading (hours) pustular lesions • Mucosal involvement rare • Common ddx: psoriasis	• > 50% BSA • Facial edema • Infrequent mucosal involvement • Eosinophilia

DRESS (drug-induced hypersensitivity syndrome)

Rash Characteristics	Morbilliform involving >50% BSA, inflamed, facial edema, infrequent mucosal involvement
Onset	Usually 1-3 (up to 6) weeks after drug exposure
Other Features	Fever, LAD, other organ involvement in 80% (liver, kidney, pancreas, heart, lung), expansion of CD4/8 T cells → Herpesviridae reactivation (HHV6)
Lab Findings	Eosinophilia, lymphocytosis/lymphopenia, atypical lymphocytes
Classic Meds	Aromatic AEDs (highest with lamotrigine), Vancomycin, Raltegravir, Dapsone, and Sulfas
DDx	SLE, mycoplasma, viral hepatitis, mononucleosis
Treatment	Withhold offending agent, supportive care Steroids, CsA, IVIg are controversial. Mortality is high

Erythema Multiforme

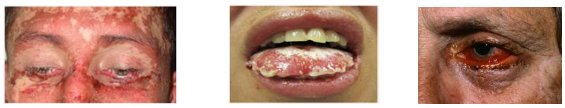
- Immune mediated
- Distinctive target lesions that are asymptomatic
  - Febrile prodrome in some cases
- Often associated with oral, ocular, genital mucosal lesions
- Less severe than DRESS or SJS or TEN
- Causes: Infection > Drugs
  - Many infections: HSV, Mycoplasma, many others
  - Cancer, autoimmune, drugs etc
- Self Limiting in 10-14 days



Stevens Johnson Syndrome and Toxic Epidermonecrolysis

Rash Characteristics	Erosive mucositis of oral, urogenital, and ocular sites SJS: <10% BSA; TEN: >30% BSA
Onset	4-28 days after drug exposure
Other Features	Fever, partial or full thickness injury with painful necrolysis, pulmonary and GI manifestations
Lab Findings	Leukopenia, no eosinophilia
Risk Factors	Aromatic AEDs, infection (mycoplasma), GVHD, HIV
Treatment	Withhold offending agent, supportive care Steroids and IVIg are controversial

Stevens Johnson and Toxic Epidermonecrolysis



- "Positive Nikolsky sign"
  - slight rubbing of the skin results in exfoliation of the outermost layer
  - NOT specific for Stevens Johnson and TEN
    - Staph scalded skin syndrome (mostly children, no mucosal involvement)
    - Pemphigus
    - Others

Question 3

- You are called to the surgical ICU to see a 29-year-old previously healthy male with a fever of 41.6°C who returned 4 hours previously from the operating room where he had arthroscopy for a rotator cuff injury.
- He did well post operatively except for some nausea that was treated.
- The patient is somnolent, flushed, diaphoretic, and rigid. His blood pressure has risen from 130/70 to 180/100 but is now dropping. He is given one ampule of Narcan, but does not respond.

Which of the following would you give?:

A. Antihistamines
B. High-dose corticosteroids
C. Dantrolene
D. IVIG
E. Dilantin

38 - Syndromes in the ICU that ID Physicians Should Know

Speaker: Taison Bell, MD

Extreme Hyperpyrexia (T>41.5C)

- Heat Stroke
  - Exertional (football player in August)
  - Non exertional (Elderly)
  - Lack of hydration and/or inability to sweat
- Drugs
  - Cocaine, ecstasy etc…
- The Pyrexic Syndromes

Malignant Hyperthermia

- Syndrome - 5% Mortality
  - Muscle contraction (masseter spasm)
  - Cardiovascular instability
  - Steep rise in CO2
- Genetic defect
  - Ca++ transport in skeletal muscle
  - Autosomal dominant
    - (excessive calcium accumulation)
- Triggers
  - Usually < 1 hour after trigger (up to 10 hours)
  - Classic: Halothane, succinylcholine

Neuroleptic Malignant Syndrome (NMS)

- Frequent trigger = haloperidol
  - Any "neuroleptic" (antipsychotic)
  - Lead pipe rigidity
  - Antiemetics such as metoclopramide
  - Withdrawal of antiparkinson drugs (L dopa)
- Onset variable: 1-3 days/within first 2 weeks
  - Time of drug initiation
  - When dose changed
- Management
  - Dantrolene
    - (direct muscle relaxant for up to 10 days)
  - Dopamine agonists (bromocriptine and others)

Serotonin Syndrome

Clinical Characteristics of Serotonin Syndrome	
Pathogenesis	Excess Serotoninergic Activity • Therapeutic drugs, drug interactions, self poisoning
Triggers	• Linezolid = MAO Inhibitor • SSRI inhibitors (Bupropion) • Antiemetics (Granisetron) • Tricyclic antidepressants (amitriptyline)
Clinical Manifestations	• Acute onset (within 24 hrs of new drug/drug change) • Hyper-reflexive>bradyreflexia • Nausea, vomiting, diarrhea, tremors followed by shivering
Treatment	• Withdraw offending medication • Consider benzodiazepines and cyproheptadine

What to Look for on the Exam

	Malignant Hyperthermia	NMS	Serotonin Syndrome
Trigger	Succinylcholine or inhaled halogenated anesthesia	Withdrawal of L Dopa in Parkinsons or Neuroleptic Drugs	SSRIs, Antiemetics, Linezolid, Lithium, Street Drugs
Onset	Rapid onset in perioperative period	Subacute over 1-3 days	6-24 hours of starting a drug or increasing dose
Exam	Masseter spasm, Lead pipe rigidity	Mental status change with dysautonomia, catatonia, mutism, stupor, coma	Shivering, myoclonus, n/v/d, hyper-reflexia, flush skin
Labs	Severe hypercarbia, rhabdomyolysis	CK rise, myoglobinemia	Nothing classic

Hypothermia: <35°C

- Causative Drugs
  - Beta blockers (metoprolol)
  - Alpha blockers (clonidine)
  - Opioids
  - Ethanol
  - Antidepressants
  - Antipsychotics
  - Aspirin
  - Oral hypoglycemics
- Syndrome
  - Hypotension due to fluid shifts
  - *Give broad spectrum antibiotics empirically if they fail to raise temperature 0.67C/hour
  - Consider adrenal or thyroid insufficiency
- Treatment
  - Rewarming
  - "ABC"s
    - Airway, Breathing, Circulation

Question 4

- You are called to the medical ICU to see a 47 y/o woman with a history of alcoholic cirrhosis with ARDS and shock
- Initially admitted to general medicine for encephalopathy in the setting of skipping lactulose doses
- On HD#3 developed ARDS, thought to be from aspiration
- Subsequently goes into distributive shock. Antibiotics are vancomycin and piperacillin-tazobactam
- Patient has daily fevers to 39°C and a persistent low-dose levophed requirement
- Labs: mild hyponatremia and hyperkalemia. Metabolic acidosis
- Micro: blood, urine, sputum, and ascitic fluid are benign
- Radiology: CXR with unchanged b/l multifocal opacities, RUQ USG benign, Abd CT benign

Which of the following would you give?:

A. Broader spectrum antibacterial treatment
B. Stress dose corticosteroids
C. Dantrolene
D. IVIG
E. Antifungal therapy

Differential Diagnosis of Shock

Ohm's Law

MAP = CO x SVR

Cardiogenic (flow)
- MI/CHF/Tamponade
- PE
- Tension PTX
- Hypovolemia

Distributive (resistance)
- Sepsis
- Toxic shock syndrome
- Aspiration
- Anaphylaxis
- Neurogenic
- Adrenal insufficiency

Question 5

A patient with end stage renal disease on dialysis through a tunneled hemodialysis catheter is admitted to the medical ICU with altered mental status, hypotension, and fever. On exam he has obvious purulence at the catheter site.

For the patient's syndrome, which of the following is NOT an evidence-based intervention?

A. Early and effective antibiotics
B. Albumin as the preferred resuscitation fluid
C. Measuring serum lactate
D. Fluid resuscitation with 30 cc's/kg crystalloid

FYI: Sepsis 3 Definition: Not Testable!

- Definition of Sepsis
  - "Life-threatening organ dysfunction due to a dysregulated host response to infection"
- Definition of Septic Shock: Sepsis
  - Absence of hypovolemia
  - Vasopressor to maintain mean blood pressure >65mmg
  - Lactate >2 mmol/L (>18 mg/dL)
- Predicting Outcome
  - Increase in the Sequential Organ Failure Assessment (SOFA) score (10% mortality)
  - Quick Sofa is relatively specific but not very sensitive

Sepsis 3 Definition: For Background (Not Testable)!

	Traditional Definition	Sepsis 3
Sepsis	Suspected or known infection with ≥ 2 SIRS criteria	Life-threatening organ dysfunction due to a dysregulated host response to infection - SOFA score ≥2 points or positive qSOFA
Severe Sepsis	Sepsis + organ failure	N/A
Septic Shock	Severe sepsis + hypotension refractory to adequate fluid resuscitation or addition of vasopressors	Sepsis with adequate resuscitation with vasopressor requirement and lactate ≥ 2 mmol/L

Increase in the Sequential Organ Failure Assessment (SOFA) score (10% mortality)
Quick Sofa is relatively specific but not very sensitive

Surviving Sepsis Campaign — Managing Sepsis — CMS

What's the Bottom Line?

- Some recommendations are plausible
  - Fluid resuscitation with 30 cc's/kg crystalloid
  - Vasopressors for MAP goal 65
    - But do not use Dopamine!

- Some are wrong
  - Early goal directed therapy
  - Tight glucose control. Better outcomes <180

- Two are unequivocally true
  - Early effective antibiotics
  - Source control

Other Things

Stress-dose steroids: conflicting data
- CORTICUS/ADRENAL
  - No change in mortality with hydrocortisone
  - **Quicker reversal of shock**
- Annane/APROCCHSS
  - Improved mortality with hydrocort/fludricort
  - **Quicker reversal of shock**

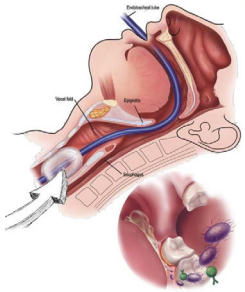
Antiendotoxin and Anticytokine therapy
- No benefit

Antithrombosis (Activated Protein C)
- Taken off the market

Surviving Sepsis Campaign Bundles

3 Hour Bundle	6 Hour Bundle
- Measure lactate level - Draw blood cultures - Administer broad spectrum antibiotics - Administer 30 cc/kg IV crystalloid	- Start vasopressors if MAP <65 despite fluid resuscitation - Reassess volume status if hypotension persists after fluid resuscitation or if initial lactate ≥ mmol/L

Ventilator Associated Pneumonia



Institute for Healthcare Improvement Ventilator Care Bundle Components

- Head of bed elevation to 45°
- Daily awakening trials and assessment of extubation readiness
- Chlorhexidine oral care
- Stress ulcer and DVT prophylaxis

www.IHI.org/topics/VAP
O'Grady. JAMA 2012
Weavind. Curr. Anesth 2013

Ventilator Associated Pneumonia National Healthcare Safety Network

Pathogen	% of Isolates
Staph aureus	24.7%
Pseudomonas aeruginosa	16.5%
Klebsiella	10%
Enterobacter	8.%
E. Coli	5%

IDSA VAP Treatment Guidelines

Cover for S. aureus, P. aeruginosa, and other GNRs in ALL patients (strong recommendation, very low-quality evidence)

Clinical Question	Recommendation
MRSA coverage	Use vancomycin or linezolid
PsA and other GNRs	Pip-tazo, Cefepime, Ceftazidime, Levofloxacin
Double GNR coverage?	Only if >10% of isolates are resistant to the primary abx
Double coverage agent	FQs, aminoglycosides (no monotherapy), polymyxins
Procalcitonin	Do not use for diagnosis. Consider to aid in discontinuation
Duration of therapy	7 days, consider longer or shorter based on clinical signs

Clin Infect Dis 2016; 63: e61-e111

38 - Syndromes in the ICU that ID Physicians Should Know

Speaker: Taison Bell, MD

Question

34 year-old woman with opiate use disorder is admitted to the medical ICU for acute respiratory distress syndrome requiring intubation. She has been receiving intravenous daptomycin through a PICC for tricuspid valve endocarditis for the past three weeks. Transthoracic echo is unchanged from prior and chest CT shows bilateral ground glass opacities with scattered areas of consolidation. Blood cultures are negative. Bronchial alveolar lavage shows a predominance of eosinophils with negative cultures.

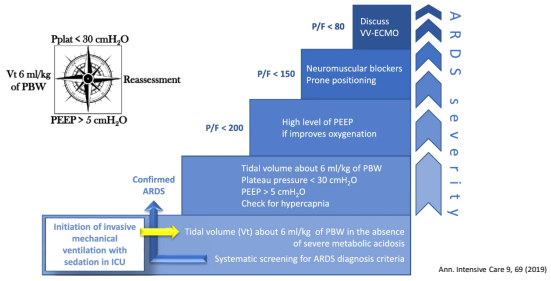
Which of the following is the most likely cause of her respiratory illness?

A. Injection drug use
B. Septic pulmonary emboli
C. Daptomycin
D. Sepsis

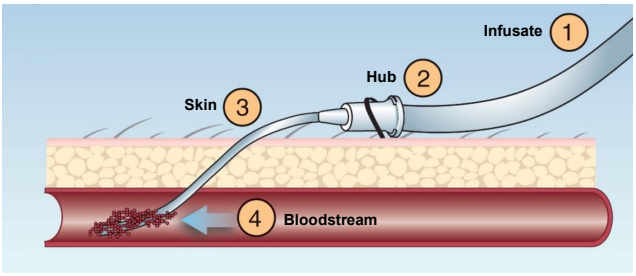
Eosinophilic Pneumonia

- Rare disorder characterized by eosinophil infiltration of the pulmonary parenchyma
- Often associated with peripheral eosinophilia
- Many drugs linked: daptomycin, nitrofurantoin, amiodarone, ACE-i's, etc.
- Daptomycin-induced EP: precise mechanism unknown but believed to be related to daptomycin binding to pulmonary surfactant leading to epithelial injury

ARDS Management



CLABSI



Antiseptic Techniques: Catheter Insertion

Hand Hygiene	• Soap & water or alcohol-based rub before/after insertion (IB) • Sterile gloves while inserting (IA)
Skin Prep	• Chlorhexidine solution before insertion and during dressing changes (IA) • Allow to fully dry before insertion (IB)
Barrier	• Maximum barrier protection: cap, mask, sterile gown, sterile gloves and full sterile drape (IB)

CID 2011:52 (1 May)

Always Remove Catheter

- On the Board Exam
  - It's almost never wrong to remove/replace catheter
- Syndromes Requiring Removal
  - Septic shock
  - Septic thrombophlebitis/Venous obstruction
  - Endocarditis
  - Positive blood cultures>72 hrs after appropriate abx
- Organisms Requiring Removal
  - Staph aureus
  - Atypical mycobacteria
  - Candida species
  - Proprionibacteria
  - Pseudomonas aerug
  - Bacillus species
  - Malssezia
  - Micrococcus

Antibiotic Impregnated Catheters and Hubs Plus Antibiotic Lock Solutions

- Not likely testable on the boards
- They have a role, but not well defined

Near Drowning/Submersion Injuries

- Prophylactic Antibiotics
  - Not indicated unless water grossly contaminated
  - Steroids not indicated
- Etiologic Agents
  - Water borne organisms common
    - Pseudomonas, Proteus, Aeromonas
- Therapy for Pneumonia
  - Directed at identified pathogens

39

Photo Opportunity II: More Photos and Questions to Test Your Board Preparation

Dr. John Bennett

39 - Photo Opportunity II: More Photos and Questions to Test Your Board Preparation

Speaker: John Bennett, MD

2020 INFECTIOUS DISEASE BOARD REVIEW

Photo Opportunity II: More Photos and Questions to Test Your Board Preparation

John E. Bennett, MD
Bethesda, MD

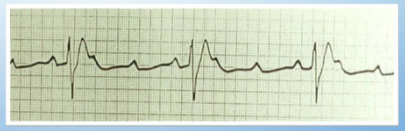
Disclosures of Financial Relationships with Relevant Commercial Interests

- None

QUESTION #1

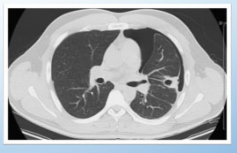
FOR THE EKG SHOWN, WHAT WOULD BE THE MOST COMMON VECTOR TO TRANSMIT THIS INFECTION TO A PATIENT IN MARYLAND?

A. MOSQUITO
B. FLY
C. TICK
D. FLEA
E. KISSING BUG



QUESTION #2

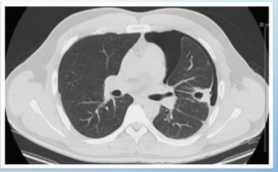
THIS 30-YEAR-OLD PREVIOUSLY HEALTHY EXCHANGE STUDENT FROM SHANGHAI, CHINA WAS IN COLLEGE IN PHOENIX, ARIZONA WHEN HE HAD THE SUDDEN ONSET OF LEFT CHEST PAIN AND HAD THIS CT FINDING. HE HAD BEEN AFEBRILE, FEELING WELL, AND ATTENDING CLASS.



QUESTION #2

THE AGENT IS MOST LIKELY WHICH OF THE FOLLOWING?

A. NORMAL ORAL FLORA
B. DIMORPHIC FUNGUS
C. AEROBIC SOIL BACILLUS
D. AMOEBA
E. ACID FAST BACILLUS



QUESTION #3

A DEPRESSED HOMELESS 52-YEAR-OLD MAN ATTEMPTED SUICIDE BY JUMPING OFF A BRIDGE INTO A CANAL IN CLEVELAND, OHIO. THE CANAL WAS SHALLOW SO HE DID NOT DROWN BUT SUFFERED A COMPOUND FRACTURE OF HIS FEMUR. TEN DAYS LATER, WHILE STILL IN THE HOSPITAL, HE BECAME FEBRILE EVEN THOUGH THE SITES OF EXTERNAL FIXATION OF HIS FEMUR APPEARED UNINFLAMED.

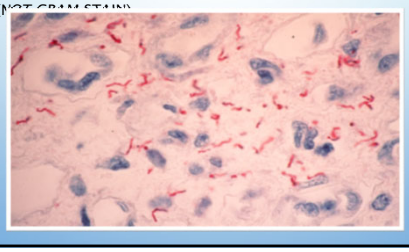
HIS WBC WAS UNCHANGED AT 10,000 BUT OVER SEVERAL DAYS HE DEVELOPED SEVERE HEADACHE AND HIS BILIRUBIN ROSE TO 4 MG/DL AND SERUM CREATININE TO 4.4 MG/DL.

39 - Photo Opportunity II: More Photos and Questions to Test Your Board Preparation

Speaker: John Bennett, MD

QUESTION #3

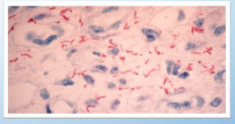
BLOOD CULTURES WERE NEGATIVE BUT RENAL BIOPSY SHOWED THESE SPIRAL STRUCTURE ON SPECIAL STAINS. (NOT GRAM STAIN)



QUESTION #3

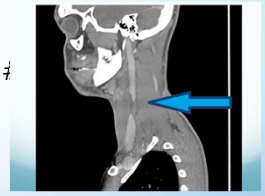
THE MOST LIKELY SOURCE OF THE ORGANISM IS WHICH OF THE FOLLOWING:

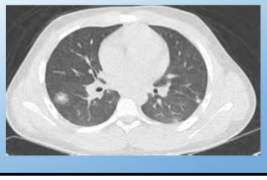
A. SEXUAL CONTACT
B. BACTERIAL SPORES IN THE CANAL
C. INSECT BITE
D. RAT BITE
E. ANIMAL URINE IN THE CANAL WATER



QUESTION #4

AN 18-YEAR-OLD MALE HAD THE ACUTE ONSET OF SORE THROAT, FOLLOWED IN TWO DAYS BY HIGH FEVER. ON PRESENTATION IN THE EMERGENCY ROOM HE WAS ACUTELY ILL, WITH A TEMPERATURE OF 105°F. CHEST X-RAY, FOLLOWED BY THE CT SHOWN HERE, SHOWED A NODULE IN THE LEFT LOWER LUNG FIELD. SWELLING AND TENDERNESS IN THE RIGHT ANTERIOR CERVICAL TRIANGLE LED TO THE CT WITH IV CONTRAST SHOWN HERE.

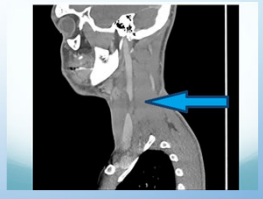




QUESTION #4

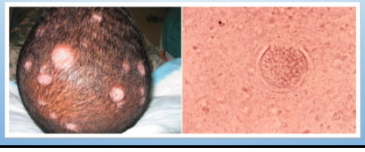
BLOOD CULTURES WERE LIKELY TO REVEAL WHICH OF THE FOLLOWING:

A. AEROBIC GRAM POSITIVE ROD
B. AEROBIC GRAM NEGATIVE ROD
C. ANAEROBIC GRAM POSITIVE ROD
D. ANAEROBIC GRAM NEGATIVE ROD
E. ENDEMIC MYCOSIS



QUESTION #5

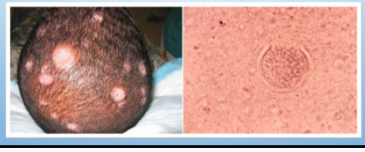
THIS 21-YEAR-OLD AFRICAN AMERICAN MALE COLLEGE STUDENT IN TUCSON, ARIZONA WAS SEEN BECAUSE OF LOW GRADE FEVER, MALAISE AND SCALP LESIONS PROGRESSING OVER THE PAST 3 WEEKS. HE HAD VISITED NOGALES, MEXICO WITH SOME OF HIS FRATERNITY BROTHERS SIX MONTHS EARLIER AND HAD SEX WITH A PROSTITUTE. ABOUT A MONTH AGO, HE WAS DRUNK AT A PARTY, FELL INTO A POND AND REQUIRED RESUSCITATION. A WET MOUNT OF PUS FROM HIS SKIN IS SHOWN BELOW.



QUESTION #5

THE MOST LIKELY ETIOLOGIC AGENT IS FOUND IN WHICH OF THE FOLLOWING LOCATIONS:

A. POND SCUM
B. DIRT
C. GENITAL LESIONS
D. BAT DROPPINGS
E. PIGEON DROPPINGS

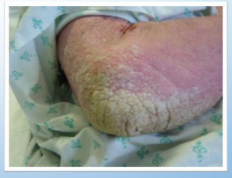


39 - Photo Opportunity II: More Photos and Questions to Test Your Board Preparation

Speaker: John Bennett, MD

QUESTION #6

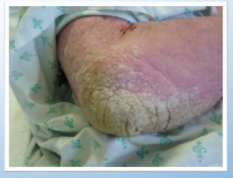
THIS 67-YEAR-OLD MAN WAS BROUGHT TO THE HOSPITAL BY THE POLICE IN WASHINGTON, DC IN BECAUSE HE WAS SLEEPING ON A GRATE IN BITTER COLD WEATHER AND, WHEN ASKED TO MOVE ALONG BY THE POLICE, BEGAN MUTTERING INCOHERENTLY. IN THE EMERGENCY ROOM HE WAS COMBATIVE AND HAD TO BE RESTRAINED. HE WAS ADMITTED FOR OBSERVATION AND HAD NUMEROUS SKIN LESIONS SUCH AS THE ONE SHOWN.



QUESTION #6

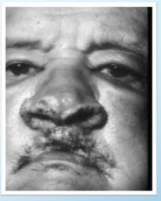
WHICH OF THE LISTED TESTS IS MOST LIKELY TO BE INFORMATIVE?

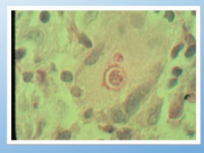
A. WET MOUNT OF SKIN SCRAPING
B. FUNGAL CULTURE OF SKIN SCRAPING
C. ACID FAST SMEAR OF SKIN SCRAPING
D. SERUM VDRL
E. HIV ELISA



QUESTION #7

A 55-YEAR-OLD RECENT IMMIGRANT FROM BRAZIL AND FORMER BANANA PLANTATION FOREMAN HAD FACIAL LESIONS WHICH HAD NOT RESPONDED TO CEPHALEXIN. PAS STAIN OF BIOPSY IS SHOWN.

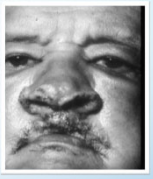


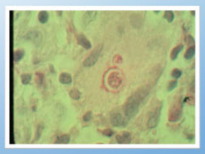


QUESTION #7

WHAT IS THE PROBABLE ORGANISM?

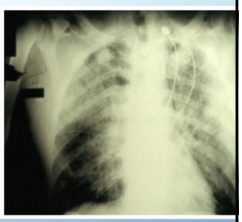
A. RHINOSPORIDIUM SEERBERI
B. PARACOCCIDIOIDES BRASILIENSIS
C. TREPONEMA PALLIDUM SUBSP PERTENUE
D. LEISHMANIA BRASILIENSIS
E. KLEBSIELLA PNEUMONIAE SUBSP RHINOSCLEROMATIS





QUESTION #8

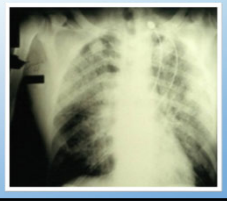
- A 22-YEAR-OLD PREVIOUSLY HEALTHY HIKER PRESENTED WITH A 4 DAY HISTORY OF MALAISE, AND MYALGIAS, DRY COUGH AND PROGRESSIVE DYSPNEA. ADMISSION TEMPERATURE WAS 39.2°, PULSE 110, RESPIRATIONS 28 AND BP110/70. ON EXAM, DIFFUSE CRACKLES WERE HEARD AT THE POSTERIOR CHEST. HEMATOCRIT WAS 52; WBC WAS 9,800; PLATELETS 110,000,.BECAUSE OF INCREASING RESPIRATORY DISTRESS, THE PATIENT WAS INTUBATED. OVER THE NEXT 24-48 HOURS, THE PATIENT PRODUCED COPIOUS RESPIRATORY SECRETIONS, AND MULTIPLE BACTERIAL CULTURES OF SECRETIONS OBTAINED THROUGH THE ENDOTRACHEAL TUBE WERE NEGATIVE , AS WAS A RESPIRATORY PANEL PCR.



QUESTION #8

THE PATIENT HAD JUST RETURNED FROM A HIKING TRIP IN IDAHO AND HAD BEEN CAMPING OUT IN A CABIN AND LEAN-TOS WHERE HE SAW NUMEROUS MICE. THE CABIN HAD THE ODOR OF MOUSE FECES. THE MOST LIKELY CAUSE OF THE PNEUMONIA IS

A. SIN NOMBRE VIRUS
B. LEGIONELLA
C. BARTONELLA QUINTANA
D. FRANCISELLA TULARENSIS
E. BORRELIA HERMSII



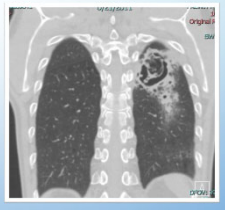
39 - Photo Opportunity II: More Photos and Questions to Test Your Board Preparation

Speaker: John Bennett, MD

QUESTION #9

PATIENTS WITH THIS CONDITION ARE MOST PRONE TO WHICH OF THESE SERIOUS COMPLICATIONS:

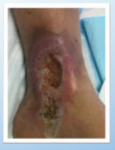
A. HEMOPTYSIS
B. BRAIN ABSCESS
C. SPREAD TO CONTIGUOUS BONE
D. SPREAD WITHIN THE LUNG
E. NON SMALL CELL LUNG CARCINOMA



QUESTION #10

THIS OTHERWISE HEALTHY PATIENT WITH A CHRONIC LEG ULCER IS MOST LIKELY TO HAVE:

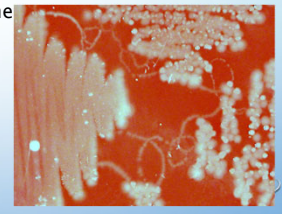
A. COMMON VARIABLE IMMUNOGLOBULIN DEFICIENCY
B. LUPUS ERYTHEMATOSUS
C. HEPATITIS C
D. ULCERATIVE COLITIS
E. CHRONIC GRANULOMATOUS DISEASE



Question #11

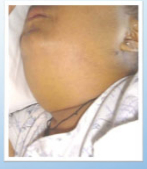
This blood agar plate inoculated with stool from a patient being treated with high dose steroids who developed pulmonary infiltrates and diarrhe

The drug most likely to benefit this patient is:
A. Praziquantel
B. Nitazoxanide
C. Metronidazole
D. Ivermectin
E. Pentamidine



QUESTION #12

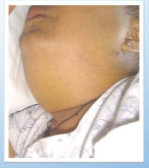
THIS 25-YEAR-OLD WOMAN FROM GUATEMALA HAD BEEN GIVEN ANTITHYMOCYTE GLOBULIN AND CYCLOSPORINE FOR HER APLASTIC ANEMIA BUT HAD AS YET NOT RESPONDED AND REMAINED PROFOUNDLY APLASTIC WHEN SHE WAS OBSERVED TO HAVE OVER 24 HOURS TO DEVELOP THIS SWELLING UNDERNEATH HER CHIN.



QUESTION #12

THERE NO LESIONS VISIBLE IN THE FRONT OF HER MOUTH BUT SHE COULDN'T OPEN VERY WIDE BECAUSE THAT CAUSED PAIN . SHE TOOK SIPS OF FLUID WITHOUT DISCOMFORT BUT WAS VERY NAUSEATED AND DRINKING VERY LITTLE.

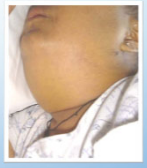
THE SWELLING WAS FIRM AND NOT APPARENTLY RED OR PAINFUL. SHE COULD SPEAK SOFTLY WITHOUT OBVIOUS HOARSENESS.



QUESTION #12

THE MOST LIKELY SOURCE OF THIS INFECTION IS WHICH OF THE FOLLOWING:

A. HERPETIC STOMATITIS
B. DENTAL ABSCESS
C. RETROPHARYNGEAL ABSCESS
D. VINCENT'S ANGINA
E. LEMIERRE'S SYNDROME

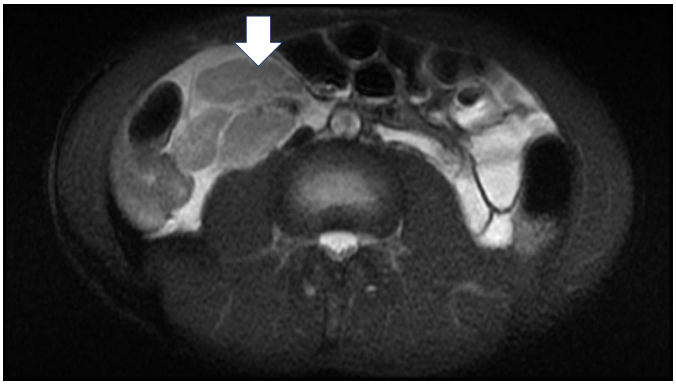


39 - Photo Opportunity II: More Photos and Questions to Test Your Board Preparation

Speaker: John Bennett, MD

QUESTION 13

- 12 YEAR OLD BOY IN WASHINGTON, DC PRESENTS WITH THE ACUTE ONSET OF RIGHT LOWER QUADRANT PAIN AND FEVER. NO PETS. NO RECENT TRAVEL. PRIVATE SCHOOL. VACCINATIONS UP TO DATE.
- EXAM: TEMP 102. RLQ TENDERNESS AND REBOUND. GOOD BOWEL SOUNDS. WBC 12, 500
- MRI: LARGE MESENTERIC NODES
- CHEST XRAY: NORMAL



QUESTION 13

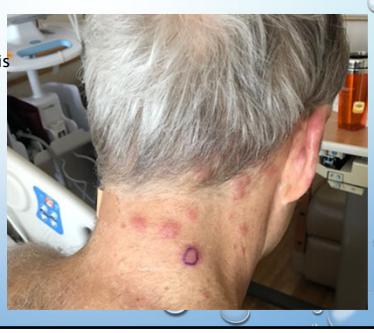
- THE MOST LIKELY ORGANISM CAUSING THIS INFECTION IS:
- A. MYCOBACTERIUM TUBERCULOSIS
- B. YERSINIA PSEUDOTUBERCULOSIS
- C. SALMONELLA TYPHI
- D. MYCOBACTERIUM AVIUM-INTRACELLULARE
- E. MUMPS

QUESTION #14

- A 52-YEAR-OLD MALE IN PRIOR GOOD HEALTH PRESENTED WITH INCREASING FATIGUE OVER THE PAST MONTH AND WAS FOUND TO HAVE MYELODYSPLASTIC SYNDROME WITH EXCESSIVE BLASTS.
- HEMOGLOBIN WAS 7.0, PLATELETS 70,000 AND ANC 598/CU MM.
- HE WAS TRANSFUSED WITH FOUR UNITS OF PACKED RED BLOOD CELLS AND STARTED ON CEFEPIME BECAUSE OF FEVER UP TO 38.5C.
- ROUTINE CHEST XRAY WAS NORMAL, AS WERE ADMISSION BLOOD AND URINE CULTURES. ON THE THIRD HOSPITAL DAY, MULTIPLE SLIGHTLY TENDER, PAINLESS RED SKIN LESIONS APPEARED ON HIS NECK, TRUNK AND LOWER EXTREMITIES. NOTE THAT IN THE PHOTO, A BLACK CIRCLE HAS BEEN DRAWN AROUND ONE OF THE LESIONS.

Question #14

The most likely diagnosis is
A. Cryptococcosis
B. Ecthyma gangrenosum
C. Pyoderma gangrenosum
D. Leukemia cutis
E. Sweet syndrome



QUESTION #15

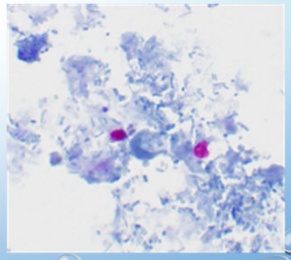
- OWNERS OF AN AQUATIC PARK WERE NOTIFIED BY THE PUBLIC HEALTH DEPARTMENT THAT 8 CHILDREN HAD DEVELOPED DIARRHEAL DISEASE IN THE WEEK FOLLOWING THEIR VISIT TO THE PARK. THE CHILDREN HAD PROFUSE, WATERY DIARRHEA, ABDOMINAL CRAMPING, AND LOW-GRADE FEVERS. THE ILLNESSES WERE ALL SELF LIMITING. THE CHILDREN ALL REPORTED EATING HOT DOGS WITH CATSUP AND VARIOUS FLAVORS OF "SLURPIES" (SHAVED ICE DRINKS) AT THE PARK.
- PARASITOLOGY EXAMINATION OF THEIR STOOL SPECIMENS WAS POSITIVE WITH ACID-FAST ORGANISM, 4-6 UM IN DIAMETER.

39 - Photo Opportunity II: More Photos and Questions to Test Your Board Preparation

Speaker: John Bennett, MD

Question #15

The most likely source of the outbreak was:
A. Shaved ice machine
B. Hot dogs
C. Contaminated water
D. Syrups on the shaved ice

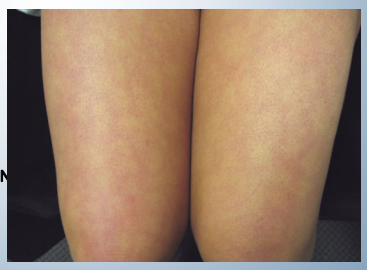


Question #16

A 23 year nurse, 8 weeks pregnant, sought advice from her obstetrician. For the past two weeks she has been taking care of a hospitalized child with sickle cell disease and aplastic crisis. For the past five days she has had low grade fever, headache, the mildly pruritic rash shown here and aching joints with stiffness in her hands and feet. She had all the usual childhood vaccinations, was taking no medications, lived alone with her husband, and had no pets. The object of concern for her unborn infant would be which of the following.

Question #16

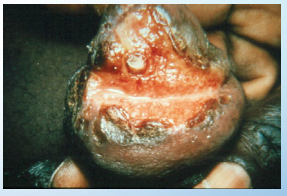
- A. DEAFNESS
- B. HYDROPS FETALIS
- C. CONGENITAL HEART DISEASE
- D. RETINOPATHY
- E. MENTAL RETARDATION



Question #17

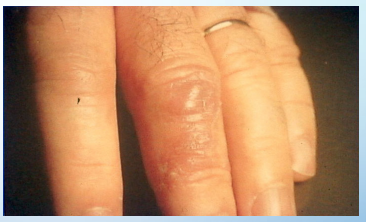
Which of the following organisms is the most likely cause of this penile lesion of 7 months duration:

A HUMAN PAPILLOMA VIRUS
B HAEMOPHILUS DUCREYI
C TREPONEMA PALLIDUM
D KLEBSIELLA GRANULOMATIS
E. CHLAMYDIA TRACHOMATIS



Question #18

This 40yr old crab fisherman working in the Chesapeake bay waters came in with a painful rash on his hand of 3 days duration. The probable organism is which of the following



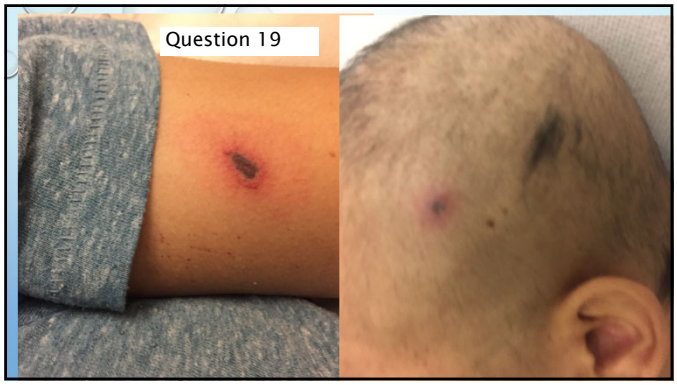
A. ANAEROBIC GRAM NEGATIVE BACILLUS
B. AEROBIC SEA-GULL SHAPED GRAM NEGATIVE BACILLUS
C. ANAEROBIC GRAM POSITIVE COCCUS
D. AEROBIC GRAM POSITIVE BACILLUS

QUESTION #19

- 21 YR MALE WITH ACUTE LYMPHYOCYTIC LEUKEMIA DIAGNOSED 14 MONTHS PRIOR, HAD MULTIPLE RELAPSES AFTER CHEMOTHERAPY AND AFTER CD19 CAR T CELL THERAPY 4 MONTHS AGO, FOLLOWED BY CYTOKINE RELEASE SYNDROME. THEN RELAPSED. RETREATED WITH ALEMTUZUMAB, ETOPOSIDE , IFOSFAMIDE, REMAINED PANCYTOPENIC. ON TRANSFER HE ARRIVED WITH TEMP 38.4C THEN AFEBRILE, WITH 4 SKIN LESIONS ON HIS HEAD AND ARMS. WBC 0.05K, PLT 17K, ALT 77. CT OF CHEST, ABDOMEN, HEAD NEGATIVE. SINUSES: FLUID IN SOME SINUSES. VANCOMYCIN, MEROPENEM, GCSF, PLT TX, RBC TX STARTED. LIPOSOMAL AMPHOTERICIN B STARTED . SKIN BIOPSY OBTAINED.

39 - Photo Opportunity II: More Photos and Questions to Test Your Board Preparation

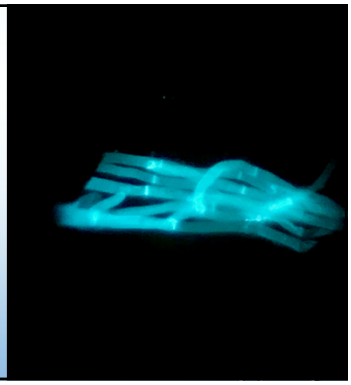
Speaker: John Bennett, MD



Question #19

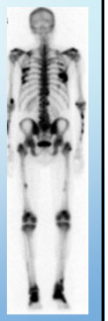
Calcofluor white stain of skin biopsy impression smear showed hypae. The most likely diagnosis is:

a. Nocardiosis
b. Mucormycosis
c. Fusariosis
d. Scedosporiosis
e. Pseudomonas



QUESTION #20

35 Yr female with cystic fibrosis was one year post bilateral lung transplant when she had the gradual onset of diffuse pains in her arms and legs, not increased by motion or weight bearing. Physical exam was unremarkable with no nail clubbing. Labs showed a normal CRP, CBC and chemistries but an elevated alkaline phosphatase of 355 iu/ml. Bone scan showed numerous areas of uptake. For the past year she had been taking sirolimus, voriconazole, multivitamins with vitamin D 1000 u/day, pancreatic lipase and insulin



QUESTION #20

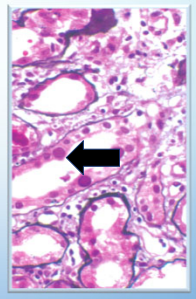
The most likely cause of her aching pains is:

a. Hypertrophic pulmonary osteoarthropathy
b. Vitamin D toxicity
c. Serolimus toxicity
d. Osteoporosis stress fractures
e. Voriconazole toxicity

QUESTION 21:

55-YEAR-OLD CMV SERONEGATIVE CAUCASIAN WOMAN WITH TYPE 1 DIABETES MELLITUS AND END STAGE RENAL DISEASE RECEIVED A CADAVERIC RENAL ALLOGRAFT FROM A CMV POSITIVE DONOR SIX MONTHS PRIOR.

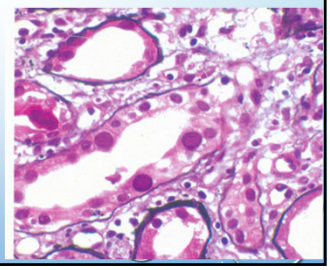
SHE NOW PRESENTS WITH DECREASING RENAL FUNCTION DESPITE INCREASED IMMUNOSUPPRESSION WITH TACROLIMUS AND PREDNISONE GIVEN FOR SUSPECTED GRAFT REJECTION. TACROLIMUS LEVELS ARE IN THE THERAPEUTIC RANGE. SHE IS AFEBRILE AND NORMAL ROUTINE URINALYSIS AND NEGATIVE URINE CULTURE . RENAL BIOPSY OF HER TRANSPLANTED KIDNEY HOWED INCLUSIONS IN THE RENAL TUBULAR CELLS.



Question 21

The most likely cause this patient's renal failure is

a. CMV
b. BK virus
c. JC virus
d. Tacrolimus toxicity
e. Adenovirus



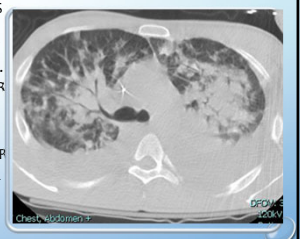
39 - Photo Opportunity II: More Photos and Questions to Test Your Board Preparation

Speaker: John Bennett, MD

QUESTION 22:

A 27-YEAR-OLD MALE PRESENTED WITH TWO (2) MONTHS OF PROGRESSIVE DYSPNEA. HE HAD NOTED THE APPEARANCE OF PURPLE INDURATED LESIONS OVER HIS ANTERIOR CHEST. CHEST CT FOUND NODULAR PERIHILAR LUNG LESIONS, PROMINENT INTERLOBULAR SEPTAE, AND PLEURAL EFFUSIONS. HE WAS REMARKABLY HYPOXEMIC WITH ROOM AIR PO_2=59 MM HG.

- BRONCHOSCOPY REVEALED SOME PURPLE LESIONS IN THE BRONCHUS; BRONCHOALVEOLAR LAVAGE REVEALED NO PATHOGENS ON SPECIAL STAINS; CYTOLOGY WAS UNREMARKABLE.
- BAL CMV PCR WAS POSITIVE AT 2000 COPIES/ML (LOG_{10}4.40IU/ML.)



Question 22:

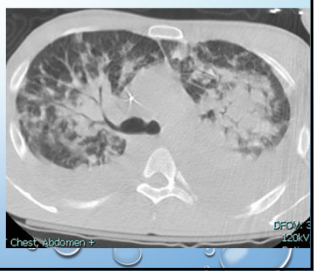
- Skin biopsy found endothelial cells with nuclei that stained positive for HHV8 on immunocytochemistry.
- He was found to be HIV positive with a CD4 of 8 cells/uL and a viral load of 80,000 copies/mL. Pleural fluid was bloody but cytology did not show malignant cells.
- Blood PCR results: CMV 5000 copies/mL (log_{10} 4.82 IU/ml); EBV 4500 copies/mL (log_{10} 2.40 IU/ml); HHV 8 = 200 copies/mL; HHV6 = 500 copies/mL.

Antiretroviral therapy was begun following usual guideline recommendations.

Question 22"

The most useful additional drug for treatment of his diffuse pulmonary disease would be which of the following:

1. Cidofovir
2. Ganciclovir
3. Foscarnet
4. Liposomal doxorubicin
5. Cyclophosphamide

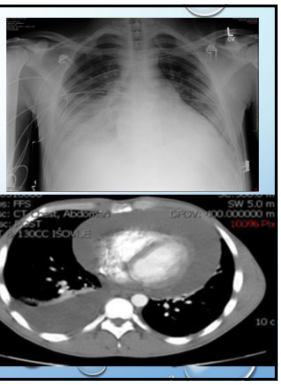


QUESTION 23

A 3A 30-year -old male with HIV (CD4 =210 cells/uL, HIV VL = 200,000 copies) has been receiving ART intermittently, and comes in now for shortness of breath, increasing over several days. .He has no fever or weight loss. Physical examination finds clear lungs but a large pleural effusion . CT shows pericardial and pleural fluid with no infiltrate in the lung.

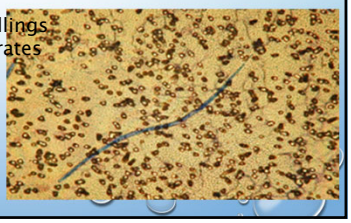
The most likely test to be useful among the following is:

A. Cytology of pleural fluid
B. PCR of pleural fluid for TB.
C. PCR of pleural fluid for HHV8
D. PCR of pleural fluid for EBV
E. PCR of pleural fluid for HHV6



Question 24:
The 35 yr year old recent immigrant from Nigeria has this organism found in his blood smear. He is at risk of having which of the following if untreated:

1. Blindness
2. Transient local skin swellings
3. Diffuse pulmonary infiltrates
4. Encephalopathy
5. Eosinophilic meningitis



THE END
THANKS FOR LISTENING.

2020 INFECTIOUS DISEASE BOARD REVIEW

GW | Office of Continuing Education in the Health Professions

25th Annual

COMPREHENSIVE REVIEW *for* INFECTIOUS DISEASE BOARD PREPARATION

DAY 4

COURSE DIRECTORS:
John E. Bennett, MD
Henry Masur, MD

COURSE CO-DIRECTORS:
Paul Auwaerter, MD
David N. Gilbert, MD
Roy M. Gulick, MD, MPH
Andrew Pavia, MD
Richard J. Whitley, MD

www.IDBoardReview.com

TUESDAY, AUGUST 25, 2020

#	START		END	PRESENTATION	SPEAKER
40	9:45 AM	-	10:15 AM	**Daily Question Preview 4**	*Paul Auwaerter, MD (Moderator)*
41	10:15 AM	-	11:30 AM	**Infections in the Neutropenic Cancer Patient and Hematopoietic Stem Cell Recipients**	*Kieren Marr, MD*
42	11:30 AM	-	12:00 PM	**Nontuberculous Mycobacteria in Normal and Abnormal Hosts**	*Kevin Winthrop, MD*
	12:00 PM	-	12:15 PM	**BREAK**	
43	12:15 PM	-	1:15 PM	**Infections in Solid Organ Transplant Recipients**	*Barbara Alexander, MD*
44	1:15 PM	-	1:45 PM	**Pneumonia: Some Cases that Could be on the Exam**	*Paul Auwaerter, MD*
45	1:45 PM	-	2:30 PM	**Board Review Session 4**	*Drs. Auwaerter (moderator), Alexander, Boucher, Marr, Mitre, and Winthrop*
	2:30 PM	-	2:45 PM	***BREAK***	
46	2:45 PM	-	3:45 PM	**Ticks, Mites, Lice and the Diseases They Transmit**	*Paul Auwaerter, MD*
47	3:45 PM	-	4:45 PM	**Worms and More Worms**	*Edward Mitre, MD*
	4:45 PM	-	5:00 PM	***BREAK***	
48	5:00 PM	-	5:30 PM	**Lyme Disease**	*Paul Auwaerter, MD*
49	5:30 PM	-	6:30 PM	**Lots of Protozoa**	*Edward Mitre, MD*

40

Daily Question Preview 4

Dr. Paul Auwaerter (Moderator)

40 – Daily Question Preview 4

Moderator: Paul Auwaerter

2020 INFECTIOUS DISEASE BOARD REVIEW

Daily Question Preview 4

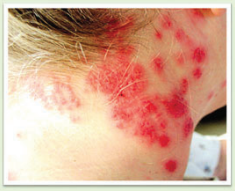
Moderator: Paul Auwaerter, MD

2020 INFECTIOUS DISEASE BOARD REVIEW — PREVIEW QUESTION

1.1

A 50-year-old woman with newly diagnosed AML developed tender, pruritic papules and plaques on her neck.

She had been febrile 38.7C for the past several days and had received a dose of G-CSF 3 days earlier, with rapid WBC increase (900 ANC).



2020 INFECTIOUS DISEASE BOARD REVIEW — PREVIEW QUESTION

1.1

Most likely etiology:

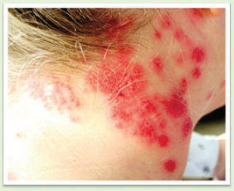
A) Candida albicans

B) Sweet's syndrome

C) Aspergillus niger

D) Varicella Zoster Virus

E) Pseudomonas aeruginosa



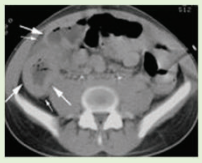
2020 INFECTIOUS DISEASE BOARD REVIEW — PREVIEW QUESTION

1.2 A 70-year-old woman with AML, neutropenic for 15 days, s/p induction chemotherapy develops fever, diarrhea, and abdominal pain.

Exam - decreased bowel sounds and tenderness with deep palpation in her RLQ. CT shows inflammation in cecum.

She was receiving Levofloxacin and fluconazole prophylaxis.

4 days prior to her admission for chemotherapy, she ate Chinese food.



2020 INFECTIOUS DISEASE BOARD REVIEW — PREVIEW QUESTION

1.2 Which is the most likely etiology?

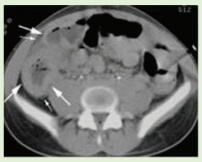
A) Norovirus

B) Clostridioides (Clostridium) difficile

C) Mixed anaerobic and aerobic bacteria

D) Candida albicans

E) Bacillus cereus



2020 INFECTIOUS DISEASE BOARD REVIEW — PREVIEW QUESTION

1.3

A 46-year-old male 18 months s/p HLA mismatched BMT. History of GVHD skin, GI tract, and BOOP 3 months ago, treated with steroids.

One month s/p Parainfluenza 3 URI

Two weeks ago had chest CT - tree-in-bud opacities in LLL. Received levofloxacin for 10 days.

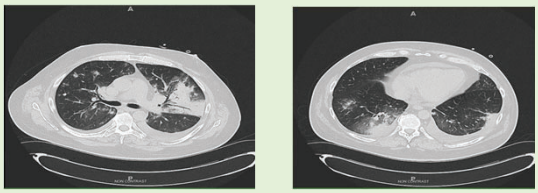
He now has increasing shortness of breath and cough.

40 – Daily Question Preview 4

Moderator: Paul Auwaerter

PREVIEW QUESTION

1.3



PREVIEW QUESTION

1.3

Blood cultures no growth. Sputum – LF GNR. Serum galactomannan is negative.
What is the most likely cause of his current process?

A) Cryptococcus neoformans

B) E. coli

C) MRSA

D) Aspergillus fumigatus

E) Fusarium spp.

PREVIEW QUESTION

1.4

72 year old female with chronic cough, normal CXR, and 1/3 sputums grow MAC.

Which one of the following you do recommend ?

A) CT scan of chest AND Additional sputum AFB cultures

B) Empiric therapy with azithromycin, ethambutol, and rifampin

C) Additional sputum AFB cultures

D) Wait for in vitro susceptibility data and then treat.

PREVIEW QUESTION

1.5

A 52-year-old female S/P cadaveric renal transplant has been receiving tacrolimus, prednisone and mycophenylate.

Week 30 post transplant her serum creatinine rose from 1.5 to 2.3 mg/dl.

Tacrolimus levels were in therapeutic range.

Urinalysis revealed one plus protein and no cells or casts.

PREVIEW QUESTION

1.5

Which would be most helpful in understanding if BK virus was causing her renal failure?

A) Presence of decoy cells in urine cytology

B) Urine BK viral load

C) Urine culture for BK virus

D) Plasma BK viral load

E) Demonstration of BK inclusions in renal tubular epithelium on renal biopsy

PREVIEW QUESTION

1.6

Liver transplant recipient presented 21 days post transplant with confusion, tremors, lethargy, anorexia

He has been on bactrim & valganciclovir prophylaxis

Rapid progressive neurologic decline > agitation & delirium > intubation

Blood & urine cultures: negative

CSF: lymphocytic pleocytosis (25 WBCs/mm3) & elevated protein
- Gram stain, bacterial, fungal cultures negative

40 – Daily Question Preview 4

Moderator: Paul Auwaerter

PREVIEW QUESTION

1.6

This presentation is most consistent with:

A) CMV encephalitis

B) HHV6 encephalitis

C) VZV encephalitis

D) Rabies encephalitis

E) Cryptococcal meningitis

PREVIEW QUESTION

1.7

A 55-year-old male with 6d fever, malaise, severe headache, dry cough, myalgia

PMH: HTN
Meds: Lisinopril/HCT
SH: Married, suburban Maryland

Works in long-term care facility
Visited pet shop 10 days earlier
- Parakeets, cockatiels

Confided infidelity in last month

PREVIEW QUESTION

1.7

Exam: ill-toxic, 40ºC P88
BP100/70 RR18 O2 97% RA
Lungs: clear
Neck: supple
Cor: no murmurs
Skin: no rashes
LP: pending

Labs:
WBC 5200, 26% B
Sputum: 1+ PMNs, no organisms

PREVIEW QUESTION

1.7

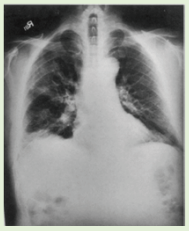
Which antibiotic will lead to the most rapid improvement?

A) Ceftriaxone

B) Gentamicin

C) Doxycycline

D) Trimethoprim/sulfamethoxazole



PREVIEW QUESTION

1.8

A 69-year-old male c/o fever and dyspnea x 3 days
-Dry cough, pleuritic chest pain
-In nursing facility for L foot, C1-2, L4-5 osteomyelitis + MRSA bacteremia

Vancomycin (5d, rash) > Ceftaroline (4d, hives) > Daptomycin (11d)

PMH: Diabetes, HTN, COPD, R BKA, bedbound
SH: 40 PPD smoker, now vaping, Baltimore MD resident, hx substance use
Meds: methadone, insulin, nifedipine, Lisinopril/HCT, inhalers

PREVIEW QUESTION

1.8

PE: T101.4° F, P 106, RR 24, 02 sat 90% on 6L O2
No lymphadenopathy, no JVD
Lungs: poor air movement, basilar crackles bilaterally
Cor: no murmur
Ext: no edema

6.0	9.5	300K	54%^{N}, 12%^{L}, 24%^{E}

ESR 150 mm/hr
CRP 15 mg/dL (0.0-0.5)

NI LFTs

40 – Daily Question Preview 4

Moderator: Paul Auwaerter

INFECTIOUS DISEASE BOARD REVIEW 2020 — PREVIEW QUESTION

1.8

The pneumonia is most caused by

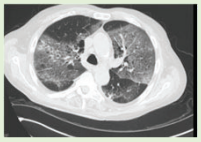
A) Vaping-associated pulmonary injury (VAPI)

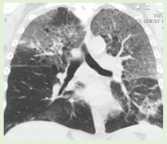
B) Allergic bronchopulmonary aspergillosis

C) Ceftaroline

D) Daptomycin

E) Strongyloides





INFECTIOUS DISEASE BOARD REVIEW 2020 — PREVIEW QUESTION

1.9

A 62-year-old male living in an exurb of Phoenix, Arizona presents in early September with a three day history of fever, myalgia, headache and rash.

He works as a lineman for a utility company.
He lives with his family in an older adobe home with dogs.

He has beginnings of petechial features on the wrists and ankles.

INFECTIOUS DISEASE BOARD REVIEW 2020 — PREVIEW QUESTION

1.9

Which of the following is the most likely diagnosis?

A) Human Monocytic Ehrlichiosis (HME)

B) Human Granulocytic Anaplasmosis (HGA)

C) Babesiosis

D) Rocky Mountain Spotted Fever (RMSF)

E) Tularemia

INFECTIOUS DISEASE BOARD REVIEW 2020 — PREVIEW QUESTION

1.10

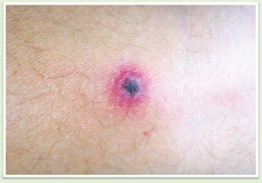
A 48-year-old male presents in October with fever and rash

Patient is a supervisor for apartment building in Queens, NY.
Lives in cellar apt.

Exam: T 390C

Brown-black 8mm eschar on RLE

~30 papulovesicular lesions on trunk



INFECTIOUS DISEASE BOARD REVIEW 2020 — PREVIEW QUESTION

1.10

Which of the following Is the most likely etiologic agent?

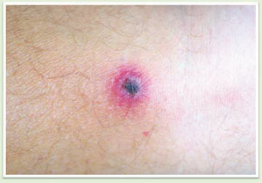
A) R. rickettsii

B) R. parkeri

C) R. akari

D) R. conorii

E) Borrelia recurrentis



INFECTIOUS DISEASE BOARD REVIEW 2020 — PREVIEW QUESTION

1.11

A 28-year-old female presents with recurrent crampy abdominal pain for several months.

She recently returned to the U.S. after living in Tanzania for two years. Colonoscopy reveals small white papules.

Biopsy of a papule reveals a parasite (egg) with surrounding granulomatous inflammation.

40 – Daily Question Preview 4

Moderator: Paul Auwaerter

INFECTIOUS DISEASE BOARD REVIEW 2020

PREVIEW QUESTION

1.11

Most likely diagnosis?

A) Entamoeba histolytica

B) Strongyloides stercoralis

C) Wuchereria bancrofti

D) Schistosoma mansoni

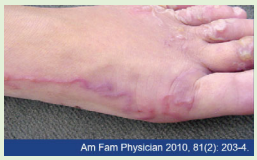
E) Paragonimus westermani

INFECTIOUS DISEASE BOARD REVIEW 2020

PREVIEW QUESTION

1.12

A 13-year-old girl developed a pruritic rash on her foot after moving to rural northeast Florida. Which of the following helminths is the most likely cause of the rash?



Am Fam Physician 2010, 81(2): 203-4.

A) Enterobius vermicularis

B) Ascaris lumbricoides

C) Trichuris trichiura

D) Toxocara canis

E) Anyclostoma braziliense

INFECTIOUS DISEASE BOARD REVIEW 2020

PREVIEW QUESTION

1.13 A 6-year-old boy from Indiana who has a pet dog and likes to play in a sandbox presents with fever, hepatosplenomegaly, wheezing, and eosinophilia. He has never travelled outside the continental U.S.

The most likely causative agent acquired in the sandbox is:

A) Anisakis simplex

B) Onchocerca volvulus

C) Enterobius vermicularis

D) Toxocara canis

E) Anyclostoma braziliense

INFECTIOUS DISEASE BOARD REVIEW 2020

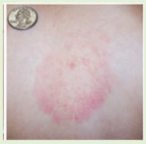
PREVIEW QUESTION

1.14

A 56-year-old man from southern Missouri –no travel

- Onset in July: Myalgia and malaise
  Rash of two days duration
- Tick bite 1 week ago

Exam: T 37.0° C
Annular "bulls-eye" ~6 cm
(same area engorged tic removed earlier in the week)



INFECTIOUS DISEASE BOARD REVIEW 2020

PREVIEW QUESTION

1.14

Which of the following is the most likely diagnosis?

A) Lyme disease due to Borrelia burgdorferi

B) Human Monocytic Ehrlichiosis, Ehrlichia chaffeensis

C) Borrelia mayonii

D) Southern tick-associated rash illness (STARI)

E) B. lonestari infection

INFECTIOUS DISEASE BOARD REVIEW 2020

PREVIEW QUESTION

1.15

A 50-year-old female alcoholic suffered a provoked dog bite. It was cleansed, tetanus toxoid given, and the dog placed under observation.

The patient is post-elective splenectomy for ITP. She received pneumococcal vaccine one year ago.

One day later, the patient is admitted to the ICU in septic shock with severe DIC and peripheral symmetric gangrene of the tips of her fingers/toes.

40 – Daily Question Preview 4

Moderator: Paul Auwaerter

INFECTIOUS DISEASE BOARD REVIEW 2020

PREVIEW QUESTION

1.15

Which one of the following is the most likely etiologic bacteria?

A) Pasteurella canis

B) Capnocytophaga canimorsus

C) Fusobacterium sp.

D) Bartonella henselae

INFECTIOUS DISEASE BOARD REVIEW 2020

PREVIEW QUESTION

1.16

A 25-year-old female suffers a cat bite on the forearm. She presents one hour later for care.

If no antibacterial is administered, the percentage of such patients that get infected is:

A) 0-10 %

B) 10-30 %

C) 30-70 %

D) 70-100 %

INFECTIOUS DISEASE BOARD REVIEW 2020

PREVIEW QUESTION

1.17

A 53-year-old male construction worker has sudden onset of pain in his left calf. Within hours the skin and subcutaneous tissue of the calf are red, edematous and tender. Red "streaks" are seen spreading proximally

A short time later, patient is brought to the ER

Confused, vomiting, and hypotensive.
Temp is 40C with diffuse erythema of the skin.
Oxygen sat. 88% on room air
WBC 3000 with 25% polys and 50% band forms.
Platelet count is 60,000

INFECTIOUS DISEASE BOARD REVIEW 2020

PREVIEW QUESTION

1.17

Which one of the following is the most likely complication of the erysipelas?

A) Bacteremic shock due to S. pyogenes?

B) Toxic shock due to S. pyogenes?

C) Bacteremic shock due to S. aureus?

D) Toxic shock due to S. aureus?

INFECTIOUS DISEASE BOARD REVIEW 2020

PREVIEW QUESTION

1.18

A 60-year-old female smoker, admitted, intubated, and ventilated due to severe COPD with Acute Respiratory Failure.

Chest X-Ray: New bibasilar infiltrates and Emphysema

Empiric ceftriaxone and azithromycin

Sputum positive for both rhinovirus and Klebsiella pneumoniae resistant to both ceftriaxone and azithromycin

Also "R" to: all fluoroquinolones, aminoglycosides, pip/tazo, and all carbapenems

INFECTIOUS DISEASE BOARD REVIEW 2020

PREVIEW QUESTION

1.18

Which one of the following antibiotics would you select for this KPC infection?

A) Tigecycline

B) Ceftazidime-avibactam

C) Aztreonam

D) Ceftolozane-tazobactam

40 – Daily Question Preview 4

Moderator: Paul Auwaerter

2020 INFECTIOUS DISEASE BOARD REVIEW

PREVIEW QUESTION

1.19

A 33-year-old woman is traveling to Uganda to do field studies in anthropology. She is two months pregnant.

Which of the following do you prescribe for malaria prophylaxis?

A) Doxycycline

B) Chloroquine

C) Mefloquine

D) Atovaquone/progruanil

E) No prophylaxis

2020 INFECTIOUS DISEASE BOARD REVIEW

PREVIEW QUESTION

1.20

A 54-year-old woman presents with fever, chills, and oliguria one week after travel to Malaysia.

Vitals: 39.0° C, HR 96/min, RR 24/min, BP 86/50

Notable labs: Hct 31%, platelets14,000/ml, Cr of 3.2 mg/dL.

Peripheral blood smear has intraerythrocytic forms that are morphologically consistent with Plasmodium malariae.

2020 INFECTIOUS DISEASE BOARD REVIEW

PREVIEW QUESTION

1.20

The most likely infectious agent causing the patient's illness is:

A) Plasmodium malariae

B) Plasmodium knowlesi

C) Plasmodium vivax

D) Plasmodium falciparum

E) Babesia microti

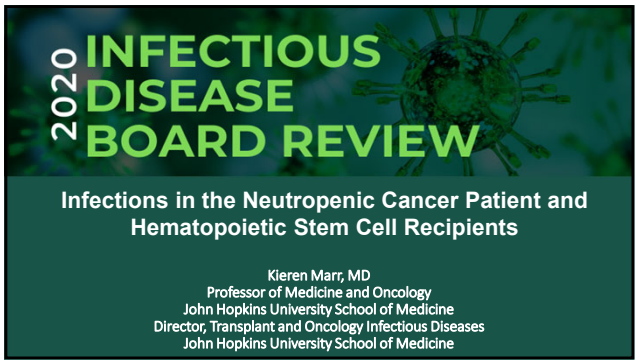
41a

Infections in the Neutropenic Cancer Patient and Hematopoietic Stem Cell Recipients

Dr. Kieren Marr

41a – Infections in the Neutropenic Cancer Patient and Hematopoietic Stem Cell Recipients

Speaker: Kieren Marr, MD



Disclosures of Financial Relationships with Relevant Commercial Interests

- Consultant – Amplyx, Cidara, Merck and Company, Sfunga Therapeutics
- Ownership Interests – MycoMed Technologies

Goals of This Review

- Immune compromised people develop "typical" infections and those specific to their underlying risks
- Focus here on testable complications specific to the host
  - Types of immune – suppressing drugs and diseases
  - Recognition of specific "neutropenic syndromes"
    - Skin lesions
    - Invasive fungal infections
    - Neutropenic colitis

Testable Concepts

- Think about the patient
  - How does underlying disease impact risks?
- Think about the treatment received
  - What type of immune suppression?
- Think about infections breaking through preventative therapies
  - A good context to test resistance and differentials
- Think about common non-infectious syndromes

Fundamentals: Host Immune Risks

- Neutropenia
  - Prolonged (>10 days) and profound (< 500 cells / mm3) associated with high risks for severe bacterial and fungal infections
    - Bacteremia, pneumonia, candidemia, aspergillosis
- Infectious risks associated with biologics – or medical immune suppression

Classic Immunologic risks

- Immune defects associated with underlying malignancy (and prior therapies)
  - AML and myelodysplastic syndromes (MDS)
    - Qualitative and quantitative neutropenia
  - Lymphoma
    - Functional asplenia
  - CLL and multiple myeloma
    - Hypogammaglobulinemia
  - Aplastic anemia
    - Severe, prolonged neutropenia

41a – Infections in the Neutropenic Cancer Patient and Hematopoietic Stem Cell Recipients

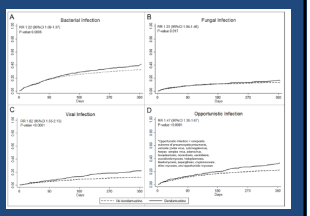
Speaker: Kieren Marr, MD

Immune modulating anti-cancer drugs

- Drugs that impact neutrophils
  - Many cytotoxic agents
    - Bacterial infections, fungal infections
- Drugs that impact T cells
  - Purine analogs (fludaribine, cladribine, clofarabine) and temozolomide
    - CD4+ T cell dysfunction: Herpes viruses (CMV, VZV), intracellular bacteria, fungi (PJP, Aspergillus)

Bendamustine

- Nitrogen-based alkylating and antimetabolite
- Indolent non-Hodgkins lymphomas, CLL
- Neutropenia *and lymphopenia* (months - years)
- Higher risks for infections (bacterial, CMV, PJP, histoplasmosis)



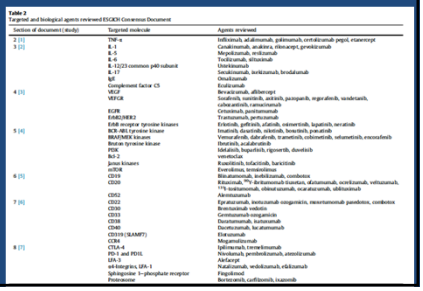
Fung et al. Clin Infect Dis 68(2): 247-55

Biological Therapies

- Generally broken into three categories
  - Biological response modifiers. Exert effects by stimulating immune system (ex. CSFs)
  - Gene therapies
  - Targeted therapies (mAbs and small molecule enzyme inhibitors)

For a more robust review

- Series of articles by European Study Group for Infections in Compromised Hosts (Supplement in Clin Microbiol and Infect 24, 2018)



Key anti-CD Monoclonal Abs

- Common antibodies that impact B and T cells
  - Rituximab (anti-CD20)
    - B cells: CLL, lymphoma
    - Loss of vaccine responses, responses to encapsulated bacteria (pneumonia). Hepatitis B reactivation, PML
  - Alemtuzimab (anti-CD52)
    - T and B cell depletion for a long time (about 6 months): lymphoma, leukemia, BMT (graft vs. host disease treatment)
    - Herpes viruses (esp. CMV), fungal infections (PJP, Aspergillus)

Tyrosine kinase inhibitors

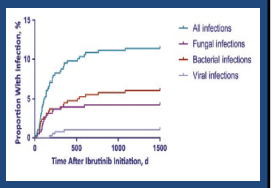
- BCR – ABL Tyrosine – kinase inhibitors
  - Inhibit signal transduction through BCR-ABL oncogene (ex. imatinib, dasatinib, nilotinib)
    - CML. Think T and B cells (VZV, Hep B reactivation)
    - Aspergillosis and other IFI
    - Autoimmune pneumonitis and colitis (infection mimic)

41a – Infections in the Neutropenic Cancer Patient and Hematopoietic Stem Cell Recipients

Speaker: Kieren Marr, MD

Bruton's tyrosine kinase inhibitors

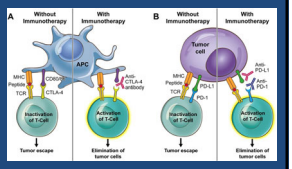
- Ibrutinib
- B cell development, macrophage phagocytosis
- Lymphoid malignancies (ex. CLL, lymphomas)
- Single-center review: 11%
- Fungal, bacterial infections
  - Aspergillosis (including CNS)
- Autoimmune – idiopathic drug "toxicities": colitis, pneumonitis



Varughese et al. Clin Infect Dis 2018; 67(5): 687-92
Bercusson A. Blood 2018 132(18): 1985-88
Blez et al. Haematologica 2019 (In press)

Checkpoint inhibitors

- Block immune checkpoints that regulate T cell activation / function – multiple tumors
- Targeting PD-1 on T cells (pembrolizumab, nivolumab, cemiplimab) or PD-L1 on tumor cells (atezolizumab, avelumab, durvalumab)
- Targeting CTLA-4 on T cells (ipilumumab)
- Induce colitis, pneumonitis
- Increased risks for infection in people receiving concurrent steroids, TNF-α targeting agents for above



Soularue et al. BMJ gut 2018

Neutropenic "syndromes"

Notes about fever during neutropenia

- Develop a differential based on preventative drugs already in use and other syndromes (pneumonia, colitis)
- Broad coverage, examination, cultures
- Inpatient – outpatient management guidelines, but not testable in this setting
- Duration of therapy is controversial
  - Cochran Database review 2019: could not make any strong conclusions regarding efficacy, safety of short vs. long course antibiotic therapy

Stern et al. CDSR 2019

Question #1

35 year old woman with AML day 15 after induction therapy.
Fever, chills, diffuse erythematous rash. Blood culture + GPC in chains
Exam – 100/62, HR 120, grade 2 oral mucositis, and a diffuse, blanching, erythematous rash. CXR - bilateral diffuse infiltrates. She is receiving levofloxacin and acyclovir.
This is most consistent with infection with which of the following organisms?

A. *Streptococcus pneumoniae*
B. Coagulase-negative *Staphylococcus*
C. *Enterococcus faecalis*
D. *Streptococcus mitis*
E. *Stomatococcus mucilaginosus*

Viridans Streptococci

- Key points: neutropenia, mucositis, high-dose cytosine arabinoside, fluoroquinolone
- Can present with fever, flushing, chills, stomatitis, pharyngitis
- VGS shock syndrome:
  - After 24-48 hours, hypotension in 1/3 of cases
  - Rash, shock, ARDS in 1/4 of cases (similar to toxic shock)
- Endocarditis unusual (<10%)
- S. mitis, S. oralis
- Vancomycin
- Mortality high (15-20%)

41a – Infections in the Neutropenic Cancer Patient and Hematopoietic Stem Cell Recipients

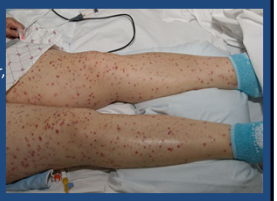
Speaker: Kieren Marr, MD

Testable contexts: Breakthrough Bloodstream Infections

- Typical patient- neutropenic, progressive sepsis
- Recognize holes in protection, specific syndromes
  - ARDS, rash, quinolones, mucositis → viridans Streptococci
  - Sepsis with β-lactams → Stenotrophomonas, ESBL
  - Sepsis with carbepenems → KPC
  - Lung and skin lesions → *P. aeruginosa*, Fungi
  - Skin lesions, gram + → *Corynebacterium jeikeium*
  - Mucositis (upper, lower tract) → *Fusobacterium* spp., *Clostridium spp., Stomatococcus mucilaginosis*

Question #2

59 year old woman with AML with neutropenia for 25 days. She has been febrile for 6 days, and is receiving meropenem, vancomycin, and acyclovir. New skin lesions that are small, papular, and tender, with no central ulceration.



A. *Rhizopus* spp.
B. Varicella zoster virus
C. *Cryptococcus neoformans*
D. Vancomycin resistant Enterococci
E. *Candida tropicalis*

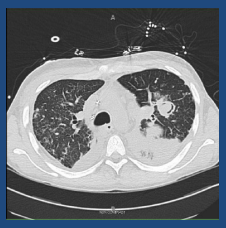
Fungal Infections

- Candida infections
  - Frequent in patients not receiving prophylactic antifungals
    - *C. albicans, C. tropicalis*
    - Mucositis, colonization, neutropenia
    - Acquired through GI tract or catheter
    - Organisms in patients receiving azole prophylaxis
      - *C. glabrata, C. krusei*
      - *C. parapsilosis*
        - » catheter / intravenous infusates
- Mold infections
  - *Aspergillus fumigatus* most common
  - Risk increases with duration of neutropenia or prior neutropenic episodes

Question #3

INFECTIOUS DISEASE BOARD REVIEW PREVIEW QUESTION

43 yr old F with AML with fever, cough and nodular lung lesions 20 days after induction therapy. On meropenem, fluconazole, acyclovir. Voriconazole begun for presumed aspergillosis. CT scan 10 days later showed lesion doubled in size with slight cavitation. ANC has risen from 25 to 800. Clinically she is improving.

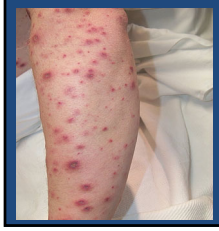


A. Change voriconazole to liposomal amphotericin B
B. Change voriconazole to posaconazole
C. Continue to follow on current therapy
D. Add micafungin
E. Bronchoscopy for diagnosis

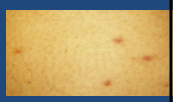
Pulmonary fungal infections

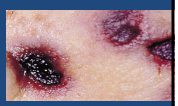
- *Aspergillus* species most common
- Nodular, tracheobronchial abnormalities (sometimes with 'halo') that enlarge before necrotizing
- Alternative microbial diagnosis
  - Fusarium, Scedosporium, others
  - Mucormycoses

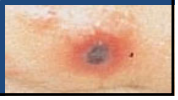
Skin Lesions



- Candidiasis
  - Small, tender papules
- Herpes
  - vesicular
- *Aspergillus*
  - ulcerative, necrotic
- Other filamentous fungi (*Fusarium, P. boydii*)
  - Multiple, erythematous, different stages
- *P. aeruginosa*
  - Ecthyma gangrenosum





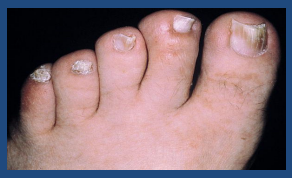


41a – Infections in the Neutropenic Cancer Patient and Hematopoietic Stem Cell Recipients

Speaker: Kieren Marr, MD

Fusarium

- Invasive pulmonary disease with skin lesions
- Locally invasive infections in neutropenic patients
  - Keratitis
  - Onychomycosis

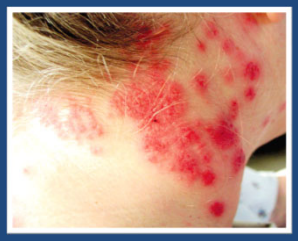


Question #4

2020 INFECTIOUS DISEASE BOARD REVIEW PREVIEW QUESTION

50-year-old woman with newly diagnosed AML developed tender, pruritic papules and plaques on her neck. She had been febrile 38.7°C for the past several days and had received a dose of G-CSF 3 days earlier, with rapid WBC increase (900 ANC). Most likely etiology:

A. *Candida albicans*
B. Sweet's syndrome
C. *Aspergillus niger*
D. Varicella Zoster Virus
E. *Pseudomonas aeruginosa*



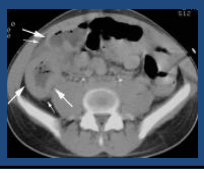
Haverstock, C. et al. Arch Dermatol 2006;142:235-b-240-b.

Question #5

70 yr old woman with AML, neutropenic for 15 days, s/p induction chemotherapy develops fever, diarrhea, and abdominal pain. Exam - decreased bowel sounds and tenderness with deep palpation in her RLQ. CT shows inflammation in cecum. Levofloxacin and fluconazole prophylaxis. 4 days prior to her admission for chemotherapy, she ate Chinese food with fried rice.

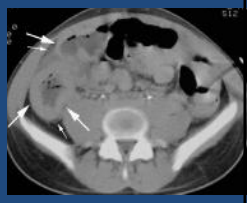
Which is the most likely etiology?

A. Norovirus
B. *Clostridioides (Clostridium) difficile*
C. Mixed anaerobic and aerobic bacteria
D. *Candida albicans*
E. *Bacillus cereus*



Neutropenic Enterocolitis

- Neutropenic enterocolitis (typhlitis)
  - Necrotizing inflammation with transmural infection of damaged bowel wall
  - Mixed infection with gram-negative, gram-positive, anaerobic bacteria, fungi
  - Can be accompanied by bacteremia
    - Hint: mixed, anaerobic (*C. septicum, C. tertium, B. cereus)*
  - Medical and (less often) surgical management

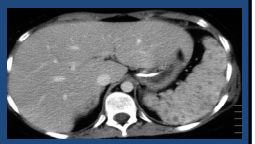


GI Infections

- Diarrhea is a common complaint
  - Mucositis from cytotoxic therapy
  - Tips for infections
    - Bloody, fever, abdominal pain
- Colitis / enteritis
  - Neutropenic enterocolitis
  - *C. difficile* colitis

Hepatosplenic Candidiasis

- Inflammatory response to fungi invaded by portal vasculature
- Presentation after engraftment: abdominal pain, increased LFTs (alk phosph), fever, leg / flank pain
- Differential: other fungi, bacteria, lymphoma
- *C. albicans* most common
  - Amphotericin B primary therapy followed by prolonged fluconazole, echinocandins



Summary: PEARLS

- Recognize typical infections associated with neutropenia and/or other immune suppression (biologic inhibitors of cellular defenses)
- Predict breakthrough bloodstream pathogens based on therapy
- Know specific syndromes
  - *S. viridans* sepsis – ARDS
  - Differential of skin lesions
  - Neutropenic patients - IFI
    - Pulmonary
    - Bloodstream
    - Hepatosplenic candidiasis
  - GI tract enterocolitis

Thank you

kmarr4@jhmi.edu

41b

Selected Syndromes in Stem Cell Transplant Recipients

Dr. Kieren Marr

41b – Selected Syndromes in Stem Cell Transplant Recipients

Speaker: Kieren Marr, MD

2020 INFECTIOUS DISEASE BOARD REVIEW

Selected Syndromes in Stem Cell Transplant Recipients

Kieren Marr, MD
Professor of Medicine and Oncology
John Hopkins University School of Medicine
Director, Transplant and Oncology Infectious Diseases
John Hopkins University School of Medicine

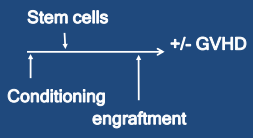
Disclosures of Financial Relationships with Relevant Commercial Interests

- Consultant – Amplyx, Cidara, Merck and Company, Sfunga Therapeutics
- Ownership Interests – MycoMed Technologies

PEARLS

- Fundamentals - risks
  - Early – mucositis, neutropenia
  - Late – GVHD (steroids, asplenia, T cell dysfunction)
- Syndromes
  - Early pulmonary syndromes
    - Bacterial, fungal pneumonia
    - Non-infectious: Alveolar hemorrhage, IPS
  - Late pulmonary syndromes
    - CMV, respiratory viruses, IFI
    - Non-infectious: BOOP
- Hemorrhagic cystitis
  - BK
  - Non-infectious: conditioning
- Diarrhea – colitis – hepatitis
  - Herpes viruses
  - Non-infectious: GVHD
- Neurologic syndromes
  - Herpes viruses (+HHV-6), west nile, angio-invasive, toxoplasmosis, PML (JCV)
  - Non-infectious: PRES, antibiotics

Fundamentals of BMT



- Immune risks for infection are temporal
  - Neutropenia (early)
    - Bacterial infections
    - Fungal infections
  - Impaired cellular and humoral immunity (late)
    - Bacterial infections
    - Fungal infections
    - Viral infections

Fundamentals of BMT

- Autologous (self) vs. allogeneic (other)
- Types of allogeneic donors
  - Related, HLA – matched (MR)
  - Related, HLA - mismatched (haploidentical)
  - Unrelated, HLA – matched (MUD) or Unrelated, HLA – mismatched (MM-URD)
- Types of stem cells
  - Bone marrow
  - Peripheral blood
  - Cord blood
- Types of conditioning regimens
  - Myeloablative
  - Nonmyeloablative

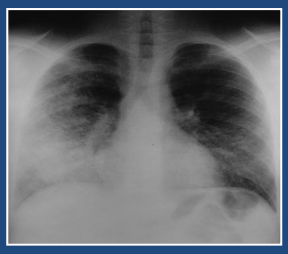
Approach for the boards

- Know common infections and non-infectious mimics
- Approach stems in context
  - Patient's age, disease, history impact risks after BMT
  - What kind of BMT did the patient have?
  - Is the patient early vs. late after BMT?

Type of BMT and timeline impacts immunity, drugs and exposures

Case #1

42 year old M AML 20 days after a matched unrelated donor BMT (nonmyeloablative) develops fever, cough, pulmonary infiltrates.
Pre-transplant: HSV+, VZV+, CMV D+/R-
Exam– 98% sat on 2L nc, T 38.3, crackles RLL
Labs- Cr 2.2, WBC 1200 cells/mL, plt 122
He's currently receiving acyclovir and fluconazole for prophylaxis.



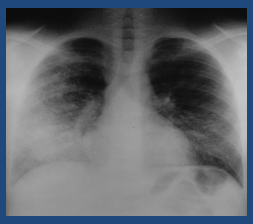
Case #1

What is the most likely cause of his current process?

A. *Candida albicans*
B. *Klebsiella pneumoniae*
C. CMV
D. Parainfluenza virus
E. Hemorrhage

Pulmonary Complications

- Bacterial pathogens
  - *P. aeruginosa, Streptococci*, Legionella, *S. aureus*
  - Aspiration events with severe mucositis early after BMT
  - Encapsulated sinopulmonary pathogens late after BMT
- Filamentous fungi early and late (*A. fumigatus)*



Pulmonary Complications (Con't)

- Respiratory virus infection follows seasonal epidemiology
  - Increased risk for lower tract involvement
  - Influenza, RSV, Parainfluenza 3, Human metapneumovirus
  - Adenovirus: reactivation and acute infection (particular issue with kids)
- Herpes viruses
  - CMV with prolonged impairment in cellular immunity
  - HSV classically described with prior airway manipulation

Early non-infectious lung injury

- Diffuse alveolar hemorrhage
  - Bleeding in alveolar space, heterogeneous etiology
    - Vasculitis, drug-induced injury, cancer-chemotherapy / thrombocytopenia
- Idiopathic pneumonia syndrome
  - Within 1st 120 days of HSCT, non-infectious
  - Risks: conventional ablative conditioning, acute GVHD (inflammatory pathogenesis?)

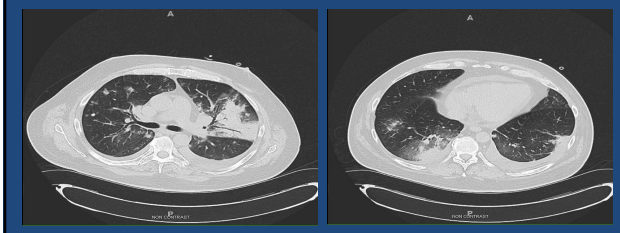
Case #2

2020 INFECTIOUS DISEASE BOARD REVIEW PREVIEW QUESTION

A 46 year old male 18 months s/p HLA mismatched BMT. History of GVHD skin, GI tract, and BOOP 3 months ago, treated with steroids. One month s/p Parainfluenza 3 URI, with chest CT - tree-in-bud opacities in LLL. Received levofloxacin for 10 days.

He now has increasing shortness of breath and cough.

Case # 2 (con't.) PREVIEW QUESTION



Case # 2 (con't.) PREVIEW QUESTION

Blood cultures no growth. Sputum – LF GNR. Serum galactomannan is negative. What is the most likely cause of his current process?

A. *Cryptococcus neoformans*
B. *E. coli*
C. MRSA
D. *Aspergillus fumigatus*
E. *Fusarium* spp.

DDx of Late pulmonary syndromes

- Infectious
  - CMV disease
  - Respiratory virus infections
  - PJP
- Non-infectious
  - Bronchiolitis obliterans syndromes

CMV Infection after BMT

- Reactivation occurs in seropositive patients (R+).
  - Reactivation alone triggers cytokine storm, GVHD, disease
  - Risk for *disease* dependent on immunity
    - Highest risk group for disease after BMT: D- / R+
      - No transferred immunity to CMV
      - This is different than SOT, where highest risk group is D+ / R-
- Primary infection in seronegative patients (R-) from community, positive graft (D+) or blood products (rare)

CMV Disease

- Pneumonitis
  - Indolent cough, fever, SOB, interstitial infiltrates
- Gastrointestinal disease
  - Esophagitis, colitis, hepatitis (rare)
- Encephalitis, retinitis less frequent

CMV Disease after BMT (con't.)

- Treatment concepts
  - Pre-emption with ganciclovir driven by PCR
    - Not prophylaxis (SOT) with ganciclovir (toxicities)
    - Prophylaxis of R+ patients with letermovir
  - Induction therapy with maintenance GCV
  - Resistance to GCV is *rare* (as opposed to SOT)
    - Most failures are due to steroids, T cell depletion
    - Recipe for GCV – resistance: long exposure to suboptimal doses of GCV in a patient with poor cellular immunity

Pneumocystis Pneumonia

- Common late after BMT
  - Steroid receipt, T-cell depletion
- Prophylaxis at least 6 months
  - Bactrim
  - Toxicities
    - Dapsone, atovaquone, aerosolized pentamidine
      - Less effective, other infections occur**
- Late diagnoses occur
  - BAL DFA less sensitive

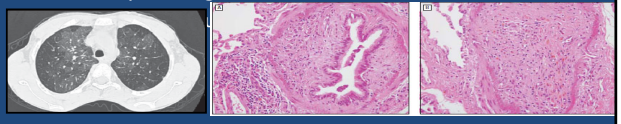
Toxoplasmosis

- Clusters of disease reported in BMT patients
  - T-depleted BMT
  - Some early. Acquisition vs. reactivation?
- Regions with high seroprevalence screen for disease with pre-emptive therapy
- Pneumonia, encephalitis, fever

Isa et al, ID Week 2014
Mears et al. Clin Infect Dis, 2010 Apr 15;50(8):1127-34

Bronchiolitis Obliterans

- Chronic GVHD of lung
  - Allorecognition of lung antigens
- Circumferential fibrosis of terminal airways ultimately leading to airflow obstruction



Williams JAMA 2009

A. Obliteration of bronchiolar lumen
B. Inflammation between the epithelium and the smooth muscle

Case #3

35 yr old F, 80 days after allogeneic BMT with 5 days of anorexia, nausea, epigastric pain, and diarrhea. CMV D-/R+, HSV+, VZV+.
Exam: faint maculopapular rash on upper body. Afebrile.
Meds: acyclovir, TMP-SMX and fluconazole.
ANC 1000, ALC 250. LFTs normal.

What is the most appropriate initial work-up and management?

A. Perform serum VZV PCR
B. Empiric corticosteroid treatment
C. Send C. diff toxin and start oral vancomycin
D. CMV PCR, stool C. diff, bacterial culture
E. #D *and* upper, lower endoscopy

Graft vs. Host Disease (GVHD)

- Acute (early after HSCT)
  - Fever
  - Rash
  - GI: hepatic, colon
- Chronic (later after HSCT)
  - Skin changes (lichen planus, sceroderma)
  - Hepatic (cholestatic)
  - Ocular (keratoconjunctivitis)
  - GI (oral, dysphagia)
  - Pulmonary syndromes

DDx of GI Disease in BMT

HEPATITIS

- GVHD
- Herpes viruses (CMV, VZV)
- Hepatitis B virus
  - Increased viral replication and liver damage
  - Hepatitis not common during neutropenia

DIARRHEA

- GVHD
- CMV
- C. difficile
- Norovirus (chronic diarrhea mimicking GVHD)
- Adenovirus

Adenovirus Infection after BMT

- More common in children, high risk BMT
  - Severe GVHD and steroids
- Enteritis, cystitis, upper respiratory infection, pneumonia, encephalitis, hepatitis
- No controlled treatment studies
  - Taper immunosuppression
  - Cidofovir most active in vitro
  - Ribavirin not effective in larger studies

Case #4

53 year old F 7 yrs s/P allo BMT presents with fever, chills, rigors. H/O severe chronic GVHD skin. PE – T 39.2. tachycardia, tachypnea, hypotension. Skin thick, cracked (Sjogren-like). Social- dog and two cats, no recent exposures. Labs- WBC 8200 / mm3, platelet 43,000/mm3. CT of her chest, abdomen, pelvis - splenic atrophy. Blood cultures positive for gram-negative rods after 5 days.

Most likely cause of her current condition:

A. *Fusobacterium nucleatum*
B. *Eikenella corrodens*
C. *Capnocytophaga canimorsus*
D. *Acinetobacter baumannii*

Case #5

40 year old M day 60 after allogeneic BMT from unrelated donor, with bloody urine for 6 days. Has skin GVHD, receiving a prednisone taper (1 mg/kg/day). Exam, faint diffuse erythematous rash. Cr 1. LFTs normal. CMV pcr negative.

The most likely etiology is:

A. Cyclophosphamide
B. CMV
C. EBV
D. BK
E. JC virus

DDx of Hemorrhagic Cystitis

- Conditioning related (early)
  - Cyclophosphamide
- BK virus (later)
- Adenovirus (later)

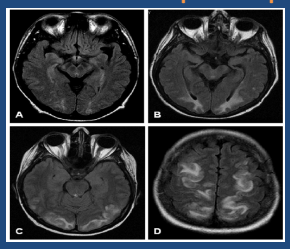
DDx of Neurologic Syndromes

- Infection
  - Herpes viruses: HSV, CMV, HHV6*
  - West nile virus
  - JCV – PML (especially with T-depleting Abs)
  - Pulmonary – CNS lesions
    - Invasive fungal infections
    - Nocardia
    - Toxoplasmosis
- Drugs: carbapenems, cefepime, PRES*

HHV-6 after BMT

- HHV-6 seroprevalence > 95% after age 2
  - Early reactivation common after BMT 38-60% SCT (type B)
  - Clinical correlates reported: rash, marrow suppression, delayed platelet engraftment, idiopathic pneumonitis
- Meningoencephalitis**
  - Nonspecific presentation (confusion, memory loss, EEG / MRI: temporal)
  - Early - within 60 days of BMT
  - RFs: MM/URD or UCB SCT, anti-T-cell
- Diagnosis: PCR of CSF
- Chromosomal integration
- ACV-resistant. Treat with ganciclovir, foscarnet, cidofovir

Posterior reversible encephalopathy (PRES)



- Usually early after HSCT (within 1st 3 months)
- Calcineurin inhibitors: Cyclosporin*, tacrolimus
- Seizures, visual changes, MS changes

VZV Infection after BMT

- Multidermatomal lesions
- Primary viral pneumonia
- Encephalitis
- Hepatitis
  - Classic: abd pain, transaminitis late
  - Can occur without skin lesions
- VZV seropositive
- Severe GVHD, acyclovir prophylaxis effective long term
- Recent study: 1% rate of infection, high rate after 1 yr

Baumrin et al. Biol Blood and Marrow Trans 2019 (in press)

PEARLS

- **Fundamentals - Risks**
  - **Early – mucositis, neutropenia**
  - **Late – GVHD (steroids, asplenia, T cell dysfunction)**
- **Syndromes**
  - **Early pulmonary syndromes**
    - **Bacterial, fungal pneumonia**
    - **Non-infectious: Alveolar hemorrhage, IPS**
  - **Late pulmonary syndromes**
    - **CMV, respiratory viruses, IFI**
    - **Non-infectious: BOOP**
- **Hemorrhagic cystitis**
  - **BK**
  - **Non-infectious: conditioning**
- **Diarrhea – colitis – hepatitis**
  - **Herpes viruses**
  - **Non-infectious: GVHD**
- **Neurologic syndromes**
  - **Herpes viruses (+HHV-6), west nile, angio-invasive, toxoplasmosis**
  - **PML**
  - **Non-infectious: PRES, antibiotics**

Thank you

kmarr4@jhmi.edu

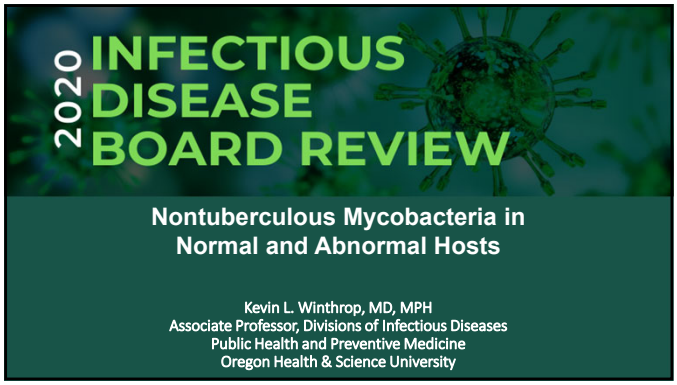
42

Nontuberculous Mycobacteria in Normal and Abnormal Hosts

Dr. Kevin Winthrop

42 - Nontuberculous Mycobacteria in Normal and Abnormal Hosts

Speaker: Kevin Winthrop, MD



Nontuberculous Mycobacterium (NTM)

- "MOTT" or "Atypical"
- Environmental organisms
  - Soil, lakes, rivers, municipal water systems
  - Resistant to chlorine and most disinfectants
- Biofilm
  - Live within amoeba, legionella, others

Laboratory Growth Characteristics

- "Slow" growers (>2 weeks in AFB media, liquid media more quickly)
  - M. avium complex (MAC), *M. kansasii, M. marinum, M. xenopi*
- "Rapid" growers (4-7 days in routine blood agar)
  - *M. abscessus, M. chelonae, M. fortuitum*
- *"Need help" growing*
  - *M. marinum, M. haemophilum, M. ulcerans,*
  - *M. genavense (often molecular ID)*

NTM Disease Clinical Manifestations

- Pulmonary (75%)
  - MAC
  - *M. kansasii*
  - *M. xenopi*
  - *M. abscessus*
  - *M. malmoense*

NTM Disease Clinical Manifestations

Skin and Soft tissue (15%)
- MAC, *M. marinum, M. abscessus, M. chelonae, M. fortuitum, M. kansasii, M. ulcerans*

Lymph node disease (5%)
- *MAC, (historically also M. scrofulaceum)*

Disseminated (5%)
- MAC, *M. kansasii, M. abscessus, M. chelonae, M. haemophilum*

Hypersensitivity pneumonitis (0%)
- *MAC and hot-tubs*

Important Bug-Setting Associations

- Corneal Disease
  - *M. chelonae*
- Healthcare/hygiene associated outbreaks
  - *M. chelonae, M. fortuitum, M. abscessus*
- Line-associated
  - *M. mucogenicum*
- HIV setting
  - *MAC, M. kansasii, M. genavense, M. haemophilum*
- Tropical setting
  - *M. ulcerans* (buruli ulcer)

Other Pearls Based on Species

- *M. gordonae*
  - *Contaminant*
- NTM are not communicable
  - Except *M. massilense* in CF
- *M. immunogenum, M. simiae*
  - Pseudo-outbreaks
- *M. szulgai*, *M. kansasii*, and *M. marinum*
  - Cross-react with IGRAs
- *M. fortuitum* lung disease
  - Aspiration
- *M. marinum*
  - Fish and fishtanks

Question #1

2020 INFECTIOUS DISEASE BOARD REVIEW **PREVIEW QUESTION**

72 year old female with chronic cough, normal CXR, and 1/3 sputums grow MAC. Which one of the following you do recommend ?

A. CT scan of chest AND Additional sputum AFB cultures
B. Empiric therapy with azithromycin, ethambutol, and rifampin
C. Additional sputum AFB cultures
D. Wait for in vitro susceptibility data and then treat.

Pulmonary NTM

2007 ATS/IDSA diagnostic criteria:

- Patient has both radiographic evidence of disease and pulmonary symptoms

AND

- At least 2 sputum cultures positive, or
- One BAL or tissue specimen with positive culture, or
- Tissue with granulomatous histopathology in conjunction with positive culture (BAL or sputum)

Griffith D et al. *AJRCCM* 2007

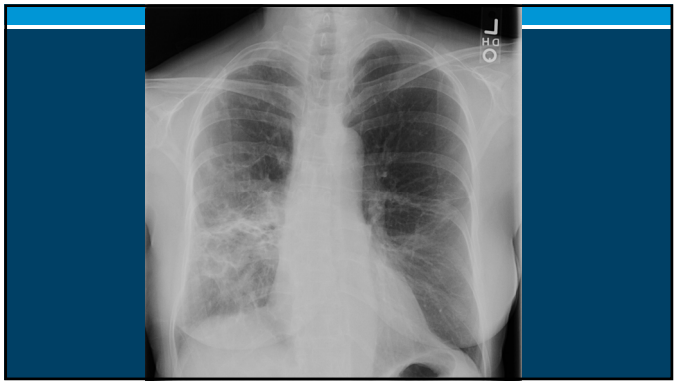
Pulmonary NTM

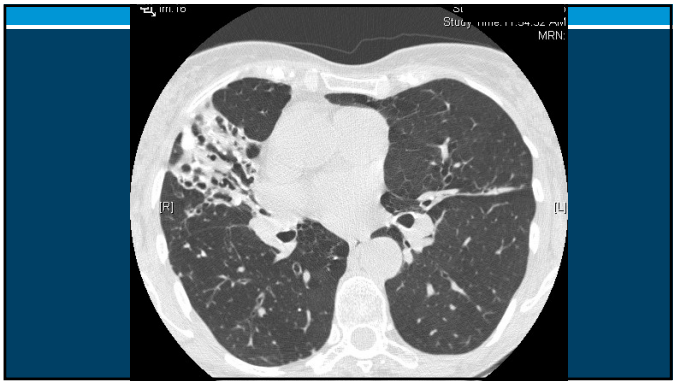
- MAC is most common etiology (60-90%)
- M. kansasii and M. abscessus
  - *M. kansasii* primarily in the South
  - Recent *M. abscessus* increase in CF
- Other organisms of importance
  - *M. xenopi* (northern US/ Canada, Europe)
  - *M. malmoense* (Europe)

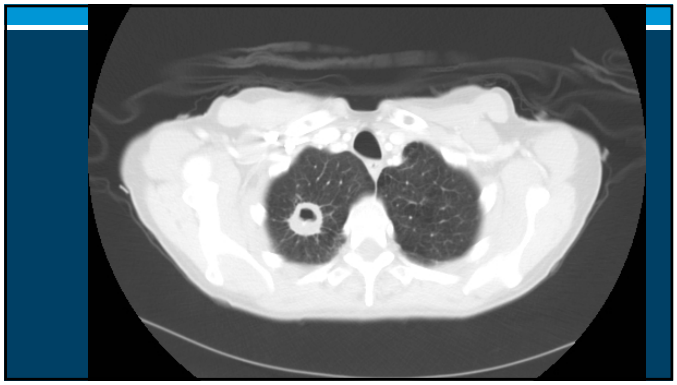
Two Types of MAC Pulmonary Diseases

- Older male, smoker, COPD
  - Apical cavitary or fibronodular disease
  - More rapidly progressive
- Older female ("Lady-Windermere")
  - Scoliosis, thin, pectus deformities*, hypomastia
  - Nodular and interstitial nodular infiltrate
  - Bronchiectasis right middle lobe / lingula
  - Bronchiolitis ("tree and bud") on HRCT
  - Slowly progressive

*Iseman MD et al. *Am Rev Respir Dis.* 1991







Pulmonary NTM Risk Factors

- Underlying lung architectural abnormalities
  - Bronchiectasis, CF, α-1, emphysema
  - Prior TB, GERD/aspiration
- Exposure/transmission
  - Gardening/soil, Hot tubs
- Immunosuppressives
  - Prednisone, inhaled corticosteroids, biologics

NTM Pulmonary Disease Diagnosis

- Diagnosis ≠ decision to treat
  - Observation vs. suppression vs. cure

MAC Therapeutic Options

- Treatment best defined for MAC
  - Start Macrolide, rifampin, ethambutol
  - Amikacin first 1-2 months for cavitary disease
  - Treatment duration 18-24 months (12 month culture negative)
  - Macrolide monotherapy is contraindicated
  - Recommended to test susceptibility for macrolide
  - TIW okay if non-cavitary or not re-infection

Pulmonary M. kansasii Therapy

- *M. kansasii* clinically more like TB
  - Thin-walled cavities, upper lobes
  - Treatment with INH, RIF, EMB
  - TIW therapy ok
  - Treatment duration: 12 months culture negativity
  - High treatment success rates (90%+)
  - RIF is key drug.

Pulmonary M. abscessus Therapy

- *M. boletti, M. massiliense, M. abscessus*
  - Inducible macrolide resistance--erm (41) gene
- "Cure" = rare
- More rapidly progressive than MAC
- 3-4 drugs for 18-24 months
  - 4-6 months "induction" phase
  - "suppressive strategy" thereafter

M. abscessus Therapy

- Parenteral agents
  - Tigecycline 50mg QD, Cefoxitin 2gm TID, Imipenem 1000mg BID, Amikacin 10mg/kg TIW
- Oral agents
  - Clofazimine 50-100mg QD, *Linezolid 600mg QD, moxifloxacin 400mg QD (rarely suscep)*
  - Surgical resection

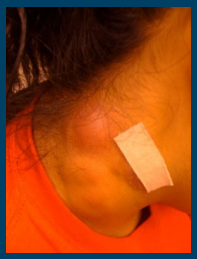
EXTRAPULMONARY NTM

1. Immunocompetent settings
2. Immunocompromised settings

Immunocompetent settings

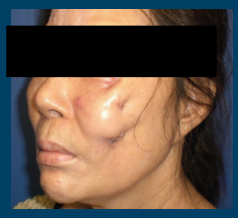
- Nail salon, trauma, surgical or injection procedures, fishtank, hot tubs
- Rapid or slow growing NTM
- Incubation period
  - Infection usually occurs 2-8 weeks after contact with contaminated water source

Children under 5 years NTM > TB



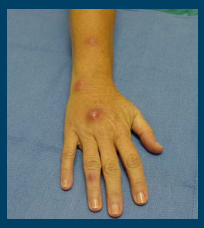
- Usually MAC
  - Males > females, age 1-2 years old
- Surgical resection alone is best therapy
- Adjunctive ABX rarely needed

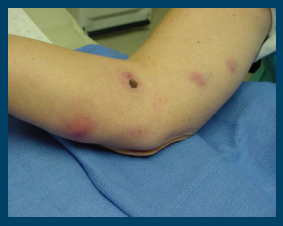
Post- plastic surgery



- Usually Rapid Grower:
  - *M. chelonae*
- Remove foreign-bodies
- Therapy as per in-vitro susceptibility
- Length 4-6 months

M. marinum---fish tank granuloma



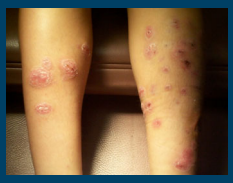


Treatment: multiple drugs

- Macrolides, sulfonamides, doxycycline, rifampin, ethambutol
- Treat with 2 agents X 3-4 months.
- Surgical debridement if necessary

Nail Salon Furunculosis

- Outbreaks and sporadic
- Rapid Growers most common (*M. fortuitum)*
- Oral antibiotics
  - 4 months fluoroquinolone and/or doxycycline
  - Can be self-limited



Tattoo-associated

- *M. chelonae*
- Tattoo-ink outbreaks
- 2-3 months oral therapy
  - Based on *in-vitro* susceptibility
  - 1-2 agents
  - Macrolides almost always

Question # 2

20 y.o. male complains of fever, night sweats and weight loss. Has generalized lymphadenopathy. HIV antibody positive; CD4 20 cells/ul. Node biopsy: non-caseating granuloma, AFB seen.

Question # 2

Based on the most likely diagnosis, which of the following do you recommend :

A. Start MAC therapy
B. Start HAART plus MAC prophylaxis
C. Start MAC therapy and HAART
D. Start HAART only

NTM in HIV

- Disseminated MAC
- GI route of infection
- Less frequent in HAART era
- Related issues
  - Clofazimine = increases mortality (do not use!)
  - Rifabutin dose adjustment with PI
  - Immune reconstitution inflammatory syndrome (IRIS)

TABLE 7. REGIMENS FOR TREATMENT AND PREVENTION OF DISSEMINATED *Mycobacterium avium* IN HIV-INFECTED PATIENTS

Preferred (A, I)*	Alternative (B, I)*
Treatment	
Clarithromycin 500 mg orally twice daily + Ethambutol 15 mg/kg orally daily ± Rifabutin† 300 mg orally daily	Azithromycin 500 mg daily + Ethambutol 15 mg/kg daily ± Rifabutin† 300–450 mg orally daily
Prevention‡	
Azithromycin 1,200 mg orally weekly	Clarithromycin 500 mg orally twice daily or Rifabutin† 300 mg orally daily

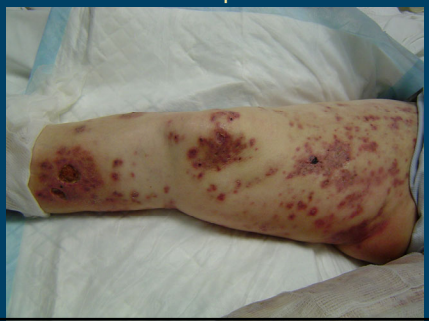
* For evidence quality, see Table 1.
† Rifabutin dose may need to be modified based on drug–drug interactions (see text).
‡ Preventive therapy indicated for persons with < 50 CD4+ cells/μl; may stop if > 100 cells/μl.

Griffith D et al. AJRCCM 2007

Immunosuppression other than HIV

- Most frequently disseminated
  - Local inoculation versus GI route
- Risk factors and conditions
- ESRD, prednisone, biologic immunosuppressives
- Cancer, transplant, leukemia (hairy cell)
- Auto-antibody and cytokine/receptor deficiency states
  - INF-gamma, IL12-23 pathway, STAT-1
- Disease split between RGM and slow growers
  - RGM more common here than in pulmonary disease

M. chelonae in cancer patient



M. chelonae and *M. fortuitum* treatment

- *M. chelonae*
  - Macrolides,flouroquinolone, linezolid
  - IV drugs include aminoglycosides, imipenem, cefoxitin, tigecycline
  - Note: tobramycin is best for *M. chelonae*
- *M. fortuitum*
  - Macrolides, flourquinolone, bactrim, doxy (50%)
  - IV drugs include aminoglycosides, imipenem, cefoxitin, tigecycline

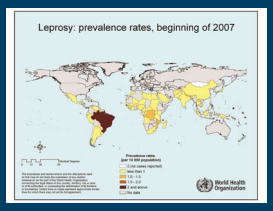
Length of treatment for disseminated infection
3 drugs (including 1 IV) X 4-6 months
Depends on immunosuppression reversal

MYCOBACTERIUM CHIMAERA

- Slow growing. M. avium complex.
- Requires molecular identification
- Over 150 cases from open heart surgery: prosthetic valve, vascular graft, LVAD, heart transplant
- Aerosol from contaminated heater-cooler units used in operating room for cardiac by-pass.
- Time to diagnosis 1.7-3.6 years post-op, with cases reported up to 6 years postoperatively.
- Mycobacterial blood cultures
- Treatment: ???

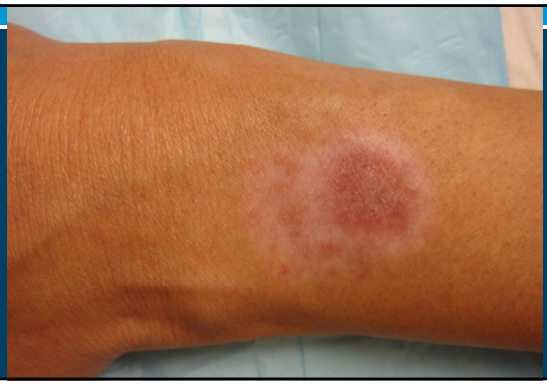
Hansen's Disease (Leprosy)

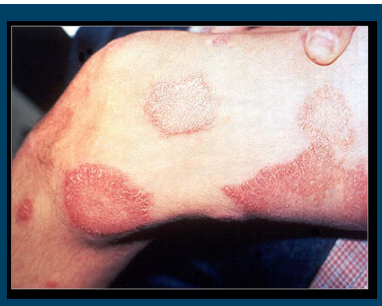
- Rare in US (40-50 cases per year)
  - Armadillos and gulf region
  - Rest imported
- Most humans resistant
  - Household contacts at risk (low risk)
  - Nasopharyngeal transmission?
- *M. leprae* does not grow in culture



Leprosy Disease Classification

- Paucibacillary (PB)
- Most common form
  - *"Tuberculoid"*
  - Bacillary load < 1 million
  - Skin biopsy: AFB negative
  - ≤5 skin lesions
- Multibacillary (MB)
  - *"Lepromatous"*
  - Massive bacillary load
  - Skin biopsy: Floridly positive for AFB
  - >5 skin lesions.





Leprosy Treatment

- PB (6 months)
  - Dapsone 100mg daily
  - *Rifampin 600mg once monthly
- MB (12 months)
  - Dapsone 100mg daily
  - Clofazamine 50mg daily
  - *Rifampin 600mg once monthly OR
  - *Clofazamine 300mg once monthly

Complications: reversal reactions, erythema nodosum
Treat with prednisone, thalidomide, other

Top 10 or 12 NTM pearls for the Boards

- Footbaths = *M. fortuitum* or other RGM
- *Plastic Surgery* = *M. chelonae* or other RGM
- Equitorial Africa = *M. ulcerans*
- HIV disseminated MAC that doesn't grow = think of *M. genavense*
- M. abscessus usually has inducible macrolide resistance (erm gene)
- Macrolide, EMB, RIF for 18-24 months for pulmonary MAC
- *M. gordonae* is 99.9% a contaminant
- ATS/IDSA pulmonary case definition: need one BAL or two sputums or tissue
- Know NTM species that cross-react with TB IGRAs
- No clofazimine in HIV related MAC
- *M. kansasii* behaves like TB---responds to TB drugs (RIF, EMB, INH)
- PZA not useful for any NTM

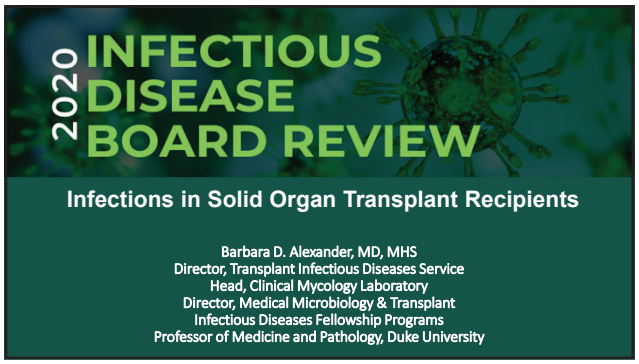
43

Infections in Solid Organ Transplant Recipients

Dr. Barbara Alexander

43 – Infections in Solid Organ Transplant Recipients

Speaker: Barbara Alexander, MD



WHAT YOU SHOULD KNOW FOR THE BOARD EXAM:

- Infection risk varies based on
  - Organ transplanted
  - Time post transplant
  - Degree of immunosuppression
  - Prophylaxis regimen
  - Unique exposures
- Key drug interactions and drug-induced syndromes
  - Calcineurin inhibitors and azoles, macrolides, rifampin (covered in Dr. Gilbert's antibiotic lecture)
  - Sirolimus associated pneumonitis
  - Calcineurin inhibitors and TTP and PRESS

Disclosures of Financial Relationships with Relevant Commercial Interests

- **Consultant – Scynexis, Astellas, Shionogi**
- **Research Grant – Lediant**
- **Clinical Trials (Site PI/Study PI) – Ansun, Astellas, Cidara, Scynexis, Shire, F2G**
- **Royalties (Chapter Author) – UpToDate**

WHAT YOU SHOULD KNOW FOR THE BOARD EXAM:

- The following major clinical syndromes:
  - CMV syndrome & disease
  - EBV & Post Transplant Lymphoproliferative Disorder (PTLD)
  - BK virus nephropathy
  - Aspergillosis, Mucormycosis & Cryptococcosis
  - Tuberculosis
  - Toxoplasmosis
  - Donor derived infections

Infections in Solid Organ Transplant (SOT) Recipients

- SOT is a life-saving intervention
  - >750,000 SOTs performed in U.S. since 1988
  - 39,718 SOTs performed in 2019
- SOT recipients
  - have compromised immunity / increased infection risk
  - are targets for common & emerging opportunistic pathogens encountered pre- and post-transplant
  - often have atypical infection presentation owing to their compromised immunity / decreased inflammatory response
  - are on complex medical regimens; drug interactions common

Data from Organ Procurement and Transplantation Network database as of June 29, 2020

PLAY THE ODDS

The data in the stem let's you "play the odds" as to the most likely diagnosis

- **Patient completing valganciclovir prophylaxis 6 weeks prior presenting with fatigue, low grade fever and leukopenia**
  - **CMV Syndrome**
- **Donor died from skiing accident in fresh water lake in Florida and recipient presents 3 weeks post transplant with encephalitis**
  - **ACANTHAMOEBA**
- **Renal transplant recipient on valganciclovir prophylaxis presents with asymptomatic renal dysfunction**
  - **BK Virus**
- **Lung transplant recipient planted vegetable garden 2 weeks prior while on posaconazole prophylaxis and presents with productive cough and cavitary lung lesion**
  - **NOCARDIA**

43 – Infections in Solid Organ Transplant Recipients

Speaker: Barbara Alexander, MD

FREQUENCY, TYPE & INFECTION SOURCE IN THE 1ST POST TRANSPLANT YEAR

Transplant Type	Infection Episodes per Patient	Bacteremia	CMV Disease * (%)	Fungal Infections (%)	Most Common Source
Kidney	0.98	5-10	8	1.3	Urinary tract
Heart	1.36	8-11	25	3.4	Lung
Lung Heart-Lung	3.19	8-25	39	8.6	Lung
Liver	1.86	10-23	29	4.7	Abdomen & Biliary tract

*CMV, Cytomegalovirus; Numbers reflect CMV disease rates in the absence of routine antiviral prophylaxis

Table Modified from: Principles and Practices of Infectious Diseases, 8th Edition, Chapter 313: Infections in Solid-Organ Transplant Recipients by Nina Singh and Ajit Limaye. Editors: Bennett JE, Dolin R, and Blaser MJ. Elsevier Saunders, Philadelphia, PA, 2015.

"LATE" BACTERIAL INFECTIONS FOLLOWING SOT

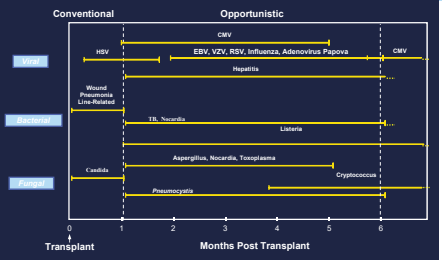
80% OF LATE BACTERIAL INFECTIONS ARE COMMUNITY ACQUIRED

- *Streptococcus pneumoniae*
  - Incidence significantly > in SOT (146/100,000) vs general population (12/100,000)
  - Vaccination recommended
- *Listeria monocytogenes*
  - Bacteremia (Gram + Rods) / Diarrhea / Meningitis
  - Ampicillin treatment of choice
  - High relapse rate, treat for at least 3-6 wks

Kumar D et al., *Am J of Transplant* 2007;7:1209

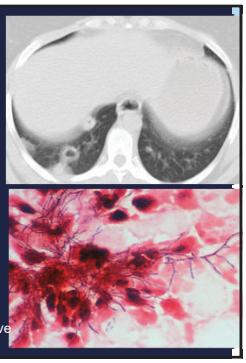
CLASSIC TIMING OF INFECTIONS FOLLOWING SOLID ORGAN TRANSPLANTATION

Timing altered by:
- Enhanced immunosuppression
- Prophylaxis regimen
- Unique exposures



LATE BACTERIAL INFECTIONS, CONT.

- *Nocardia* species
  - 1%-6% of all SOT recipients
  - Presents most often as pulmonary nodules, CNS (15-20%), skin (15%), or bone (2-5%) lesions
  - Diagnosis: Culture and/or histopathology
    - Branching, filamentous Gram + Rods
    - Partially acid-fast by modified Kinyoun stain
    - *Nocardia* is *Neurotropic*; brain imaging critical
  - Treatment:
    - High dose TMP-SMX drug of choice
    - Otherwise, based on susceptibility data & site of infection
  - TMP-SMX dose used for PCP prophylaxis not protective



"EARLY" BACTERIAL INFECTIONS FOLLOWING SOT

Type & site of early bacterial infection varies based on organ transplanted, surgical approach/technique & transplant center

- Risk of peritoneal infection greater in liver transplantation with Roux-en-Y biliary drainage
- Recipient colonization with resistant organisms (e.g. MRSA, VRE, CRE) pre-transplant, confers risk of post-transplant infection
- Cluster with unusual pathogen - environmental problem? (e.g. *Legionella, M. abscessus* from hospital water distribution systems)

CMV DISEASE AFTER SOT

INDIRECT AND DIRECT EFFECTS

INDIRECT Effects:
- Acute and Chronic Rejection
- Opportunistic Super-Infections (Gram negative bacteria & Molds)

DIRECT Effects:
- CMV Syndrome – most common presentation
  - CMV in blood + fever + malaise, leukopenia, atypical lymphocytosis, thrombocytopenia, or elevated liver enzymes
- Tissue Invasive Disease
  - Evidence of CMV on biopsy + compatible signs/symptoms

RISK OF CMV DISEASE AFTER SOT

CMV Serologic Status	Risk Category	Incidence of Disease (%)
D+/R-	High	50+
D+/R+ or D-/R+	Intermediate	10-15
D-/R-*	Low	0
ALA Therapy (R+)		
Induction	Intermediate	25-30
Rejection	High	65

D, Donor; R, Recipient; ALA, Antilymphocyte Antibody

*Should receive leukocyte depleted blood products

CMV DISEASE AFTER SOT

- Typically occurs 1-3 months post-transplant
  - Or after prophylaxis is stopped
- Disease of GI Tract and Eye may not have concurrent viremia
  - Diagnosis often requires biopsy/aspiration
- Viral load may continue to rise during first 2 weeks of Rx
  - Don't repeat PCR until Day 14 of treatment
- Treat for 2-3 weeks…
  - DO NOT STOP TIL VIREMIA CLEARs (high risk for relapse)

CMV DISEASE AFTER SOT
PROPHYLACTIC APPROACHES

UNIVERSAL

All SOT recipients receive therapy during highest risk periods

- Options include IV or oral ganciclovir or valganciclovir
- Expensive, may induce resistance, some pts exposed unnecessarily

PREEMPTIVE

Treatment based on asymptomatic viral replication in blood

- Requires serial monitoring with detection assay
- Optimal duration of treatment, drug to use, & viral threshold for initiating therapy not yet determined

NOTE: Letermovir not studied / approved for use in SOT population, only HSCT

CMV DISEASE AFTER SOT
GANCICLOVIR RESISTANCE

- **Suspect resistance if prolonged (> 6 weeks) ganciclovir exposure AND:**
  - No reduction in viral load after 14 days of treatment
  - No clinical improvement after 14 days of treatment
- **Management of suspected ganciclovir resistance:**
  - Reduce immunosuppression
  - Switch to foscarnet (± CMV hyperimmune globulin)

Lurain et al.JID 2002; Limaye et al Lancet 2000; Limaye et al JID 2002; Kotton et al Transplantation 2013.

CMV DISEASE AFTER SOT
PROPHYLAXIS

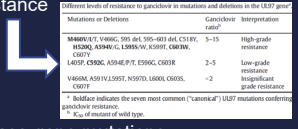
Bottomline:

- D+/R- or ALA for rejection → Universal
  - First 3-6 months post-transplant
  - At least 1 month post-ALA for rejection
- R+ → Universal or Preemptive
  - First 3-6 months post-transplant

CMV DISEASE AFTER SOT
ANTIVIRAL RESISTANCE

Key mutations have been associated with resistance

- UL97 CMV Phosphotransferase gene mutations (most common)
  - Imply ganciclovir resistance



Different levels of resistance to ganciclovir in mutations and deletions in the UL97 gene

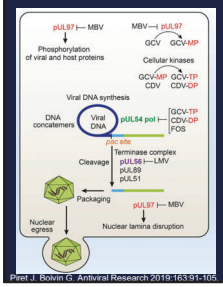
Mutations or Deletions	Ganciclovir ratio[a]	Interpretation
M460V/I/T, V466G, 595 del, 595–603 del, C518Y, **H520Q, A594V/G, L595S/W, K599T, C603W,** C607Y	5–15	High-grade resistance
L405P, **C592G**, A594E/P/T, E596G, C603R	2–5	Low-grade resistance
V466M, A591V,L595T, N597D, L600I, C603S, C607T	<2	Insignificant grade resistance

[a] Boldface indicates the seven most common ("canonical") UL97 mutations conferring ganciclovir resistance.
[b] K_{is} of mutant of wild type.

- UL54 CMV DNA Polymerase gene mutations
  - May confer resistance to ganciclovir, foscarnet, & cidofovir

Lurain et al JID 2002; Limaye et al Lancet 2000; Limaye et al JID 2002; Kotton et al Transplantation 2013; Torre-Cisneros at al Transplantation Reviews 2016.

CMV DISEASE AFTER SOT ANTIVIRAL RESISTANCE (ON THE HORIZON)



Piret J, Boivin G. Antiviral Research 2019;163:91-105.

Letermovir (LMV)
- Interferes with cleavage / packaging of viral genome by inhibiting pUL56 subunit of CMV terminase complex
- Resistance mutations usually in pUL56 (rarely pUL89 or pUL51 subunits) of CMV terminase complex; do not confer cross-resistance to other antiviral drugs
- Appears to have low barrier to resistance; only a few case reports for use in SOT with GCV resistant infections…
- Only approved for prophylaxis in HSCT population
- No activity against other herpes viruses ⚠

Maribavir (MBV)
- Interferes with viral nuclear egress by inhibiting viral pUL97 kinase.
- UL97 inhibition also prevents1st phosphorylation step of ganciclovir (GCV) resulting in antagonistic effect when used together
- Resistance mutations usually in UL97 gene; can confer cross-resistance to GCV
- Phase 3 clinical trial of GCV resistant disease just finished enrolling….stay tuned!

EPSTEIN BARR VIRUS POST TRANSPLANT LYMPHOPROLIFERATIVE DISORDER (PTLD)

EBV transformed B-lymphocytes give rise to PTLD
- A few cases may arise from T-lymphocytes

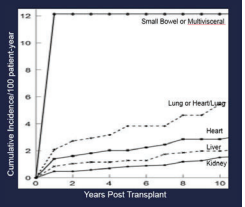
Risk factors:
- 1° EBV infection
  - Donor seropositive, Recipient seronegative
- Antilymphocytic antibody therapy (T-cell depletion)
- Organ transplanted
  - Intestine > Lung > Heart > Liver > Kidney

CASE 1

- 54 yo male 60 days post-cardiac transplant was treated for rejection with steroids when fever and a non-tender anterior cervical mass appeared.
- Biopsy showed nodal replacement by lymphocytes, many of which stained positively for Epstein-Barr virus as well as for the B cell marker, CD20.
- His plasma EBV viral load was 10,000 copies /ml.

EPSTEIN BARR VIRUS POST TRANSPLANT LYMPHOPROLIFERATIVE DISORDER (PTLD)

- ~3% Cumulative 10 year incidence in SOT population
- Incidence varies based on organ transplanted
  - Small Bowel / Multivisceral – up to 32%
  - Lung / Heart / Liver - 3-12%
  - Kidney - 1-2%
- Biphasic pattern of disease after SOT:
  - First peak (20% cases) occurs 1st post-tx year
  - Second peak occurs 7-10 years post-tx



Olagne, J, et al. Am J Transplant. 2011 Jun;11(6):1260-9.

QUESTION #1

The most appropriate treatment for this condition is:

A. Cidofovir
B. Ganciclovir
C. Acyclovir
D. Cyclophosphamide
E. Rituximab

EPSTEIN BARR VIRUS *POST TRANSPLANT* LYMPHOPROLIFERATIVE DISORDER (PTLD)

Clinical manifestation - wide range
- Febrile mononucleosis-like illness with lymphadenopathy
- Solid tumors
  - Often involve transplanted graft
  - 50% are extranodal masses
  - 25% involve CNS

Definitive diagnosis requires tissue biopsy
- Classification based on histology and clonality
- Molecular (PCR) tests available
  - WHO Standard for Assay Calibration available
  - Whole Blood vs Plasma controversial
  - Misses EBV-negative, localized, and donor-derived PTLD
  - Used as an aid for Diagnosis and Pre-emptive monitoring with stepwise reduction in immunosuppression to reduce PTLD rates

Petit B et al. Transplantation. 2002;73(2):265.
Peters AC, et al. Transplantation. 2018; 102(9):1553.

EPSTEIN BARR VIRUS *POST TRANSPLANT LYMPHOPROLIFERATIVE DISORDER (PTLD)*

Treatment:

- Antivirals not effective on latently infected lymphocytes
- Reduce Immunosuppression (Response ~ 45%)
- Rituximab: Anti-CD20 monoclonal antibody (Response ~ 55%)
- Cytotoxic Combination (CHOP, ACVBP) Chemotherapy
  - Reserved for non-responsive disease
  - High treatment associated mortality (13%-50%)
- Adoptive Immunotherapy (EBV cytotoxic T-cells)
  - Under study, not readily available

Allen et al. Am J Transplantation 2013;13:107-120

POLYOMAVIRUS *BK VIRUS NEPHROPATHY*

- Ubiquitous, DNA virus
  - 1° infxn – URI during early childhood
  - 80% worldwide population sero+
  - Renal & uroepithelial cells, site of latency
- Cause of nephropathy post renal transplant
  - Up to 15% of renal recipients effected
  - Time to onset 28-40 weeks (majority within 1st yr post tx)
  - Manifests as unexplained renal dysfunction (as does rejection)

Hayashi RY et al. UNOS Database; Abstract 76, 2006 World Transplant Congress; Ramos et al. *J Am Soc Nephrol* 2002;13:2145; Hirsch et al. Transplantation 2005;79:1277-1286

CASE 2

PREVIEW QUESTION

- 52 yo female S/P cadaveric renal transplant receiving tacrolimus, prednisone and mycophenylate.
- Week 30 post transplant serum creatinine rose from 1.5 to 2.3 mg/dl.
- Tacrolimus levels were in therapeutic range.
- Urinalysis revealed one plus protein and no cells or casts.

BK VIRUS NEPHROPATHY *DIAGNOSIS*

- Replication in urine precedes replication in blood precedes nephropathy
- Renal Bx - "Gold Standard" for diagnosis
- Blood PCR
  - Sensitive (100%) but less specific (88%)
  - Cannot rule out rejection
  - Useful as indicator for biopsy
- Urine Cytology, Electronmicroscopy, & PCR
  - Detection in urine: Low PPV but High NPV

Hirsch et al, Transplantation 2005;79:1277-1286; Nickeleit et al, NEJM 2000;342 (18):1309-1315; Ramos et al. *J Am Soc Nephrol* 2002;13:2145

QUESTION #2

PREVIEW QUESTION

Which would be most helpful in understanding if BK virus was causing her renal failure?

A. Presence of decoy cells in urine cytology
B. Urine BK viral load
C. Urine culture for BK virus
D. Plasma BK viral load
E. Demonstration of BK inclusions in renal tubular epithelium on renal biopsy

BK VIRUS NEPHROPATHY *TREATMENT*

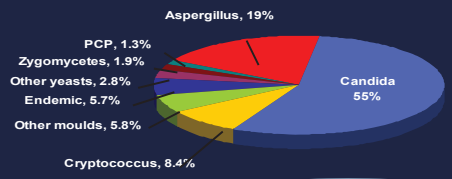
- Reduce immunosuppression
- Case series with variable success using:
  - Low-dose cidofovir
  - Leflunomide
- New drugs & randomized controlled trials needed
- Preemptive monitoring key to prevention

Hirsch et al. Transplantation 2005;79:1277-1286; Farasati et al. Transplantation 2004;79:116; Vats et al. Transplantation 2003;75:105; Kabambi et al. Am J Transplant 2003;3:186; Williams et al N Engl J Med 2005;352:1157-58.

43 – Infections in Solid Organ Transplant Recipients

Speaker: Barbara Alexander, MD

INVASIVE FUNGAL INFECTIONS IN SOLID ORGAN TRANSPLANT RECIPIENTS



Type of fungal infection varied depending on organ transplanted

TRANSNET data
Slide courtesy of P. Pappas, MD.
Pappas P et al. CID. 2010;50:1101-1111.

ANTIFUNGAL PROPHYLAXIS FOR SOLID ORGAN TRANSPLANT RECIPIENTS

Lung	Liver	Pancreas	Small bowel
• All recipients • *Candida* & Molds	• High-risk recipients • *Candida*	• High-risk recipients • *Candida*	• All recipients • *Candida*
Per ISHLT Guidelines	Per AST Guidelines		

Husain S, et al. *J Heart Lung Transpl.* 2016;35:261-82. Silveira FR, Kusne, AST ID COP. *Am J Transpl.* 2013;13:220-27. Singh NM, Husain S, AST ID COP. *Am J Transpl.* 2013;13:228-41

INVASIVE FUNGAL INFECTIONS ACCORDING TO ORGAN TRANSPLANTED N=16,808

	Kidney	Heart	Pancreas	Liver	Lung	Small Bowel
12 Month IFI Incidence (%)	1.3	3.4	4.0	4.7	8.6	11.6
IFI Type (%)					70% Molds	
Candidiasis	49	49	76	68	23	85
Aspergillosis	14	23	5	11	44	0
Other molds	7	10	3	6	26	0
Cryptococcosis	15	10	5	6	2	5
Endemic	10	3	6	5	1	0
Pneumocystosis	1	3	1	0	2	0
Other	4	2	4	4	2	10

Pappas P. Alexander B. Andes D. et al. CID 2010:50:1101-1111

TUBERCULOSIS

- 34-74 fold higher risk of active disease in SOT recipients than general population
- Incidence 1% - 6% (up to 15% in endemic areas)
- Median onset 9 months post-tx (0.5-144 months)
- 33% of infections are disseminated at diagnosis
- Treatment
  - Rifampin-based regimens associated with graft loss/rejection in 25%
- Mortality ~30%
- Treat latent TB prior to transplant when possible

INVASIVE FUNGAL INFECTIONS *RISK FACTORS AFTER SOT*

Each solid organ group will have unique risks for IFIs

Strongly influenced by medical & surgical factors including technical complexity

Liver
- •Re-transplantation
- •Pre-tx fulminant hepatic or renal failure
- •Heavy *Candida* colonization peri-tx
- •Large volume intra-operative transfusions
- •Bleeding complications requiring re-operation
- •Choledochojejunostomy

CANDIDA

Lung
- •Vulnerable anastomotic site
- •Continuous environmental exposure
- •*Aspergillus* colonization of airways
- •CMV pneumonitis
- •Acute rejection
- •Obliterative bronchiolitis

ASPERGILLUS

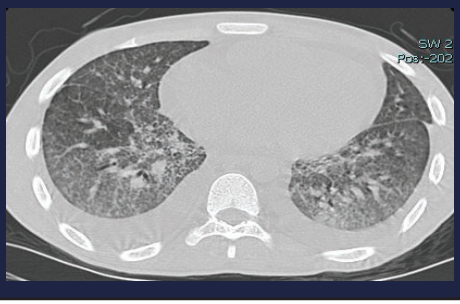
CASE 3

- 35 yo female s/p heart transplant in France 90 days prior presented with fever, dyspnea and a diffuse pneumonia on chest CT.
- She was receiving prednisone, tacrolimus & mycophenolate.
- Both recipient & donor were CMV negative; she was not on CMV prophylaxis.
- She was on inhaled pentamidine for PCP prophylaxis.

43 – Infections in Solid Organ Transplant Recipients

Speaker: Barbara Alexander, MD

CHEST CT



TOXOPLASMOSIS

- Acquired from donor, reactivation, blood transfusion or ingestion of contaminated food or water
- Donor seropositive/Recipient seronegative at high risk
- HEART > LIVER > KIDNEY TRANSPLANT
- DIAGNOSIS:
  - PCR
  - Giemsa smear of BAL
  - Brain aspirate for tachyzoites
  - Immunoperoxidase stain of endocardial biopsy or other tissue
- TREATMENT: sulfadiazine-pyrimethamine-leucovorin

CASE 3

Trimethoprim-sulfamethoxazole was started empirically and she began improving.

Bronchoalveolar lavage (BAL) was negative for:

- pneumocystis by direct fluorescent antibody stain & PCR,
- fungi by calcifour white / potassium hydroxide stain,
- mycobacteria by AFB smear,
- bacteria by Gram stain, and
- respiratory viruses by multiplex PCR

Routine bacterial BAL and blood cultures were negative.

CASE 4

INFECTIOUS DISEASE BOARD REVIEW **PREVIEW QUESTION**

Liver transplant recipient presented 21 days post transplant with confusion, tremors, lethargy, anorexia

- On bactrim & valganciclovir prophylaxis
- Rapid progressive neurologic decline → agitation & delirium →intubation
- Blood & urine cultures: negative
- CSF: lymphocytic pleocytosis (25 WBCs/mm^3) & elevated protein
  - Gram stain, bacterial, fungal cultures negative
- Brain MRI: non-revealing
- Empiric intravenous ganciclovir, vancomycin, ceftriaxone & ampicillin
- Day 6 Repeat MRI: diffuse encephalitis
- Expired 13 days after neurologic symptom onset
- Donor was previously healthy presenting with subarachnoid hemorrhage
  - Toxicology screen: + cocaine & marijuana
  - Brain CT: expanding subarachnoid hemorrhage
  - Recently on camping trip

QUESTION #3

Assuming trimethoprim-sulfamethoxazole was causing her improvement, which additional test on the BAL might have explained her improvement?

A. PCR for CMV

B. PCR for toxoplasmosis

C. PCR for tuberculosis

D. Galactomannan

E. Cold enrichment culture for Listeria

QUESTION #4

INFECTIOUS DISEASE BOARD REVIEW **PREVIEW QUESTION**

This presentation is most consistent with:

A. CMV encephalitis

B. HHV6 encephalitis

C. VZV encephalitis

D. Rabies encephalitis

E. Cryptococcal meningitis

43 – Infections in Solid Organ Transplant Recipients

Speaker: Barbara Alexander, MD

"EXPECTED" DONOR-DERIVED INFECTIONS

- **Expected = known before tx or for which there are recognized standard prevention guidelines**
  - Cytomegalovirus (CMV)
  - Epstein–Barr virus (EBV)
  - Toxoplasmosis

*United Network for Organ Sharing / Organ Procurement and Transplant Network
Ison M et al. Am J Transplant. 2009;9:1929-1935.

VACCINATION RECOMMENDATIONS FOR SOT

Update vaccinations pre SOT:

- Hepatitis A, Hepatitis B, Flu, TDaP, Pneumococcal
- Live Varicella, MMR vaccines (only if ≥8 weeks until transplant)
- HIB, Meningococcal if planned splenectomy (e.g. Multivisceral Tx)

Recommended post SOT:

- Pneumococcal
- Tetanus-diphtheria toxoid
- Inactivated Influenza

Live virus vaccines are NOT recommended after SOT including:

- Measles Mumps Rubella
- Varicella
- Inhaled influenza
- Oral polio
- Yellow fever
- BCG
- Small pox
- Salmonella typhi (oral)

"UNEXPECTED" DONOR-DERIVED INFECTIONS
VIRUSES, VIRUSES, & PARASITES, OH MY…

- Lymphocytic choriomeningitis virus (LCMV)
  - Hamsters and rodents
  - 4 outbreaks (3 USA, 1 Australia); 9 deaths

- Rabies virus
  - Unreported bat bite in donor
  - 3 outbreaks (2 USA, 1 Germany); 8 deaths

- Chagas' Disease (Trypanosoma cruzi)
  - Reduviid bug (Latin America)
  - Screening tests lack sensitivity
  - Multiple transmissions reported

- HIV, Hep C, Hep B, West Nile Virus (WNV)
  - Remember the "Window" prior to development of antibodies
  - Nucleic Acid Tests decrease "window" to ~5-10 days (HIV), 6-9 days (HCV)

Fisher SA et al. N Engl J Med. 2008;354:2235-2249. MMWR Morb Mortal Wkly Rep. 2008;57:799-801. Kusne S et al Transpl. 2005:11:1295-1297. Maier T et al. CID 2010;50:1112-1119 Mattner F et al Infection. 2007;35(4):219-24. Grossi PA, et al. Am J Transpl. 2009:9:S19-S26.

SOLID ORGAN TRANSPLANT
PATIENT TRAVEL

- **REGIONAL EXPOSURES**
  - **COCCIDIOIDOMYCOSIS: Southwest U.S.**
  - **HISTOPLASMOSIS: Central/Mid-Atlantic U.S.**
  - **VISCERAL LEISHMANIASIS: Spain, Mediterranean Basin**
  - **MALARIA: Tropics**
  - **BABESIA MICROTI: Northeast & Upper Midwest U.S.**
- **AND ALL THE "NORMAL" RISKS TO TRAVELERS**
  - **DIARRHEA**
  - **STDs**
  - **MDR-TB**
  - **BLOOD SUPPLY (need for TRANSFUSIONS), etc.…**
- **AVOID LIVE VACCINES: Yellow Fever, Oral typhoid, etc.**
- **DRUG INTERACTIONS →Transplant meds + travel related prophylactic agents**

TYPICAL PRESENTATIONS OF UNEXPECTED DONOR DERIVED INFECTIONS

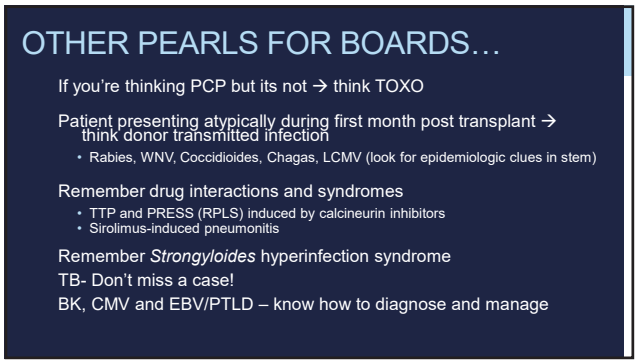
- Most present in the first 3 months post transplant
- Look for epidemiologic clues for potential donor exposure in the stem (e.g. donor from Latin America)

PATHOGEN	PRESENTATION
LYMPHOCYTIC CHORIOMENINGITIS VIRUS	ENCEPHALITIS
RABIES	ENCEPHALITIS
TOXOPLASMOSIS	DIFFUSE PNEUMONIA MYOCARDITIS RETINITIS ENCEPHALITIS
WEST NILE VIRUS	MENINGITIS ENCEPHALITIS POLIOMYELITIS-LIKE FLACCID PARALYSIS
CHAGAS' DISEASE	FEVER MYOCARDITIS
ACANTHAMOEBA	SKIN LESION ENCEPHALITIS
BALAMUTHIA MANDRILLARIS	ENCEPHALITIS
VISCERAL LEISHMANIASIS	PANCYTOPENIA HEPATOSPLENOMEGALY
MALARIA	FEVER

KEY DRUG TOXICITIES / SYNDROMES

- TTP / PRESS (RPLS) induced by calcineurin inhibitors
- Sirolimus-induced pneumonitis
  - Progressive interstitial pneumonitis (22% in one study)
  - Risk factors: late switch to sirolimus & impaired renal function
  - Symptoms: dyspnea, dry cough, fever, and fatigue
    - Radiographic & bronchoalveolar lavage consistent with bronchiolitis obliterans organizing pneumonia & lymphocytic alveolitis
  - Recovery with sirolimus withdrawal

Euvrard S et al. N Engl J Med. 2012;367(4):329. Champion L et al. Ann Intern Med 2006;144:505. Weiner SM et al. Nephrol Dial Transplant. 2007;22(12):3631.



44

Pneumonia: Some Cases That Could Be on the Exam

Dr. Paul G. Auwaerter

44 – Pneumonia: Some Cases that could be on the Exam

Speaker: Paul Auwaerter, MD

2020 INFECTIOUS DISEASE BOARD REVIEW

Pneumonia: Some Cases that Could be on the Exam

Paul G. Auwaerter, MD
Sherrilyn and Ken Fisher Professor of Medicine
Clinical Director, Division of Infectious Diseases
Johns Hopkins University School of Medicine

Case 1

2020 INFECTIOUS DISEASE BOARD REVIEW **PREVIEW QUESTION**

- 55 M 6d fever, malaise, severe headache, dry cough, myalgia
- PMH: HTN
- Meds: Lisinopril/HCT
- SH: Married, suburban Maryland,
  - Works in long-term care facility
  - Visited pet shop 10d earlier
    - Parakeets, cockatiels
  - Confided infidelity in last month

Exam: ill-toxic, 40ºC P88
BP100/70 RR18 O2 97% RA
Lungs: clear
Neck: supple
Cor: no murmurs
Skin: no rashes
LP: pending
Labs:
WBC 5200, 26% B
Sputum: 1+ PMNs, no organisms

Disclosures of Financial Relationships with Relevant Commercial Interests

- **Scientific Advisory Board – DiaSorin, Adaptive BioTherapeutics**
- **Grantee – MicroBplex, NIH/SBIR (Lyme disease diagnostics)**
- **Equity – JNJ**

Question 1

2020 INFECTIOUS DISEASE BOARD REVIEW **PREVIEW QUESTION**

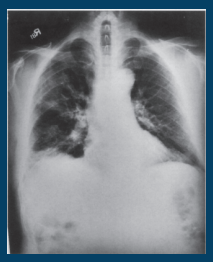
Which antibiotic will lead to the most rapid improvement?

A. Ceftriaxone

B. Gentamicin

C. Doxycycline

D. Trimethoprim/sulfamethoxazole



Community-acquired Pneumonia:

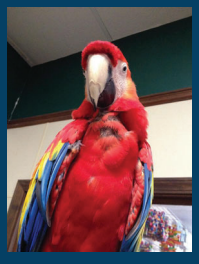
Pathogen[1a]	Cases (%)
Streptococcus pneumoniae	20-60
Haemophilus influenzae	3-10
Staphylococcus aureus	3-5
Gram-negative bacilli	3-10
Legionella species	2-8
Mycoplasma pneumoniae	1-6
Chlamydia pneumoniae	4-6
Viruses	2-15
Aspiration	6-10
Others	3-5

- Pathogen identification
  - 39-76% historically[1]
    - Culture
    - Serology
    - Antigen detection
    - Molecular methods
  - EPIC study (2015)[2]
    - Pathogen only detected in 38%
      - Viral 23% (rhinovirus 9%)
      - Bacterial 11%

[1]Mandell, et al. CID 2003;37(11)1405
[2]Jain, et al. NEJM 2015;373:835

Chlamydia psittaci

- AKA parrot fever, psittacosis, ornithosis
- Underdiagnosed
  - 1.03 % in studies of CAP
  - < 50 cases/yr in US
  - Most "atypical pneumonia"
- Risks: exposure to birds
  - May be healthy or ill
  - Pets, poultry, pigeons
  - Native birds
    - Lawn mowing



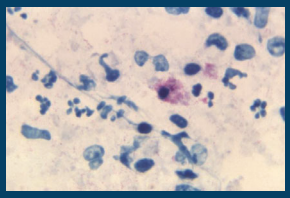
Hogerwerf L et al, Epidemiol Infect. 2017;145(15):3096

44 – Pneumonia: Some Cases that could be on the Exam

Speaker: Paul Auwaerter, MD

Microbiology

- Two states:
  - Extracellular: infectious, elementary body
    - Bird feces or respiratory secretions → aerosol → human
    - Direct contact
  - Intracellular: replicative



May appears as intracellular Gram negatives

Case 2

2020 INFECTIOUS DISEASE BOARD REVIEW — PREVIEW QUESTION

69M c/o fever and dyspnea x 3 days
-Dry cough, pleuritic chest pain
-In nursing facility for L foot, C1-2, L4-5 osteomyelitis + MRSA bacteremia
Vancomycin (5d, rash) → Ceftaroline (4d, hives) → Daptomycin (11d)

PMH: Diabetes, HTN, COPD, R BKA, bedbound
SH: 40 PPD smoker, now vaping, Baltimore MD resident, hx substance use
Meds: methadone, insulin, nifedipine, Lisinopril/HCT, inhalers

PE: T101.4°F, P 106, RR 24, 02 sat 90% on 6L O_2
No lymphadenopathy, no JVD
Lungs: poor air movement, basilar crackles bilaterally
Cor: no murmur
Ext: no edema

6.0 — 9.5 — 300K 54%^{N}, 12%^{L}, 24%^{E}

ESR 150 mm/hr NI LFTs
CRP 15 mg/dL (0.0-0.5)

Chlamydia psittaci

- Range of illness:
  - Mild, bronchitic to severe/ARDS
  - Clue: temperature/pulse dissociation
- Diagnosis:
  - Molecular/PCR, sputum (best)
  - Acute/convalescent serology (microimmunofluorescence, MIF)
  - Culture: tissue culture (difficult)
- Treatment:
  - Preferred: doxycycline
  - Alternatives:
    - Macrolides
    - Fluoroquinolones

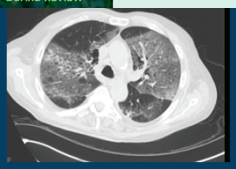
Wolff BJ et al. Diagn Microbiol Infect Dis 2018;90(3):167-170
Hogerwerf L et al. Epidemiol Infect 2017;145(15):3096-3105

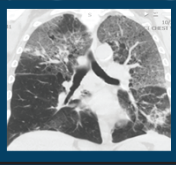
Question 2

2020 INFECTIOUS DISEASE BOARD REVIEW — PREVIEW QUESTION

The pneumonia is most caused by

A. Vaping-associated pulmonary injury (VAPI)
B. Allergic bronchopulmonary aspergillosis
C. Ceftaroline
D. Daptomycin
E. Strongyloides





Case courtesy of L. Leigh Smith, M.D.

Helpful clues for "Atypical" CAP

Clinical feature	C. psittaci	C. pneumoniae	M. pneumoniae	L. pneumophila
Cough	++	+	++	+
Sputum	-	+	++	+++
Sore throat	-	++	-	-
Headache	+++	+	-	+
Confusion	+	-	-	++
CXR change	Minimal	Minimal	More than sx	Multifocal
Low Na^+	-	-	-	++
Doxycycline response	Rapid, < 48h	Prompt	Prompt	Slower

Adapted from Stewardson, Grayson. Inf Dis Clin N Amer 2010; 24(1):7

Acute eosinophilic PNA due to daptomycin

May present like atypical pneumonia or interstitial fibrosis

- Acute
  - Older men (40% > 60 yrs)
  - Daptomycin duration median 19d [2-54d]
  - Fever, dyspnea and cough
  - Hypoxemia
    - Pulse oxygen saturation [SpO_2] <90% on RA or PaO_2 <60 mmHg
  - Diffuse pulmonary opacities
- Need to exclude alternative causes
  - e.g., fungal or parasitic PNA
  - Improvement with drug cessation
- Hypersensitivity reaction (early)
  - Acute & subacute
  - Ground glass findings +/- effusions
  - Eosinophilia (peripheral or BAL)
    - BAL cell count > 25% eosinophils
- Later presentations
  - Interstitial pneumonitis
  - Bronchiolitis obliterans
  - Mixed ground glass, fibrosis, consolidation

Hirai et al. J Infect Chemother 2017;23(4):245
Lai et al. CID 2010;5(1):737

44 – Pneumonia: Some Cases that could be on the Exam

Speaker: Paul Auwaerter, MD

Drug-induced pneumonitis/pneumonia

- Treatment:
  - Discontinue = resolution
  - Corticosteroids: no proven role, but often used
    - If significant hypoxemia: prednisone 40-60 mg PO daily with taper x 14d.
- Other drugs: incomplete list
  - Antibiotics:
    - INH
    - Daptomycin
    - Nitrofurantoin
    - Sulfonamide abx
    - Minocycline
    - Ampicillin
  - CV:
    - Amiodarone
    - Flecainide
  - Chemotherapy:
    - Bleomycin
  - Others
    - NSAIDs
    - Phenytoin

Legionella pneumonia

- Risks factors (and who to test)
  - Travel beyond home (e.g., hotel, hospital) last two weeks
    - May cause HAP
  - Severe pneumonia/ICU
  - Proximity to known outbreaks
  - Age > 50 yrs
  - Smoking
  - Comorbidities: diabetes, liver/renal dz, COPD, immunosuppressed
- Acquisition:
  - Aerosolization
  - Drinking water (aspiration)

1976 Bellvue Stratford Hotel, Philadelphia

Case 3

67M COPD, alcoholic liver disease, diabetes, pancreatic CA

POD #5 s/p Whipple developed nausea, vomiting, fever, cough, confusion and hypoxemia → respiratory failure

Labs
WBC 18,000 15%B, 60%P
Glucose 310 Na 128 sCr 1.7

Intubation → ICU, respiratory sample:
Heavy PMNs, no organisms on Gram stain

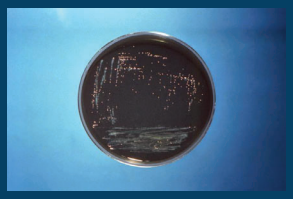
Therapy:
Vancomycin and piperacillin/tazobactam x 3 d

No improvement, febrile, respiratory culture negative
ID consultation called

Legionella

- Environmental/water pathogen
  - Ponds, lakes
  - Water systems (hot > cold), chillers, misters, A/C
  - May be nosocomial pathogen
- Legionellosis
  - Legionnaires' disease (99%)
    - Pneumonia
    - Most typical of the atypicals
  - Pontiac Fever (1%)
    - Febrile, flu-like illness
- Microbiology: 60 species
  - *L. pneumophila* serotype 1 (most common)

Legionella culture

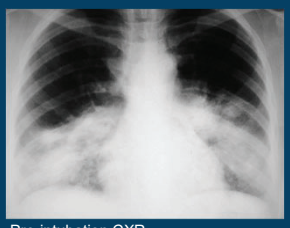


Culture media: BCYE agar
Small, pearly white colonies

Question 3

You are aware of a recent *Legionella mcdadei* outbreak in the hospital. Which test below, would most help you securing a diagnosis of *L. mcdadei* pneumonia?

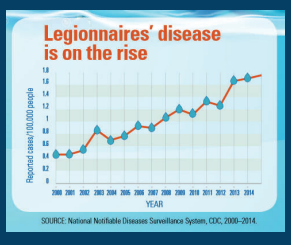
A. Legionella urinary antigen
B. Legionella culture of respiratory secretions
C. Legionella PCR, respiratory
D. Legionella direct fluorescent antigen (DFA) stain of respiratory sample
E. Paired Legionella acute/convalescent serology



Pre-intubation CXR

Outbreaks: Known and Unknown Sources

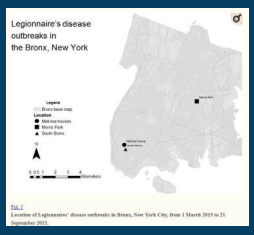
- 5,000 cases/year U.S.
  - 20 Outbreaks
- 4X > cases since 2000
- 90% of CDC investigations caused by insufficient water system management
- WHERE?
  - Hotels
  - Long-term Care Facilities
  - Hospitals



44 – Pneumonia: Some Cases that could be on the Exam

Speaker: Paul Auwaerter, MD

Outbreaks: Known and Unknown Sources



MacIntyre CR, et al Emerg Microbes Infect 2018;7:36

Case 4

23M cough, malaise, dyspnea, fever x 1 wk, just returning from overseas

PMH: negative, no asthma

Meds: atovoquone/proguanil

ROS: no diarrhea, had rash on feet/legs post marathon now resolved

SH: Laguna Phuket (Thailand) triathlon 3 wks earlier

Non-smoker

PE: Appears ill, BP 98/70, P 100
T 38.5ºC
No lymphadenopathy
Bronchial breath sounds lower fields, occasional wheezing
No murmur
No hepatosplenomegaly, abdominal tenderness
No rash

Legionella diagnostics

Test	Sensitivity (%)	Specificity (%)	Notes
Culture	20-80	100	Slow, technically difficult, BCYE agar Detects all species
Urinary Ag	70-100	95-100	Only *L. pneumophila* serogroup 1, rapid, may cross-react occasionally w/ other serogroups
PCR	Unknown	Unknown	Not FDA approved, home-brew tests, some are specific for *L. pneumophila*
DFA	25-75	≥ 95	Technically demanding
Paired serology	80-90	> 99	Not helpful for acute care, 5-10% population with (+) titers

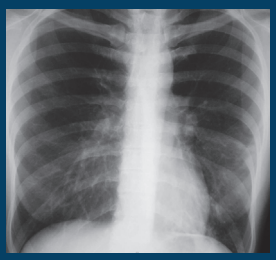
Source: CDC, cdc.gov/legionella/clinicians/diagnostic-testing (accessed 7/16/2019)

Studies

WBC 18,000
63N, 13L, 24E

CXR: mild bilateral patchy infiltrates

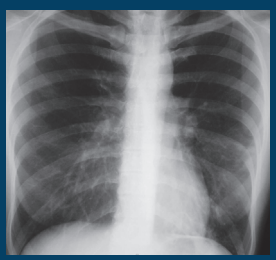
Blood smear: no parasites



	Legionnaires' disease	Pontiac fever
Clinical	Pneumonia	Flu-like symptoms
CXR	Consolidation, multifocal	No infiltrates
Epidemiology	Sporadic & epidemic	Epidemic
Onset after exposure	2-10 days	24-48 hrs
Attack rate	< 5%	> 90% (including healthy)
Diagnosis	Sputa: Culture Molecular tests DFA Urine antigen	No recovery of organism by culture Acute/convalescent serology Urine antigen, up to 50% in some reports
Mortality	10-30%	0 %

Which of the following is the most likely explanation?

A. Allergic bronchopulmonary aspergillosis
B. Hookworm infection
C. Malaria
D. Tropical pulmonary eosinophilia
E. Drug reaction



44 – Pneumonia: Some Cases that could be on the Exam

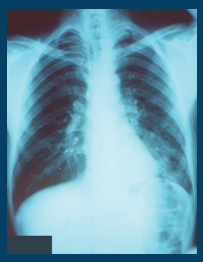
Speaker: Paul Auwaerter, MD

Löffler's syndrome

- Fever, malaise
- Respiratory symptoms: none—mild—moderate
- Migratory pulmonary infiltrates
- Peripheral eosinophilia
- Migration of parasites
- Dx:
  - Larvae in respiratory specimen
  - Stool O & P
- Treatment
  - Anti-helminthics
  - Corticosteroids
  - May spontaneously resolve

Case 5:

- 18F c/o fever, dry hacking cough, malaise x 3d
- Allergy: erythromycin (N/V)
- Appears well, T38ºC, RR 16, P 80, BP 110/70
  - Oropharynx: normal
  - TMs: normal
  - Chest: some crackles left lower lobe



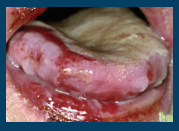
Acute eosinophilic pneumonia

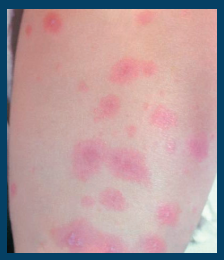
- Features
  - Fever, cough
  - Hypoxemia
  - Diffuse, bilateral infiltrates
  - Eosinophils
    - Peripheral
    - BAL (> 10%)
    - Lung biopsy
- Drug causes:
  - Antibiotics:
    - Daptomycin
      - 38 reported cases (2018)
        - Male, elderly
        - Renal failure
      - Black box warning
    - Nitrofurantoin
    - Minocycline
    - Ampicillin
    - Sulfonamides
- Others:
  - NSAIDs
  - Phenytoin
  - L-tryptophan

Uppal, Antimicrob Resist Infect Control 2016;5:55; Higashi, Intern Med 2018;57(2):253-258

Case 5

- Azithromycin prescribed
- Next day, full body rash and mucosal lesions develop





Acute or chronic eosinophilic pneumonia

- Helminthic
  - Migration (Loffler's)
    - Ascaris
    - Hooksworms
    - Strongyloides
  - Lung invasion
    - Paragonimiasis
- Tropical Pulmonary Eosinophilia
  - Wuchereria bancrofti
  - Brugia malayi
- Idiopathic hypereosinophilia
- Acute eosinophilic pneumonia
- Chronic eosinophilic pneumonia
- Allergic bronchopulmonary aspergillosis (ABPA)

Case 5

What is the most likely etiology?

A. Mycoplasma pneumoniae
B. Enterovirus D68
C. Measles
D. Lyme disease
E. Drug reaction (azithromycin)

44 – Pneumonia: Some Cases that could be on the Exam

Speaker: Paul Auwaerter, MD

Mycoplasma pneumoniae

- "Walking pneumonia"
  - CXR: appears worse than patient
- < 10% may have extra-pulmonary manifestations
  - Stevens-Johnson syndrome (SJS), E. multiforme
    - Most common infectious cause (children/adolescents)
    - Male > female
  - Hemolytic anemia
  - Hepatitis
  - CNS: encephalitis, meningitis

Case 6

31F fever, cough, myalgia, headache, dyspnea over 1 week ago

- No help w/ azithromycin x 3d
- 18 mos daughter, recent bronchitis

PMH: not significant

SH: ½ ppd smoker

PE: ill

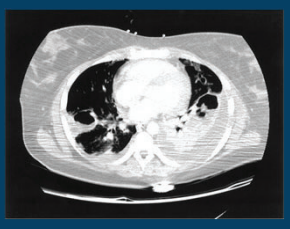
T38.3, RR 35, BP 125/70, P 128

Coarse breath sounds, rales bilateral and decreased L base

Mycoplasma pneumoniae

Finding/method	Pro	Con	Notes
Bullous myringitis		Description w/ experimental infection	Urban legend that is wrong or if true, rare
Molecular	High sensitivity & specificity	Limited FDA approvals, Expensive platforms needed	New gold standard In house assays not standardized
Serology	Available commercially	Non-specific Acute/convalescent	False +'s and –'s Not timely
Culture	100% specific Antibiotic susceptibilities	Poor sensitivity Time consuming	Only reference labs Special transport media Difficult to perform
Cold agglutinin titers	Occur in 50-70%	Non-specific	Association w/ hemolysis

Case 6



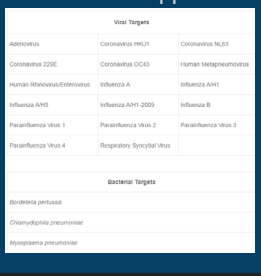
Data:
WBC: 11, 300 38%P, 48%B

RA ABG: 7.37/35/58

Sputum Gram stain: > 25 WBC/hpf
Some Gram (+) cocci
Sputum Cx: pending

Respiratory Film Array:
Influenza (+)
RSV (+)

Respiratory Molecular Targets, a current FDA-approved example



Film Array
Multiplex, 20 pathogens
Results in 1 hr

Viruses and some bacteria
- Sensitivity: 87, 98-100%
- Specificity: 89, 99-100%

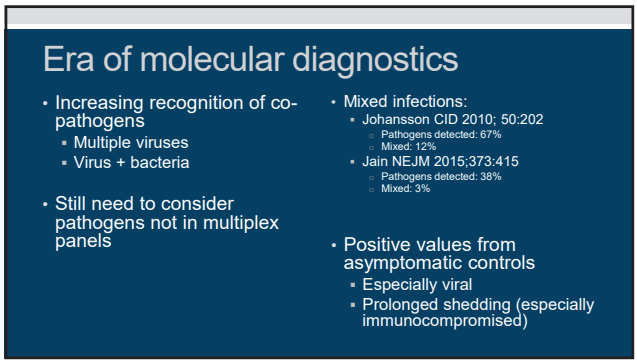
Case 6

Pt placed on oseltamivir, ceftriaxone and azithromycin. Which of the below should be recommended by the ID consultant?

A. Disregard RSV as likely false positive
B. Institute ribavirin PO for RSV
C. Continue ceftriaxone, but replace azithromycin with moxifloxacin
D. Change from oseltamivir to peramivir injection
E. Attempt aspiration of left pleural fluid, start linezolid

44 – Pneumonia: Some Cases that could be on the Exam

Speaker: Paul Auwaerter, MD



45

Board Review Session 4

Drs. Auwaerter (Moderator), Alexander, Boucher, Marr, Mitre, and Winthrop

45 – Board Review Session 4

Drs. Auwaerter (Moderator), Alexander, Boucher, Marr, Mitre, and Winthrop

2020 INFECTIOUS DISEASE BOARD REVIEW

Board Review Session 4

Moderator: Paul Auwaerter, MD
Faculty: Drs. Alexander, Boucher, Marr, Mitre, and Winthrop

2020 INFECTIOUS DISEASE BOARD REVIEW

Answer Keys with Rationales

The answer key, including rationales, will be posted tomorrow to the "Board Review Answer Keys" section on the online materials site.

#1

A 55-year-old male is referred to you because of a three day history of spiking fevers, myalgias, dysuria, and vague perineal pain. He has some urinary dribbling which is new.

His prostate is tender on palpation. A urinalysis reveals many white blood cells and gram negative rods. The urine culture grows E. coli (CFU >105/ml) which is sensitive to multiple antibiotics including ciprofloxacin.

CBC reveals a white blood count of 15,000 cells/uL with 90% neutrophils.

He is treated with ciprofloxacin for ten days which he took as prescribed, stopping a week ago. He initially resolved all symptoms, but now has myalgias again as well as more deep pelvic pain and a return of his fever, which is 38-39C.

#1

Assuming that the prostate is the source of the fever and pelvic pain, the best management option would be:

A) Perform prostatic massage in order to obtain a quantitative culture of urine collected in initial post-massage, midstream and remaining urine and treat based on result

B) Repeat a urinalysis and culture and treat based on results; no other evaluation is necessary

C) Retreat with ciprofloxacin

D) Order trans rectal ultrasound

E) Order trans rectal biopsy

#2

A 19 year old college-sophomore develops a sudden fever to 103°F, chills, malaise, hoarseness, painful swallowing, neck soreness and swelling over two days.

She is evaluated at a local emergency department. She had a WBC 15,300 with 88% PMNs, negative rapid Group A strep screen and negative rapid influenza test (RIDT). She is discharged with an amoxicillin prescription for pharyngitis.

Two days later she is evaluated by otolaryngology because of persistent symptoms. She is thought to have a ranula (mucous filled sublingual cyst) as an explanation. Her primary care physician prescribes levofloxacin in addition to the amoxicillin.

The physician arranges for an infectious diseases evaluation, when she is unimproved 6d into her illness.

#2

Her symptoms have continued, but she describes some shortness of breath and chest pain but no cough. On exam, temperature 101.7°F, pulse 113, BP 94/70, respirations 22 and mildly labored. She appears ill and is slightly anxious.

Her oropharynx has no lesions or exudates, but the tongue appears slightly enlarged.
Her neck has bilateral anterior swelling with tenderness with erythema (see photo).

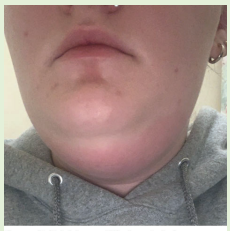


Photo provided by P.G. Auwaerter MD (patient authorized)

#2

Which of the following answers reflect what should be should be pursued next?

A) Monospot test for Mononucleosis

B) Chest CT with angiography

C) Neck and chest CT

D) Lateral neck film

E) TSH (Thyroid Stimulating Hormone)

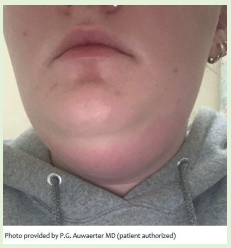


Photo provided by P.G. Auwaerter MD (patient authorized)

#3

A 35-year-old woman is seen for 5 weeks of progressive cough paroxysms, pleuritic pains, chest tightness and dyspnea.
Her primary care provider had tried albuterol as well as a course of amoxicillin/clavulanate with no benefit.

Her past medical history includes early menopause with the institution of estrogen replacement, recurrent urinary tract infections, insomnia and depression.

Her current medications include Premarin, vaginal estrogen, venlafaxine and nitrofurantoin and have been unchanged for 3 months.

Physical examination: largely unremarkable. On the pulmonary exam, she has no percussive dullness but does have fine bibasilar crackles bilaterally

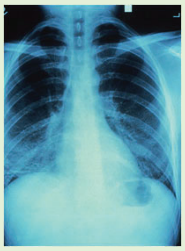
#3

Her laboratories are remarkable for a white blood cell count of 11,800 cells/mL with 63% neutrophils, 36% lymphocytes and 1% eosinophils.

Her chemistry profile is normal.

The urinalysis is acellular.

An erythrocyte sedimentation rate is 48 mm/h.



#3

Which treatment decision will most likely lead to the resolution of her symptoms?

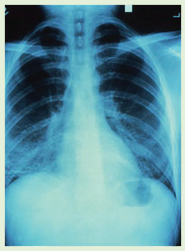
A) Initiate Azithromycin x 5 days

B) Start INH, RIF, PZA, ETB

C) Start Ceftaroline x 7 days

D) Discontinue nitrofurantoin

E) Prednisone 60 mg daily with taper



#4

An 88-year-old man is evaluated in referral for a history of prostate cancer and recurrent urinary tract infections who has severe groin and suprapubic pain, limiting his walking and physical activities.

His history is significant for prostate cancer diagnosed 12 years earlier treated with brachytherapy. He had a transurethral resection of the prostate 6 months earlier for urinary retention with relief. He has had several urinary tract infections, including an ESBL-E. coli and K. pneumoniae over the past years that resolved with treatment. His last antibiotic received was four months ago, ten days of ciprofloxacin.

He otherwise has only hypertension. He is a widower and lives alone with a pet dog in Northern Virginia. He has no known history of TB or potential contacts.

#4

Over the last 3 months, he has had progressive pain with walking or standing. His family has noted that he now walks with a waddle and requires a cane for stability. He has had no recent dysuria or unusual frequency.

A CT scan suggested abnormalities at the symphysis pubis, and a subsequent MRI showed extensive bone marrow edema in this region with some bony erosions symmetrically at the symphysis, along with edema in surrounding abductor muscles.

He was hospitalized at an outpatient facility. 2 fine needle aspirations of the affected area were negative for bacterial or fungal pathogens.

#4

Urinalysis was without pyuria, and urine culture was negative. Following the second aspiration and based on the imaging, that patient received six weeks of vancomycin and meropenem. The patient states it has had little impact on his pain syndrome.

Repeat MRI imaging is slightly worse, according to the radiologist. Erythrocyte sedimentation rates have continued to range between 45-60 mm/h (normal < 30 mm/h), and a C reactive protein remains elevated 1.5 mg/dL (normal 0.0-0.5 mL).

He now sees you one week after completing his outpatient parental antibiotic therapy (OPAT).

#4

Which course of action will likely lead to durable improvement for this patient?

A) Employing a course of NSAIDs or corticosteroids over six weeks

B) Arrange for an open biopsy of bone and tissue for bacterial, fungal and AFB cultures

C) Resume vancomycin and meropenem to complete a 12-week total course

D) Change to linezolid and ceftazidime/avibactam

E) Obtain a full-body triple-phase bone scan

#5

A 42-year-old male had a heart lung transplant 2 years prior and was doing well when he presented to his transplant team complaining of diffuse body aches, particularly in the extremities. He had no arthritis on examination and full range of motion in joints.

The patient was afebrile, and his routine CBC, chemistry profile, cardiac echo, and pulmonary function tests were unchanged except for a serum alkaline phosphatase which was for the first time twice the upper limit of normal. Other liver function tests were normal.

A bone scan showed numerous scattered areas of uptake. Routine films of the extremities showed patches of periosteal thickening and a few calcified excrescences.

#5

He had been followed for 18 months for pulmonary nodules which had been associated with an elevated serum galactomannan test.

He had been treated ever since the nodules were recognized 18 months previously with voriconazole.

He is receiving tacrolimus (Prograf) and mycophenylate mofetil (CellCept) plus trimethoprim-sulfamethoxazole prophylaxis for PCP, acyclovir for recurrent orolabial Herpes simplex and once daily multivitamins with vitamins A and D.

A repeat chest CT showed no change from the small nodules seen two months prior.

#5

The most likely cause of these joint manifestations is:

A) Drug interaction with Vitamin D

B) Drug interaction with Vitamin A

C) Voriconazole toxicity

D) Tacrolimus toxicity

E) Mycophenylate mofetil toxicity

#6

A 50-year-old woman underwent a successful renal transplant 7 years ago. She has had no complications, and is taking tacrolimus, prednisone and mycophenolate. There have been no changes to her regimen, and she has been doing well.

During the past two weeks, she has had intermittent diarrhea without fever. The biofire screen for stool pathogens was negative (22 target pathogens including Clostridioides difficile toxin a/b and an array of bacteria, viruses, and parasites).

She is referred to you for evaluation, with her primary care physician pointing out that she as two urine cultures that each show >100,000 E coli, with 5-10 wbc. Ultrasound shows no dilatation of renal pelvis or ureter in the transplanted kidney.

#6

The E. coli is sensitive to cephalosporins and quinolones.
The patient denies any urinary symptoms such as frequency or dysuria.

What would you recommend with regard to the urine findings?

A) No treatment

B) Ciprofloxacin for 3 days

C) Ciprofloxacin for 14 days

D) Ceftriaxone x 1 dose followed by 6 days of cephalexin

E) MR scan of pelvis before a therapeutic decision is made

#7

A 55-year old female has been waitlisted for a deceased donor kidney transplant for treatment of end-stage-renal disease secondary to diabetic nephropathy for the past 5 years.

She received a call stating that an appropriate deceased donor has been identified.

You are notified that the donor's RPR and TP-Ab are positive at the time of procurement.

You reviewed the donor history and it is unclear if the donor has ever been treated.

#7

Which is the most appropriate next step?

A) Turn down the organ offer

B) Accept the kidney and recommend no treatment for the donor and recipient

C) Accept the kidney and treat the recipient only if the recipient seroconverts both RPR and FTA during monitoring monthly for 12 months

D) Accept the kidney and treat the recipient with 2.4 million units of intramuscular benzathine penicillin G weekly for 3 weeks

#8

A 75-year-old male with chronic lymphocytic leukemia was started on ibrutinib monotherapy 20 weeks ago. He has been on trimethoprim-sulfamethoxazole and acyclovir prophylaxis since the initiation of ibrutinib therapy.

For the past week, he has had a cough non-productive of sputum. He was not febrile until today, when he noted a temperature of 38.5 C with slight worsening of his cough, and perhaps some pleuritic pain.

He lives in Annapolis, Maryland, has not traveled outside the East Coast and has no unusual exposures.

His CBC shows that his counts are stable: he is not neutropenic

#8

You are waiting for other lab tests to come back.
A chest CT scan shows a multiple 0.5-1.0 cm nodular lung lesions.
One lesion is probably cavitating.

The most likely cause of these lung lesions is

A) Pneumocystis resistant to TMP-SMX

B) Toxoplasma resistant to TMP-SMX

C) Candida auris

D) Aspergillus fumigatus

E) Nocardia brasiliensis

#9

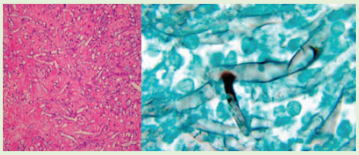
A 63-year-old male with diffuse large B-cell lymphoma underwent CD-19 CAR-T cell therapy for treatment of underlying lymphoma.

His post-transplant course was complicated by development of grade 4 cytokine release syndrome (CRS) and neurotoxicity, requiring treatment with high dose corticosteroids (methylprednisolone 1 gram IV daily for 3 days), tocilizumab and anakinra.

On day 15 post CAR T-cell infusion, the patient was noted to have anisocoria and an MRI brain showed infarcts in both cerebral frontal lobes. He was noted to have absent brainstem reflexes and family decided to withdraw care and consented to an autopsy.

#9

A photomicrograph (H&E stained) of his brain biopsy obtained during autopsy is shown on the left: a methenamine silver stain is shown on the right.



#9

Which of the following would optimally be used to treat this infection?

A) Micafungin

B) Itraconazole

C) Ivermectin

D) Amphotericin B

E) Trimethoprim-sulfamethoxazole

#10

A 67-year-old male with multiple myeloma is status post autologous stem cell transplantation 9 months prior to presenting in the month of December with subacute onset of shortness of breath on exertion, which has progressively been worsening.

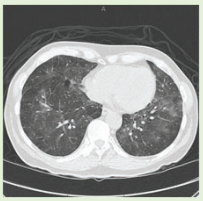
His post-transplant course has been uncomplicated, though the patient traveled to Arizona two months prior to admission (7 months post transplant) and he lives on a ranch in West Texas. His medication list is notable for acyclovir 800mg po BID and lenalidomide maintenance treatment.

He was seen in clinic, where he was noted to be febrile to 101F, which prompted a hospital admission for further workup.

#10

His WBC count is 2870 (34% eosinophils).
His oxygen saturation was 90% on room air.

- Respiratory viral panel on nasopharygeal wash and BAL: negative
- Serum 1,3-beta-D-glucan: <31 ng/ml
- Bronchoalveolar lavage galactomannan: negative
- Coccidioides serology (both immunodiffusion IgG and IgM and complement fixation): negative pre stem cell transplant and currently
- Strongyloides IgG: negative pre stem cell transplant and currentlyHis CT chest is shown:



#10

A bronchoscopy with bronchoalveolar lavage and transbronchial biopsy is performed.

Which of the following is the most likely finding on the biopsy?

A) Scattered interstitial eosinophils, organizing diffuse alveolar damage in alveolar parenchyma with negative AFB and GMS stains

B) Spherules 20 – 80 m in diameter on fungal staining (Gomori Methenamine Silver stain-GMS) consistent with coccidioidomycosis

C) Branching, septated hyphae

D) Filariform larvae of a nematode

E) Beaded, branching, gram positive rods, positive on modified acid fast stain

#11

You are consulted by the mother of teenage twins. She is very concerned because both of her 15-year-old daughters have had diarrhea for more than a week.

Their family physician said it was a virus, but the mother is concerned that they are not getting better and are missing school. Additionally, she reports that six of the girls' friends have "the same thing."

A quick investigation discloses that six days before their gastrointestinal illness began the twins had celebrated their 15th birthday along with ten invited friends at a recreational water park. At the park they all swam in a pool and sat in a water spray.

The mother, who has remained well, "didn't go near the water."

#11

No food was ingested at the park; some of the girls drank chocolate milk, others drank carbonated beverages.

The six of ten girls who became ill all have watery diarrhea; none have fever.

Three also report nausea and abdominal cramps.

All became ill 5-7 days after the birthday celebration.

#11

Which one of the following is most likely responsible for this outbreak of gastroenteritis?

A) Norovirus

B) Listeria

C) Giardia

D) Cryptosporidium

E) Rotavirus

2020 INFECTIOUS DISEASE BOARD REVIEW

PREVIEW QUESTION

#12

A 45-year-old man living on Eastern Long Island, New York had been ill for 5 days with fever (T102.7°F) and flu-like symptoms including headache. Two days ago, when he noticed an enlarging oval red rash of about 10 cm on the back of his right thigh. He was started on doxycycline for presumed Lyme disease.

Today, while fevers have not abated though the rash is fading, he became faint on standing at home, and he is brought to the Emergency Room where his blood pressure is normal but he is quite anemic.

His past medical history is only remarkable for a motorcycle accident 10 years earlier which he suffered splenic injury requiring splenectomy.

#12

On examination, he appears ill with pulse 100, blood pressure 98/70 and temperature recorded as 101°F. There is an ovoid homogenous rash over the posterior right thigh and a left upper quadrant abdominal scar.

Laboratories:

- WBC 3300 (50% PMNs, 35% lymphs, 15% monos)
- Hemoglobin 4.7gm/dL
- Platelet count 105,000
- Total bilirubin 3.8mg/dL
- ALT 110 U/L
- LDH 650 IU/mL

He develops adult respiratory distress syndrome (ARDS) and progressive renal failure and disseminated intravascular coagulation.

#12

Which of the following is the most likely cause of his progressive problems indicative of severe sepsis:

A) Borrelia burgdorferi

B) Francisella tularensis

C) Babesia microti

D) Anaplasma phagocytophilum

E) Rickettsia rickettsii

#13

A 48-year-old physician presents with complaints of severe fevers, abdominal pain, diarrhea, and back pain for 5 days. The patient returned from a 6-month medical mission to Sudan 2 weeks ago. The patient took doxycycline daily for malaria prophylaxis while there, but reports she would occasionally forget a dose.

She experienced frequent insect bites, especially when she took hikes along the banks of the White Nile River.

She was usually careful about what she ate, but about once a week would eat home cooked meals prepared by coworkers at the medicine clinic.

#13

On exam, her heart rate is 110 bpm, BP is 100/70, respiratory rate is 24/min, and temperature is 38.6 °C. Lung sounds are clear to auscultation bilaterally. Abdomen is soft with moderate tenderness in the right upper and right lower quadrants.

Abnormal laboratory values include a white blood cell count of 18,400/mm3 with 45% neutrophils, 24% lymphocytes, 6% monocytes, 24% eosinophils, and 1% basophils. AST is 158 units/L and ALT is 144 units/L.

Ova and parasite examinations on stool and urine samples, sent by the patient's primary physician three days ago, are negative.

#13

Which of the following organisms is most likely causing her illness?

A) Salmonella typhi

B) Plasmodium falciparum

C) Onchocerca volvulus

D) Schistosoma mansoni

E) Ancylostoma duodenale

#14

A 27-year-old male with sickle cell disease presents with a chest syndrome crisis: he has his typical fever, chest pain, and leukocytosis. He is cultured, and started on vancomycin and levofloxacin.

His initial chest radiograph shows bilateral infiltrates: an x-ray one week prior showed only some chronic scarring.

Sputum gram stain, acid fast stain, and culture show only modest amounts of normal flora. His CBC and Chem 12 show a leukocytosis, hemolytic anemia, and mild LFT abnormalities.

#14

Careful physical examination reveals no localizing physical findings: a tunneled double lumen subclavian line, in for 4 months, appears unremarkable.

After 96 hours, the laboratory reports that one blood culture is growing a non-branching beaded Gram positive bacillus that is acid fast stain positive.

Three additional blood cultures are drawn (one through each lumen of the subclavian line) and one peripherally: at 48 hours they are all reported to be positive for an acid fast non branching rod.

#14

Which of the following organisms would be most likely?

A) Nocardia asteroides

B) Mycobacterium mucogenicum

C) Rhodococcus equi

D) Legionella micdadei

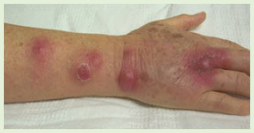
E) Mycobacterium tuberculosis

#15

This 55-year-old microscope repairman has an aquarium at home with tropical fish.

This very slightly tender nodule appeared on the dorsum of his hand a week ago and has grown slightly larger.

He otherwise feels well.



#15

Among the following techniques to culture the organism, which is the most important?

A) Addition of ferric citrate to mycobacterial agar

B) Use of fresh chocolate agar

C) Sabouraud's agar without antibiotics

D) Incubation on mycobacterial agar at 30°C

E) NNN medium

46

Ticks, Mites, Lice and the Diseases They Transmit

Dr. Paul G. Auwaerter

46 – Ticks, Mites, Lice and The Diseases They Transmit

Speaker: Paul G. Auwaerter, MD

2020 INFECTIOUS DISEASE BOARD REVIEW

Ticks, Mites, Lice, and The Diseases They Transmit

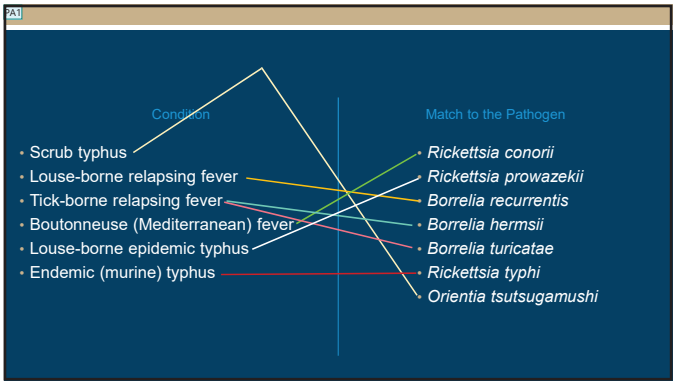
Paul G. Auwaerter, MD
Sherrilyn and Ken Fisher Professor of Medicine
Clinical Director, Division of Infectious Diseases
Johns Hopkins University School of Medicine

Disclosures of Financial Relationships with Relevant Commercial Interests

- Scientific Advisory Board – DiaSorin, Adaptive BioTherapeutics
- Grantee – MicroBplex, NIH/SBIR (Lyme disease diagnostics)
- Equity – JNJ

Why the board exam loves these infections
PLAY THE MATCH GAME

Condition	Pathogen
Scrub typhus	*Rickettsia conorii*
Louse-borne relapsing fever	*Rickettsia prowazekii*
Tick-borne relapsing fever	*Borrelia recurrentis*
Boutonneuse (Mediterranean) fever	*Borrelia hermsii*
Louse-borne epidemic typhus	*Borrelia turicatae*
Endemic (murine) typhus	*Rickettsia typhi*
	Orientia tsutsugamushi



Tick-borne Diseases of North America General Principles I

- Initial, early presentation non-specific:
  - "Flu-like illness" (e.g. fever, headache, myalgia)
- Diagnosis is clinical
  - Treatment is empiric—must start prior to return of diagnostic testing
- Characteristic rash/lesion +/- especially early
- Asymptomatic:symptomatic ratio is high

Ref: Diagnosis and Management of Tickborne Rickettsial Diseases: Rocky Mountain Spotted Fever and Other Spotted Fever Group Rickettsioses, Ehrlichioses, and Anaplasmosis — United States. A Practical Guide for Health Care and Public Health Professionals, MMWR May 13, 2016 / 65(2);1–44

Tick-borne Diseases of North America General Principles II

Seasonal but not always
Geography informs etiology but often changes over time
Lab tip-offs:
- Thrombocytopenia
- Leukocytosis or leukopenia
- Elevated LFTs

Doxycycline is preferred therapy for most
(all ages including children, e.g., Lyme, RMSF, ehrlichiosis…)
Prognosis is worse at age extremes < 10 and > 60 yrs
Convergence in tick vectors
Co-infection probably underestimated

The Major Tick-borne Diseases of North America

- Lyme disease
- Rocky Mountain spotted fever (RMSF)
- Ehrlichioses
- Anaplasmosis
- Relapsing fever (*Borrelia* spp.)
- Babesia

Other Tick-borne Diseases of North America

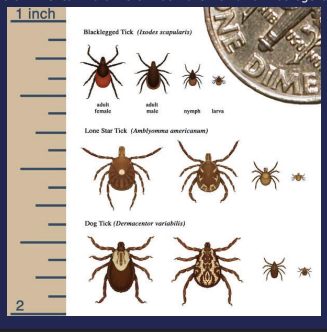
- Tick paralysis
- Southern tick associated rash illness (STARI)
- Viruses:
  - Powassan (Deer Tick Virus Lineage II, flavivirus)
  - Colorado tick fever (coltivirus)
  - Heartland virus (phlebovirus)
  - Bourbon virus (thogotovirus)
- Spotted Fever Group Rickettsia (partial)
  - R. parkeri
  - Rickettsia 364D aka R. philippii (Pacific Coast tick fever)
- Coxiella burnetii
- Tularemia
  - (< 10% tickborne)
- Other Borrelia
  - B. miyamotoi
  - B. mayonii

Ticks: arachnids, not insects

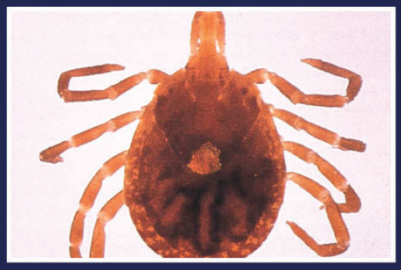
- **Number of species**
  - **896 species or subspecies**
- **Hematophagous arthropods**
  - **parasitize every class vertebrates ≅ entire world**
- **Two major families**
  - **Ixodidae, 702 species (hard ticks, attach & engorge)**
  - **Argasidae, 193 species (soft ticks, bite multiply & briefly)**
- **Four basic life stages**
  - **egg → larva → nymph → adult**
- **Vectors of human disease**
  - **#1 mosquitos**
  - **#2 ticks**

Parola, Raoult CID 2001; 32:897-928
Guglielmone, Zootaxa 2010;2528:1-28

Common North American Hard Ticks That Transmit Human Pathogens (Ixodidae) 1



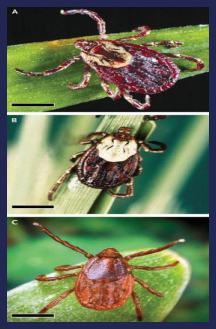
Common North American Hard Ticks (Ixodidae) 2



Amblyomma americanum (Lone star tick)

Common North American Hard Ticks (Ixodidae) 3

Dog ticks

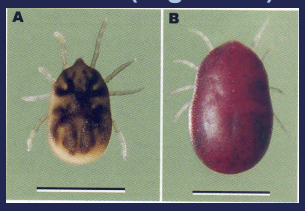


D. variabilis

D. andersoni

R. sanguineus

Ornithodoros Hermsi nymphal Tick
Soft tick (Argasidae)



A: shows the nymph before its infective blood meal (from California)

B: shows it after feeding

These are soft ticks that feed briefly at multiple spots

Scale bars = 2 mm

Question #1:

ID INFECTIOUS DISEASE BOARD REVIEW

PREVIEW QUESTION

62M living in an exurb of Phoenix, Arizona presents in early September with a three day history of fever, myalgia, headache and rash.

He works as a lineman for a utility company. He lives with his family in an older adobe home with dogs. He has beginnings of petechial features on the wrists and ankles.

Which of the following is the most likely diagnosis?

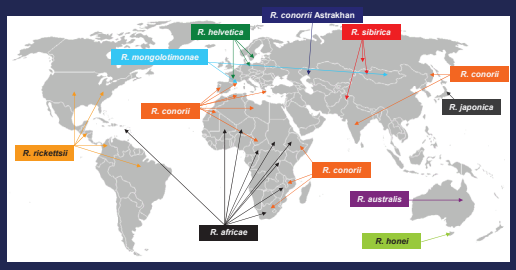
A. Human Monocytic Ehrlichiosis (HME)
B. Human Granulocytic Anaplasmosis (HGA)
C. Babesiosis
D. Rocky Mountain Spotted Fever (RMSF)
E. Tularemia

Rickettsial species: two major groups
(not a comprehensive pathogen list)

Spotted Fever Group (SFG)	Typhus Group

• RMSF (R. rickettsii)
• R. parkeri
• 364D
• Rickettsialpox (R. akari)
• R. conorii
• R. africae
• R. japonica
• R. australis
• …many more
	• Epidemic typhus
	  ◦ R. prowazekii
	  ▪ Body louse
	  ▪ Worldwide
	• Murine/endemic typhus
	  ◦ R. typhi
	  ▪ Rat flea
	  ▪ Temperate--tropical, usually

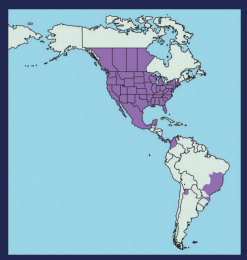
Tick-borne Rickettsia World Wide: many species



➢ 24 species causing human disease. List continues to grow.

Parola, Clin Microbiol Rev 2013;26(4):657-702

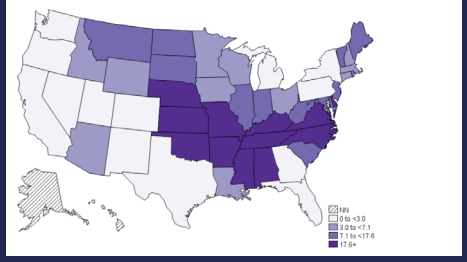
Approximate Geographic Distribution of R. rickettsii in the American Continents



Ongoing epidemic in Northern Mexico (2015-present)

Alavarez-Hernandez, Lancet ID 2017;17(6):e189-196
Tinoco-Gracia, EID 2018;24(9):1723-25

Epidemiology Figure 4 – Annual incidence (per million persons) of SFR in the United States, 2018



Source: CDC (accessed 7/10/20)
Δ category from RMSF to "spotted fever rickettsioses" 2010
Includes RMSF, *R. parkeri*, Pacific Coast tick fever, and Rickettsialpox.

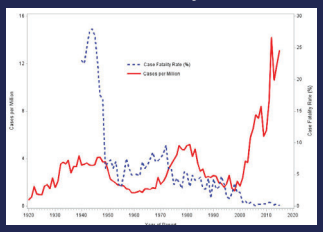
Rocky Mountain Spotted Fever Signs and Symptoms

Fever	99%
Headache	91%
Rash	88% (49% first 3 days)
Myalgia	83%
Nausea/vomiting	60%
Abdominal pain	52%
Conjunctivitis	30%
Stupor	26%
Edema	18%
Meningismus	18%
Coma	9%

Adapted from Helnick CG et al. *J Infect Dis* 150:480, 1984

RMSF in the United States

Incidence/Case Fatality 1920-2015



CDC, https://www.cdc.gov/rmsf/stats/index.html (accessed 7/12/20)

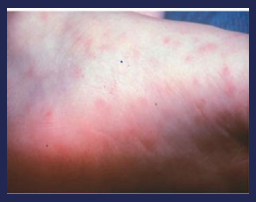
Risk Factors for Fatal RMSF ('99-'07)

- Native Americans
- Age extremes: 5-9, 70+
- Use of chloramphenicol (not doxycycline)
- Delay in diagnosis:
  - Treatment after 5 days illness
- Immunosuppression

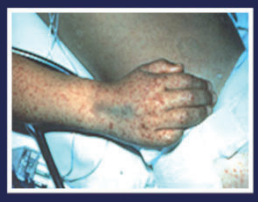
Am J Trop Med Hyg 2012;86:713-9

Rocky Mountain Spotted Fever

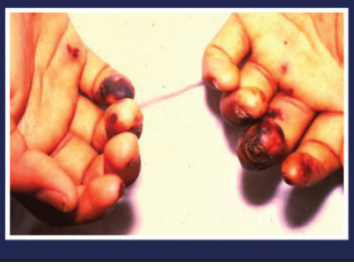
Early: rash absent or maculopapular
Starts on extremities



Later rash: petechial



Fulminant RMSF Gangrenous features (usually seen with multi-organ Failure)



RMSF diagnosis and treatment

- Start treatment upon suspicion: DON'T WAIT
- Labs: leukocytosis, thrombocytopenia, transaminitis
- Dx:
  - Preferred:
    - Skin bxp immunohistochemistry (DFA): timely diagnosis, ~70% sensitive.
    - PCR: *R. rickettsii*-specific
      - Skin bxp or swab (not routinely available, contact local health department → CDC)

RMSF diagnosis and treatment

- Other diagnostics
  - Culture: cell culture-based (BSL3 agent)
  - Serology: obtain acute/convalescent samples
    - Not usually of timely clinical value.
    - IFA : gold standard; cross reacts w/ other SFG species.
      - May be helpful in confusing cases.
    - Caveats: DON'T USE AS SCREENING TEST
      - False positives (especially IgM) common
        - Georgia blood donor study 11.1% IgG > 1:64, but of these only 28% fit case definition for Spotted Fever Group rickettsiosis [Straily A, JID 2020;221:1371]
        - Single IgG titer insufficient for reliable diagnosis
      - Background seroprevalence up to 20% in some regions
        - Asx infection likely common
      - Both RMSF IgM & IGG can persist
        - May mislead diagnosis, cause necessary treatment

OUTCOME: RMSF ACCORDING TO THE DAY DOXYCYCLINE STARTED

	% mortality
Day 1-5	0
Day 6	33
Day 7-9	27-50

Most lethal of Rickettsial infections: "Black measles"
In US mortality with treatment ~2-5% (higher with delays)

Clin Infect Dis 2015; 60:1659-66

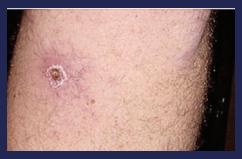
Question #2:

31M from Tidewater region of Virginia presents in June with three days of fever and rash.

Exam: unremarkable but T39.2°C, discrete black eschar on leg, scattered maculopapular rash elsewhere

Which of the following is the most likely etiologic agent?

A. Rickettsia rickettsii
B. Ehrlichia chaffeensis
C. Rickettsia parkeri
D. Anaplasma phagocytophilum
E. Rickettsia akari

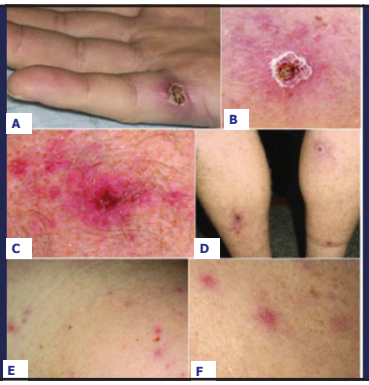


"American Boutonneuse Fever" Rickettsia parkeri

- Transmission: Lone Star or Gulf Coast ticks (*A. maculatum*)
  - Southeastern US, Gulf Coast
- AKA "Maculatum fever"
  - Also seen in Southern South America including Argentina, Uruguay, parts of Brazil
- Symptoms
  - Headache, myalgia
  - Skin
    - Faint salmon-colored rash
    - Single or multiple eschars
- Diagnosis
  - Spotted fever group serology,
  - Immunohistochemistry
  - PCR or culture from skin bxp or swab of eschar

MMWR Morb Mortal Wkly Rep 2016; 65(28): 718-9
Kelman, Infection 2018;46(4):559-563

Examples of R. parkeri-associated rashes



Source: CDC

Darker color: Gulf Coast tick range; lighter color: Lone star tick; Red dots: R. parkeri

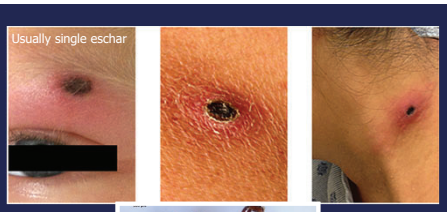
Pacific Coast Tick Fever

Rickettsia philipiii (Rickettsia 364D)
Described in 2008

Transmitted by Pacific Coast tick (*Dermacentor occidentalis*)

Northern Baja → Southern Oregon, Most cases

Common symptoms:
Eschar
Fever
Headache



Dermacentor occidentalis

Pladgett K
PLOS Neg Trop Dis 2016

Question 3

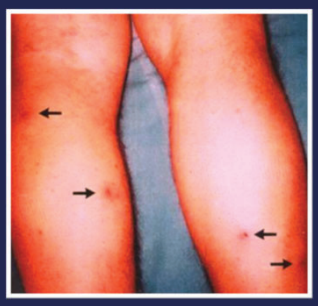
28F presents 8d after from a safari in Tanzania
Fever, mild headache, fatigue x 5d
Prior to travel, immunized against yellow fever
Took malaria prophylaxis: atovaquone/proguanil

Temperature is 38.6º, P76, R14, BP 116/70
Exam is unremarkable except for four punctuate eschars on the legs and bilateral inguinal lymph node enlargement

Lab:
Thick and thin blood smears (x 2) negative

Four Inoculation Eschars (Arrows)

R. africae

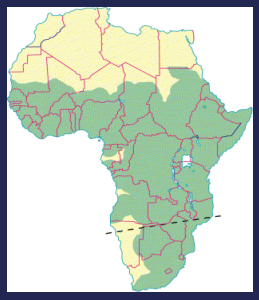


Question #3 Continued:

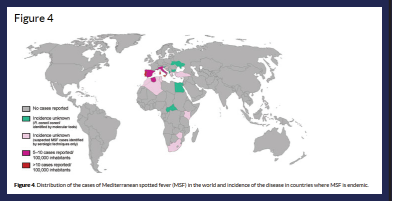
Which Of The Following Is The Most Likely Etiologic Agent?

A. Rickettsia conorii
B. Rickettsia africae
C. Rickettsia rickettsii
D. Anaplasma phagocytophilum
E. Ehrlichia chaffeensis

Range of R. africae
African Tick Bite Fever
(green)



Range of R. conorii
Mediterranean Spotted Fever



Rovery, EID 2008;14(9)

Clinical Characteristics of R. africae Infection

	%
fever ≥ 38.5º	88
neck muscle myalgia	81
inoculation eschars	95
multiple eschars	54
lymphadenopathy	43
rash (vesicular)	46(45)
death	0

Raoult D, et al. N Engl J Med 2001; 344:1504-10

African Tick Bite Fever

- Seroprevalence:
  - High in residents, R. africae, 30-56%
- Amblyomma ticks (cattle, ungulates)
  - Clusters of cases, multiple eschars
- Incubation period 6-7d
- Dx:
  - Biopsy or swab: PCR or MIFA
  - Serology
- Rx: doxycycline
- Complications unusual

Rickettsiosis and The Returning Traveler
Common Cause of Fever After Malaria, Typhoid

Most common
- R. africae (88%)

Others
- Murine typhus (~ 3%)
- Mediterranean spotted fever
- Scrub typhus

Occasional
- RMSF, epidemic typhus, N. Asian or Queensland tick typhus

Jensenius M, CID, 2004; 39: 1493-9
Inter J Infect Dis 2004; 8: 139

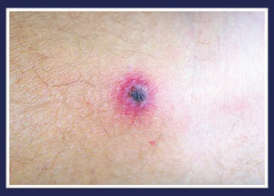
Question #4:

2020 INFECTIOUS DISEASE BOARD REVIEW — PREVIEW QUESTION

48M presents in October with fever and rash

Supervisor for apartment bldg in Queens, NY. Lives in cellar apt.

Exam: T 39^{0}C
brown-black 8mm eschar on RLE
~30 papulovesicular lesions on trunk



Question #4:

2020 INFECTIOUS DISEASE BOARD REVIEW — PREVIEW QUESTION

Which of the following Is the most likely etiologic agent?

A. R. rickettsii
B. R. parkeri
C. R. akari
D. R. conorii
E. Borrelia recurrentis

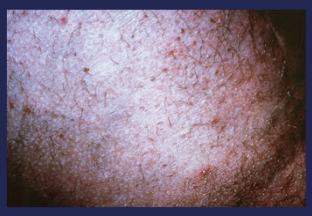
Rickettsialpox

Organism
- R. akari

Reservoir
- House mouse

Vector
- Mouse mites

Clinical
- Single eschar
- Rash: papulovesicular (20-40) or maculopapular
- Diagnosis
  - PCR swab eschar/vesicle
- Treatment: doxycycline



Maculopapular rash due to R. akari (CDC)

Partial DDx of Vesicular Rash

HSV
VZV
Pox viruses
Rickettsialpox
African tick bite fever
Queensland tick typhus

Scrub Typhus

"Scrub typhus is probably the single most prevalent, under-recognized, neglected, and severe but easily treatable disease in the world"

Paris DH et al. Am J Trop Med Hyg 2013;89:301-7

Scrub Typhus

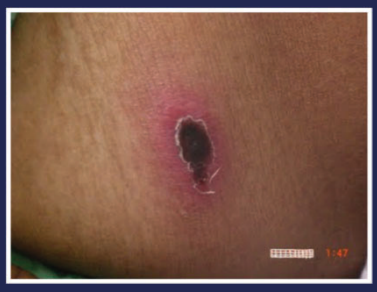
Organism
- O. tsutsugamushi (> 70 strains)

Vector
- Trombiculid mite (chiggers)

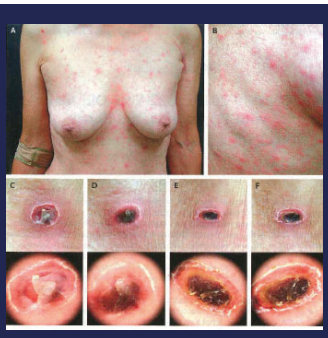
Geography
- Triangle from Japan to Eastern Australia to Southern Russia (rural)
  - Southern China an endemic focus (Yunnan province)

Clinical
- ~1 million cases/yr
- Severe (~ 35%) high fever
- Eschar, painful/draining lymph nodes, rash, delirium
  - Meningitis and meningoencephalitis with progressive infection
  - Development of multiorgan system failure
  - Case fatality rates up to 70%

Treatment
- Doxycycline x 7 days, relapses common
  - Alt: azithromycin (AAC 2014;58:1488-93)



Eschar is often associated with regional lymphadenitis



Question #5:

31M presents in January with 3d fever, HA, malaise, and myalgia.

Works as counselor at wilderness camp in Pennsylvania.

Flying squirrels common at camp including residing in the walls of his cabin.

Exam is notable only for fever (39.6^0; no rash), tachycardia (P110)

A diagnostic test for which of the following is most likely to be positive

A. Murine typhus
B. Epidemic typhus
C. RMSF
D. Tularemia
E. Relapsing fever

If I say “flying squirrel”
You say “epidemic typhus” or
“R. prowazekii”

MMWR 2003; 9 (10); Lancet Infec Dis 2008;8(7):417
- Rare infection in US (1976-2001, 39 cases)
- Generally East Coast
- None with louse exposure (the classic vector), so not “epidemic” but sporadic
- Most with flying squirrel exposure (Glaucomys volans)

Body louse: infestation = pediculosis
Pediculus humanus humanus

49

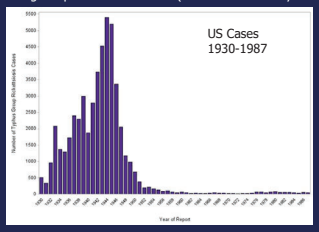
Typhus: Two Forms

	Epidemic	Endemic
Organism	***R. prowazekii***	***R. typhi***
Vector	Louse (body, head)	Flea (rat, cat)
Who	War refugees, crowded conditions/poor hygiene	Worldwide (U.S. Southern California, Texas, Hawaii)
Severity	Lethal	Mild
Treatment	Tetracycline Doxycycline Chloramphenicol	Tetracycline Doxycycline Chloramphenicol
Prevention	Boil clothes, delouse (lindane, malathion, permethrin, DDT)	Flea prevention (cats, domestic animals) Reduce rodent population
Recrudesce	Brill-Zinsser Disease (years-decades)	None known

Murine (or endemic) typhus

- In US, mostly seen in California, Hawaii, and Texas
- Infected flea feces →
  - Skin
- Most don't recall fleabite
- Usually non-specific febrile infection
  - Likely quite underdiagnosed
  - ~50% with rash
  - Occasional severe disease:
    - Meningoencephalitis
    - Pneumonitis
    - Shock

Historically, decline w/ better sanitation
No longer reportable since 1987 (Outbreak LA County 2018)



Dittrich, Lancet Global Health 2015;3:e104; Blanton Am J Trop Med 2017;96(1):53

CDC, accessed 7/10/2020 https://www.cdc.gov/typhus/murine/history.html

Murine (or endemic) typhus

- Dx:
  - Serology *R. typhi* (IFA)
    - Acute/convalescent, 4x rise
    - Cross-reacts with R. prowazekii and SFG rickettsia
  - PCR
    - Blood, often negative
- Treatment: No RCTs
  - Doxycycline (preferred)
    - Azithromycin: recent open label trial found azithromycin inferior to doxy
  - Alternatives: limited data
    - Chloramphenicol
    - Levofloxacin
    - Ciprofloxacin

Dittrich, Lancet Global Health 2015;3:e104; Blanton Am J Trop Med 2017;96(1):53

Newton, CID 2019;68(1 March):739

Other location-specific tick-borne Rickettsioses: partial

- Queensland tick typhus, *R. australis*
  - Australia-Queensland, New South Wales, Tasmania, coastal areas of eastern Victoria
- North Asian tick fever, *R. sibeirica*
  - North China; Mongolia; Asiatic areas of Russia
- Tick-borne lymphadenopathy (TIBOLA) or *Dermacentor*-borne necrosis erythema and lymphadenopathy (DEBONEL), ascribed to *R. slovaca* or *R. raoulti:*
  - Europe and Asia.
- Far-Eastern tick-borne rickettsiosis, *R. beilongjiangensis:*
  - Far East Russia and northern China.
- Oriental spotted fever, *R. japonica:*
  - Japan.
- Thai tick typhus, *R. bonei:*
  - Thailand, Australia, Tasmania, Flinders Island
- Australian spotted fever:
  - *R. marmionii*, Australia.

Question #6:

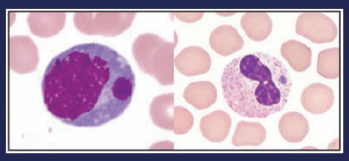
- 43F visited southern Missouri on vacation, returns 7d later with fever, headache and diffuse myalgia x 3d
- Physical examination: no findings
- Laboratory evaluation :
  - WBC: 2.1/mm³ (80% PMNs, 10% lymphocytes, 8% monocytes
  - Hemoglobin: 7.0 g/dL, hematocrit: 24%
  - Platelets: 105,000/mm³
  - AST: 364 U/L, ALT: 289 U/L
  - renal function: normal

Question #6

Which of the following is the most likely etiologic agent?

A. Anaplasma phagocytophilum
B. Ehrlichia chaffeensis
C. Borrelia hermsii
D. Babesia divergens
E. Borrelia burgdorferi

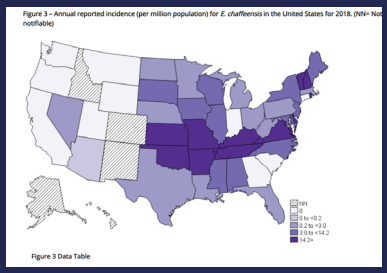
Morulae



HME HGA

Human Monocytic Ehrlichiosis (HME)

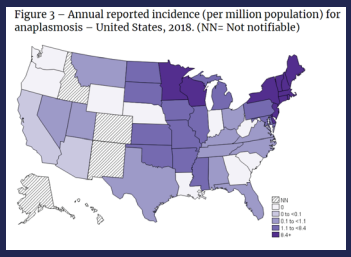
- E. chaffeensis
- Vector: Lone star tick
- Rash: ~30%
  - Maculopapular or petechial
- Labs: LFTs ↑, leukopenia, thrombocytopenia
- Mortality 2.7%
- Diagnosis
  - PCR
  - Morulae (2-38%)
  - Serology: acute/convalescent
  - Treatment: doxycycline



Source: CDC (accessed 7/10/20)

Human Granulocytic Anaplasmosis

- Anaplasma phagocytophilum
- Vector: Ixodes scapularis
- Rash rare
- Labs: LFTs, leukopenia, thrombocytopenia
- Mortality 0.3-0.7% (immunosuppressed ↑ 16 x)
- Diagnosis: same as HME (but morulae seen > 25%)



Geography: cross reactivity with HME accounts For Southern state representation

Source: CDC (accessed 7/10/20)

Other Ehrlichia (less common)

Organism	Vector	Geography	Risk	Mortality
E. ewingii (a canine ehrlichia)	Lone star	Most cases in Southcentral US	Immune compromised	Low
E. muris	*Ixodes persulcatus* *H. flava*	Europe, Russia, Japan, West Coast US	Older patients	Low
Ehrlichia muris eauclairensis (former Ehrlichia muris-like agent)	Deer tick	Wisconsin, Minnesota	Elderly, immune compromised	Low

Question #7:

- 48F c/o headache and fatigue worsening over 2 months since May tick bite
  - PMH: negative
  - SH: Married, works from home, has a dog, resides in suburban eastern PA
  - Treated with doxycycline for Lyme disease, no benefit
- Physical examination: afebrile, normal vital signs, no findings

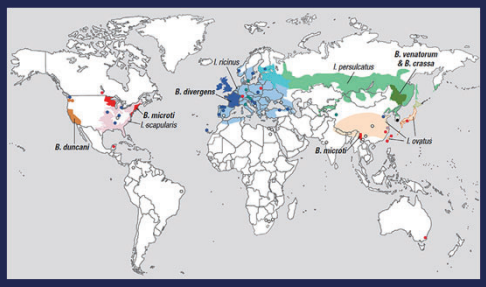
- Laboratory evaluation :
  - WBC: 7.0 cells/mm³ (70% PMNs, 18% lymphocytes, 12% monocytes
  - Hemoglobin: 11.8 g/dL, hematocrit: 35%
  - Platelets: 145,000/mm³
  - ALT: 22 U/L
  - Babesia IgG 1:128 (positive ≥ 1:64)
  - Blood smear: no parasites

Question #7:

- The best recommended next step:

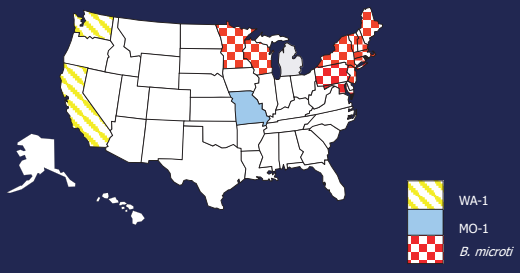
A. Check Babesia ducani serology
B. Check Babesia PCR
C. Repeat blood smear
D. Azithromycin + atovaquone for 7-10 days
E. None of the above

Babesia spp: Global



Vannier et al, NEJM 2012 366;2397

Babesiosis: USA



Babesia species

- Malaria-like parasite, resides in RBCs
- Geography: Babesia microti (most common in U.S.)
  - Nantucket, Martha's Vineyard, Long Island, Mid-Atlantic/New England, upper Midwest (similar to Lyme disease)
- > 1700 cases per year (2014 data)
  - Range of illness: "flu-like" to fatal
- Reservoir, vector
  - White-footed mouse;
  - Tick transmission: Ixodes scapularis
- Severe disease risks:
  - asplenic, HIV, chemotherapy, age >55, transplant
- Pearl: most common cause of blood transfusion-related infection in US

Severe Babesiosis

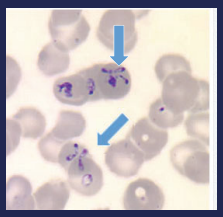
- n=34, Long Island NY
- Clinical manifestations
  - 41% Multi-organ failure
    - ARDS, DIC, CHF, ARF
  - 3 deaths
- Risk factors:
  - age >60
  - splenectomy,
  - immunosuppression (e.g., HIV, rituximab)
- Labs
  - increased LTFs,
  - thrombocytopenia
  - anemia (Hb<10),
  - parasitemia (>10%)

Mortality in immunocompromised > 20%

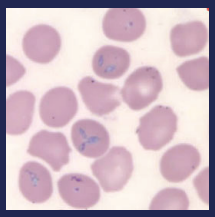
Hatcher JC, et al. Clin Infect Dis 2001; 32:1117-25

Babesiosis: Smear Diagnosis

Maltese Cross Tetrads



Species level identification only by PCR



Diagnosis of Babesiosis

- May observe hemolysis
- Wright-Giemsa stained thin blood smears
  - 1-3μ intraerythrocytic merozoites
    - Parasitemia range: 0-80% (may be confused with malaria)
    - Maltese cross: diagnostic (not seen w/ malaria)
    - Quick, if technical expertise available
- PCR: now widely available
  - Highly specific, but often send-out test = delay
- Serology (IFA)
  - High titer or acute/convalescent c/w active or recent infection
    - Low titer, negative smear: don't treat!

Treatment of Babesiosis

- Severe (new 2020 IDSA guidelines)
  - Atovaquone 750 mg PO q12h +Azithromycin 500 mg IV q24h
    - Previous: quinine/quinidine + clindamycin
  - Duration: 7-10d (may require longer for persistent parasitemia or immunosuppressed)
- Blood exchange transfusion: severe only
  - B. divergens, many require
  - B. microti, some cases
  - Limited evidence for benefit
- Mild-moderate severity
  - Azithromycin PO plus atovaquone PO

Vannier, et al. Infect Dis Clin N Am 2015;29(2):357-370

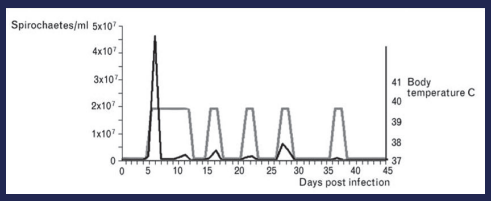
Tickborne Relapsing Fever US

Borrelia spp. (mainly B. hermsii)
- Ornithodorus soft ticks (brief, painless)

Epidemiology
- Western states; 14-45 cases/yr
- Rustic housing and rodents
- Elevation 1500-8000 feet

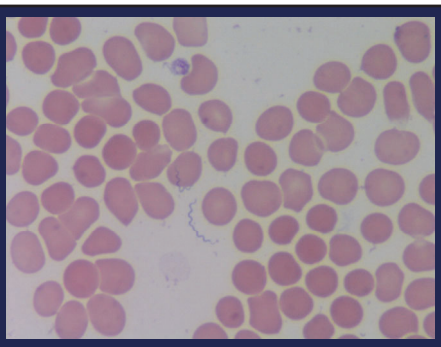
Clinical Manifestations
- Fever (relapsing), HA, myalgia, N/V
  - Can be severe : ARDS
- Laboratory
  - AKI, ↓ platelets,
- **Rx: PCN, doxycycline**
  - Jarisch Herxheimer reaction in 54%

MMWR 2012;61:174-6



Relapsing Fever: recurrent bacteremia (black line) correlates with sudden fever (grey).

After initial bacteremia, relapses are lower and fever duration somewhat shorter.



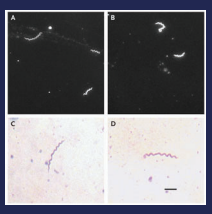
Diagnosis: observation of spirochetes in blood film, PCR

Louse-borne Relapsing Fever (LBRF)

Organism:	Borrelia recurrentis
Vector:	Human body louse
Geography:	Worldwide, but now seen in Sudan, Ethiopia, Somalia, Bolivia… (Refugee camps, famine, natural disasters)
Clinical Illness	More severe than TBRF, (incl. jaundice)
Therapy	Doxycycline

Newer Borrelia species: B. miyamotoi

- Unusual vector: Ixodes ticks (larvae?)
- Epidemiology = Lyme disease
- Appears similar to HGA
  - Meningoencephalitis in immunocompromised
  - ↓ wbc, ↓ plt, ↑ LFTs
- Diagnosis: blood smear (observing spirochetes), PCR, serology
- Treatment: similar to Lyme disease

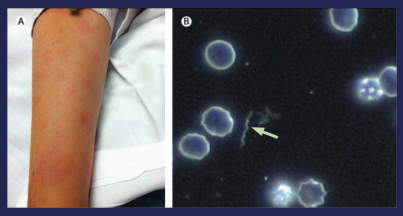


Spirochetes in CSF

Gugliotta, NEJM 2013

Telford, Clin Microbiol Infect 2015

Borrelia mayonii



5 of 6: acute febrile illness with rash (macular)
1 of 6: 1 months knee pain/swelling
To date: only see in in Minnesota and Wisconsin

Pritt et al. Lancet ID 2016;16(5):556

Cluster of Tick Paralysis Cases

- Four cases within 20 miles of each other
  - Ages 6, 58, 78, 86 years
- Ticks on neck or back
  - Usually dog ticks or Rocky Mt wood ticks
- Ascending motor paralysis without sensory loss
- Treatment: remove tick = cure
- Pathogenesis: neurotoxin in tick saliva

MMWR 2006; 55: 933-5

Question #8:

A 59 y.o. white male from Missouri presents with fever (39^0), headache, myalgia, anorexia, nausea, one week after removing an engorged tick from his groin. No travel.

Exam: unremarkable except ill appearing, no rash.
Lab: wbc 2300 plt 42,000 ALT 111

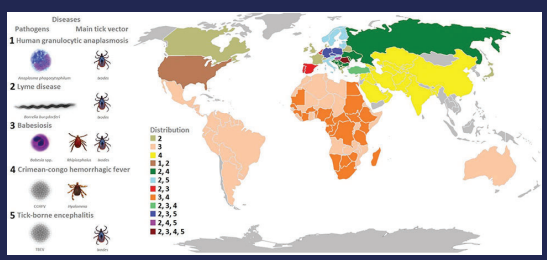
Suspect ehrlichiosis (but no morulae on blood smear)

Question #8:

After sending appropriate diagnostic tests the patient has not improved after three days of doxycycline. Which of the following is the most likely etiologic agent?

A. R. rickettsii
B. B. burgdorferi
C. R. parkeri
D. Heartland virus
E. Severe fever with thrombocytopenia syndrome virus

But wait: There's More (#4) and More (#5)



Front Cell Infect Microbiol, 2017;7:114

Tick-borne infections: some testable points

- Rash: RMSF rash appears after several days of fever and viral-like prodrome
  - Meningococcal rash is earlier
  - No bite site (tache noire)
  - Give doxycycline, even for kids
- Blood smear maybe helpful
  - Morulae: PMN = Anaplasma, Monocyte = Ehrlichia
  - Spirochete: relapsing fever Borrelia or B. miyamotoi
  - Erythrocyte inclusions: Babesia

46 – Ticks, Mites, Lice and The Diseases They Transmit

Speaker: Paul G. Auwaerter, MD

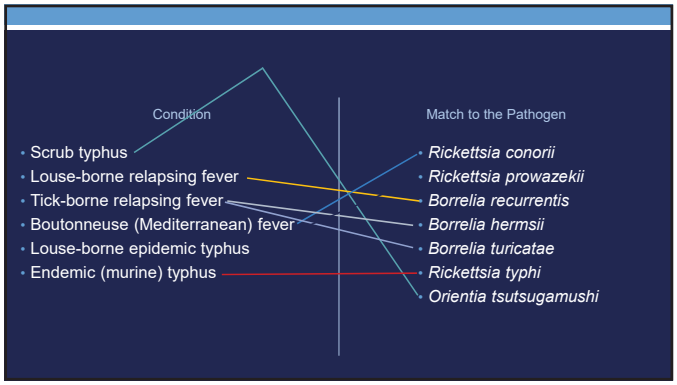
Tick-borne infections: some testable points?

- Babesia:
  - Most common cause of blood transfusion infection in US
  - Splenectomy = risk severe infection
- Co-infections in the US: may complicate some infections especially after black-legged tick (*I. scapularis)* bite
  - Lyme disease + Babesia OR Lyme disease + HGA mostly
- Flying squirrels: epidemic typhus
- Rodent infested urban house: Rickettsialpox
  - Mouse mites. Tache noire first → > dozen papules/vesicles

Key features of select tick, louse, and mite-borne diseases

Disease	Usual Organism	Geography	Eschar	Rash	High fever	Comment
TICK-BORNE						
RMSF	R. rickettsii	N,C,S ,America	No	Yes	Yes	Serious
STARI	Unknown	S, SC, MA	No	Yes (EM)	No	Mild
R. parkeri	R. parkeri	Gulf, South, Atlantic	Yes (≥1)	Yes	No	
African tick bite fever	R. africae	Sub-Saharan Africa	Yes (≥1)	Yes	No	Mild
HME	E. chaffeensis	S, SC, MA	No	Yes (+/-)	Yes	Cytopenias Transaminitis
HGA	A. phagocytophilum	NE, NY, MA, MW	No	Yes (+/-)	Yes	Cytopenias Transaminitis
Babesiosis	B. microti	NE, NY, MA, MW	No	Yes (+/-)	Yes	
TBRF	B hermsii	W Mountains	No	No	Yes	Spirochetes in blood smear
LOUSE-BORNE						
Epidemic typhus	R. prowazekii	Worldwide	No	Yes	Yes	War, refugee camps serious
MITE-BORNE						
Rickettsialpox	R. akari	Worldwide	Yes (1)	Yes (V)	No	Mouse exposure
Scrub typhus	O. tsutsugamushi	India, Asia, N. Australia	Yes	Yes	Yes	Serious

C	Central	NY	New York
EM	Erythema Migrans	RMSF	Rocky Mountain Spotted Fever
HGA	Human Granulocytic Anaplasmosis	S	South
HME	Human Monocytic Ehrlichiosis	SC	South Central
MA	MidAtlantic	SE	Southeast
MW	Mid-West	STARI	Southern Tick Associated Rash Illness
N	North	TBRF	Tick-borne Relapsing Fever
NE	New England	V	Vesicular
		W	West



Thank You!
and
The End.

47

Worms and More Worms

Dr. Edward Mitre

2020 INFECTIOUS DISEASE BOARD REVIEW

Worms and More Worms

Edward Mitre, MD
Professor, Department of Microbiology and Immunology
Uniformed Services University of the Health Sciences

Disclosures of Financial Relationships with Relevant Commercial Interests

- None

What are helminths?

What are helminths?

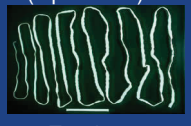
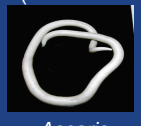
The most complex and fascinating organisms that routinely infect people

Pathogenic Helminths

Eukaryotic, multicellular animals

----- phylum Platyhelminths -----

--Its own phylum!!--

TREMATODES (flukes)	CESTODES (tapeworms)	NEMATODES (roundworms)
		
Fasciolopsis	*Taenia*	*Ascaris*

Images CDC DPDx

How helminths differ from other pathogens

- **Lifespan → most live for years**
- **Metazoans – eukaryotic, multicellular organisms**
- **often have complex lifecycles**
- **induce Th2 responses with eosinophilia and IgE**
- **with few exceptions*, DO NOT MULTIPLY WITHIN HOST**

(Strongyloides, Paracapillaria, Hymenolepis)*

Major Helminth Pathogens

TREMATODES	CESTODES	NEMATODES
Blood flukes *Schistosoma mansoni* *Schistosoma japonicum* *Schistosoma haematobium*	Intestinal tapeworms *Taenia solium* *Taenia saginata* *Diphyllobothrium latum* *(Hymenolepis nana)*	Intestinal *Ascaris lumbricoides* *Ancylostoma duodenale* *Necator americanus* *Trichuris trichiura* *Strongyloides stercoralis* *Enterobius vermicularis*
Liver flukes *Fasciola hepatica* *Clonorchis sinensis* *Opisthorchis viverrini*	Larval cysts *Taenia solium* *Echinococcus granulosus* *Echinococcus multilocularis*	Tissue Invasive *Wuchereria bancrofti* *Brugia malayi* *Onchocerca volvulus* *Loa loa* *Trichinella spiralis* *Angiostrongylus cantonensis* *Anisakis simplex* *Toxocara canis/cati* *Gnathostoma spinigerum* *(Dirofilaria repens)* *(Baylisascaris procyonis)*
Lung flukes *Paragonimus westermani*		
Intestinal flukes *Fasciolopsis buski* *Metagonimus yokagawai*		

World Prevalence

Ascaris	> 400 million
Trichuris	> 200 million
Hookworm	> 200 million
Schistosoma	> 150 million

http://ghdx.healthdata.org/gbd-data-tool

ID Board Prevalance

Low

Parasitology ~ 9 out of 180 total questions

In addition to all helminths, includes:

- Protozoa
- Ectoparasites
- Principles of Travel Medicine

Question #1

2020 INFECTIOUS DISEASE BOARD REVIEW — PREVIEW QUESTION

28 yo F presents with recurrent crampy abdominal pain for several months. She recently returned to the U.S. after living in Tanzania for two years. Colonoscopy reveals small white papules. Biopsy of a papule reveals an egg with surrounding granulomatous inflammation.

Most likely diagnosis?

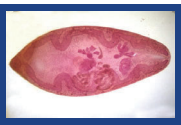
A. *Entamoeba histolytica*
B. *Strongyloides stercoralis*
C. *Wuchereria bancrofti*
D. *Schistosoma mansoni*
E. *Paragonimus westermani*

Major Helminth Pathogens

TREMATODES	CESTODES	NEMATODES
Blood flukes *Schistosoma mansoni* *Schistosoma japonicum* *Schistosoma haematobium*	Intestinal tapeworms *Taenia solium* *Taenia saginata* *Diphyllobothrium latum* *(Hymenolepis nana)*	Intestinal *Ascaris lumbricoides* *Ancylostoma duodenale* *Necator americanus* *Trichuris trichiura* *Strongyloides stercoralis* *Enterobius vermicularis*
Liver flukes *Fasciola hepatica* *Clonorchis sinensis* *Opisthorchis viverrini*	Larval cysts *Taenia solium* *Echinococcus granulosus* *Echinococcus multilocularis*	Tissue Invasive *Wuchereria bancrofti* *Brugia malayi* *Onchocerca volvulus* *Loa loa* *Trichinella spiralis* *Angiostrongylus cantonensis* *Anisakis simplex* *Toxocara canis/cati* *(Gnathostoma spinigerum)* *(Dirofilaria repens)* *(Baylisascaris procyonis)*
Lung flukes *Paragonimus westermani*		
Intestinal flukes *Fasciolopsis buski* *Metagonimus yokagawai*		

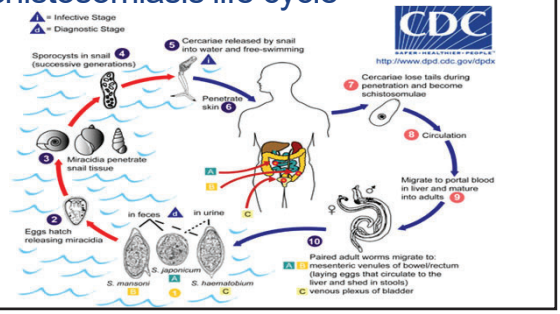
Trematodes (flukes)

- flat, fleshy, leaf-shaped worms
- usually have two muscular suckers
- usually hermaphroditic (except Schistosomes)
- require intermediate hosts (usually snails or clams)
- praziquantel treats all (except *Fasciola hepatica*)

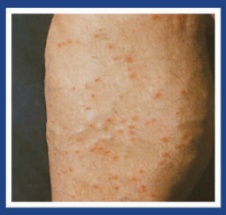


Paragonimus (CDC DpDx)

Schistosomiasis life cycle



Acute Schistosomiasis (Cercarial dermatitis or Swimmer's Itch)



Urticarial plaques and pruritic papules upon reexposure to cercariae penetrating skin in a sensitized individual.

Can occur in response to human or avian schistosomes.

Acute Schistosomiasis: Katayama Fever

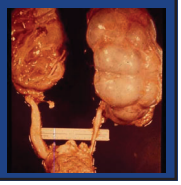
- Occurs in previously unexposed hosts.
- Occurs at onset of egg-laying (3-8weeks)
- Symptoms: fever, myalgias, abdominal pain, headache, diarrhea, urticaria
- Eosinophilia, ↑ AST, ↑ alkaline phosphatase
- **No reliable way to confirm the diagnosis acutely as serology and stool O/P frequently negative.**

Schistosomiasis

Chronic disease
→ granulomatous colitis (*S. mansoni*)
→ portal hypertension (*S. mansoni*)

→ granulomatous cystitis *(S. haematobium)*
→ bladder fibrosis and cancer *(S. haematobium)*
→ obstructive uropathy (S. haematobium)

→ CNS disease (eggs to brain/spinal cord, esp *S. japonicum*)

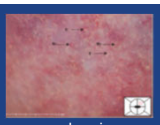


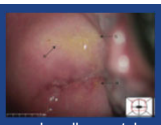
Schistosomiasis

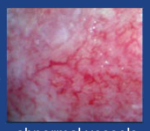
Chronic genital disease
increasingly recognized
primarily due to *S. haematobium*

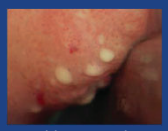
men
- epididymitis
- prostatitis

women (see vaginal and cervical lesions)
- pelvic pain
- dysmenorrhea
- dyspareunia
- post-coital bleeding
- endometritis/salpingitis


sand grains


sandy yellow patches

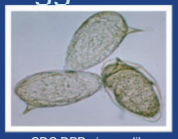

abnormal vessels


rubbery papules

WHO Female Genital Schistosomiasis Pocket Atlas

Schistosome eggs

S. mansoni
(lateral spine)


CDC DPDx image library

S. haematobium
(terminal spine)


CDC DPDx image library

When to consider Schistosomiasis

- Fresh water exposure in an endemic region.
- Clinical syndrome compatible with acute schistosomiasis (F, abd pain, myalgias, eosinophilia)
- Clinical syndrome compatible with chronic schistosomiasis (abdominal/pelvic pain, blood in stool, loose stools, evidence of portal HTN, hematuria, eosinophilia)

Major Helminth Pathogens

TREMATODES	CESTODES	NEMATODES
Blood flukes *Schistosoma mansoni* *Schistosoma japonicum* *Schistosoma haematobium*	Intestinal tapeworms *Taenia solium* *Taenia saginata* *Diphyllobothrium latum* *(Hymenolepis nana)*	Intestinal *Ascaris lumbricoides* *Ancylostoma duodenale* *Necator americanus* *Trichuris trichiura* *Strongyloides stercoralis* *Enterobius vermicularis*
Liver flukes *Fasciola hepatica* *Clonorchis sinensis* *Opisthorchis viverrini*	Larval cysts *Taenia solium* *Echinococcus granulosus* *Echinococcus multilocularis*	Tissue Invasive *Wuchereria bancrofti* *Brugia malayi* *Onchocerca volvulus* *Loa loa* *Trichinella spiralis* *Angiostrongylus cantonensis* *Anisakis simplex* *Toxocara canis/cati* *Gnathostoma spinigerum* *(Dirofilaria repens)* *(Baylisascaris procyonis)*
Lung flukes *Paragonimus westermani*		
Intestinal flukes *Fasciolopsis buski* *Metagonimus yokagawai*		

Fasciola hepatica (a liver fluke)

→acquired by eating encysted larvae on aquatic vegetation (e.g. water chestnuts)

→fluke migration through the liver: RUQ pain and hepatitis

→arrive at biliary ducts in liver and mature over 3-4 months

→can induce biliary obstruction

Dx: eggs in stool exam (low sensitivity), serology

Rx: triclabendazole (FDA approved in 2019!)
(***note: the only trematode that don't respond well to praziquantel)

Clonorchis sinensis

"Chinese Liver Fluke"

- eggs→snails→freshwater fish
- Acquisition by ingestion of undercooked fish
- Flukes develop in duodenum then migrate to liver bile ducts
- Can live for 50 years, making 2000 eggs/day

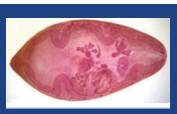
Opisthorchis viverrini

"Southeast Asian Liver Fluke"

- similar lifecycle
- also acquired by eating fish

Both can cause
biliary obstruction
cholelithiasis
cholangiocarcinoma

Paragonimus westermani
"lung fluke"



CDC

eggs→snails→freshwater crabs and crayfish
Ingestion of undercooked seafood
Adults migrate to LUNGS, frequent EOSINOPHILIA
Symptoms:

- *fever, cough, diarrhea during acute migration*
- *later, may have chest pain as worms migrate through lungs*
- *can develop chronic pulmonary symptoms*

Dx: Sputum and/or stool exam for eggs.

NOTE: Cases of Paragonimus kellicotti acquired in U.S. by ingestion of raw crayfish in rivers in Missouri

CID 2009 Sep 15;49(6):e55-61.
Clin Microbiol Rev 2013 Jul;26(3):493-504

Intestinal Flukes

Fasciolopsis buski
("Giant Intestinal Fluke" 2cm w x 8 cm)

- acquisition: eating encysted larval stage on aquatic vegetation
- symptoms: usually asymptomatic
  - can cause diarrhea, fever, abdominal pains, ulceration, and hemorrhage

Dx: eggs in stool

Metagonimus yokagawi
(2.5mm x 0.75mm)

- acquisition: eating larvae in undercooked fish
- symptoms: diarrhea and abdominal pain

Question #2

A 25 yo F reports passing thin, white, flat tissue fragments in her stool several times over the past few weeks. She is healthy and has been in Madagascar for 3 years as a Peace Corps volunteer. The microbiology lab confirms the tissue fragments are parts of a helminth.

A long-term complication that can occur as a result of infection with certain species of this type of helminth is:

A. HTLV-1 infection
B. bladder cancer
C. appendicitis
D. liver abscess
E. seizures

Major Helminth Pathogens

TREMATODES	CESTODES	NEMATODES
Blood flukes *Schistosoma mansoni* *Schistosoma japonicum* *Schistosoma haematobium*	Intestinal tapeworms *Taenia solium* *Taenia saginata* *Diphyllobothrium latum* *(Hymenolepis nana)*	Intestinal *Ascaris lumbricoides* *Ancylostoma duodenale* *Necator americanus* *Trichuris trichiura* *Strongyloides stercoralis* *Enterobius vermicularis*
Liver flukes *Fasciola hepatica* *Clonorchis sinensis* *Opisthorchis viverrini*	Larval cysts *Taenia solium* *Echinococcus granulosus* *Echinococcus multilocularis*	Tissue Invasive *Wuchereria bancrofti* *Brugia malayi* *Onchocerca volvulus* *Loa loa* *Trichinella spiralis* *Angiostrongylus cantonensis* *Anisakis simplex* *Toxocara canis/cati* *Gnathostoma spinigerum* *(Dirofilaria repens)* *(Baylisascaris procyonis)*
Lung flukes *Paragonimus westermani*		
Intestinal flukes *Fasciolopsis buski* *Metagonimus yokagawai*		

Cestodes (tapeworms)

- all except *D. latum* have suckers with surrounding hooklets on the scolex (head) to attach to intestinal lining
- have flat, ribbon-like bodies composed of proglottid segments which contain reproductive organs
- have no digestive systems (food absorbed through soft body wall of worm)

INTESTINAL TAPEWORMS

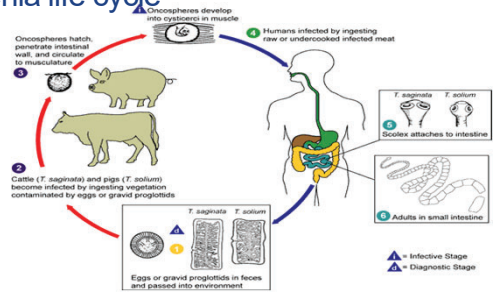
Taenia solium
tapeworm is acquired by eating larvae in pork
adult tapeworm causes few symptoms

Taenia saginatum
acquired by eating larvae in undercooked beef
causes few symptoms
can grow to 10 m

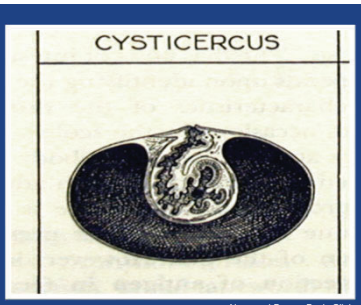
Diphyllobothrium latum *(can grow > 10 m)*
acquired by ingesting fish with larvae
***B12 deficiency in up to 40% of patients**

Dx: eggs/proglottids in stool **Rx**: praziquantel (not FDA-approved)

Taenia life cycle

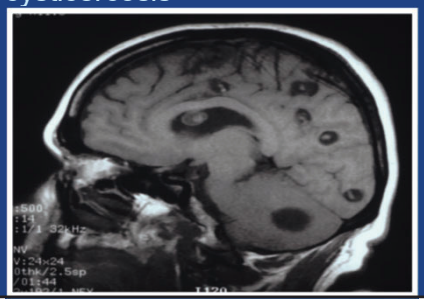


Cysticercus: a fluid filled bladder containing the invaginated head (scolex) of the larval form of a tapeworm.



Neva and Brown, Basic Clinical Parasitology 6th Edition

Neurocysticercosis



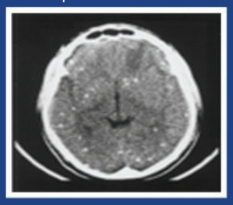
Neurocysticercosis

Can cause:

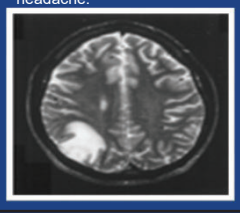
- seizures
- hydrocephalus
- headaches
- focal neurologic deficits

Neurocysticerosis

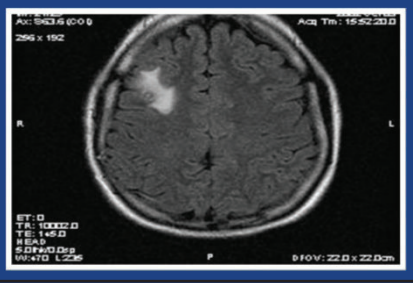
Multiple old calcifications



Perilesional edema – typically occurs around dying cysts and is a frequent finding on initial presentation of seizure or terrible headache.



Cysticercosis – single lesion disease is diagnostic challenge



Neurocysticercosis

Diagnosis:

Definitive = tissue biopsy
multiple cystic lesions each with scolex on imaging
retinal cysticercus seen on fundoscopic exam

Presumptive = suggestive lesions on imaging

Cysticercosis serology → supportive (sensitive if high burden of disease)

Treatment: *Medical therapy decreases risk of future seizures, but has immediate risk of increasing seizures/brain inflammation*

If hydrocephalus or diffuse cerebral edema, treat with steroids and/or surgery, not anti-parasitic therapy

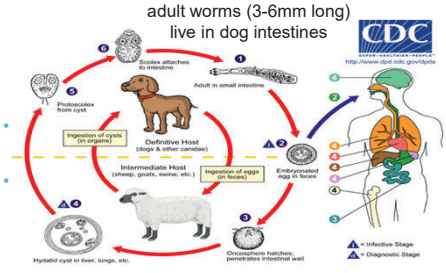
If no increased ICP: 1-2 viable cysts → albendazole for 1-2 viable cysts
> 2 viable cysts → albendazole + praziquantel

AND corticosteroids started before anti-parasitic therapy

****2017 IDSA Guidelines for Diagnosis and Treatment of Cysticercosis****

Echinococcus granulosus

adult worms (3-6mm long)
live in dog intestines



humans = accidental hosts

infected by ingestion of eggs in dog feces

Echinococcus granulosus

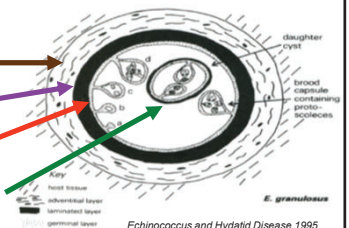
hydatic cyst = "watery vessel"

surrounding inflammatory response of fibrosis and chronic inflammation

outer acellular laminated layer

inner, nucleated germinal layer (PLURIPOTENTIAL TISSUE!)

internal cystic fluid and daughter cysts



Echinococcus and Hydatid Disease 1995.

Echinococcus granulosus - presentation

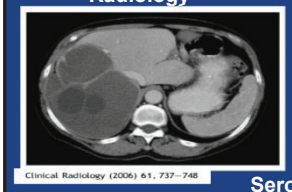
Most cysts (65%) in the liver
25% in the lung, usually in the right lower lobe
Rest occur practically everywhere else in the body

Common presentations
- allergic symptoms/anaphylaxis due to cyst rupture after trauma
- cholangitis and biliary obstruction due to rupture into biliary tree
- peritonitis b/c intraperitoneal rupture
- pneumonia symptoms due to rupture into the bronchial tree

Uncommon presentations
- bone fracture due to bone cysts
- mechanical rupture of heart with pericardial tampanode
- hematuria or flank pain due to renal cysts

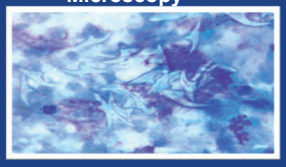
Echinococcus granulosus - diagnosis

Radiology



Clinical Radiology (2006) 61, 737–748

Microscopy



Serology

IgG ELISA about 85% sensitive for liver cysts of E. granulosus

only 50% sensitive in cases of single pulmonary cyst

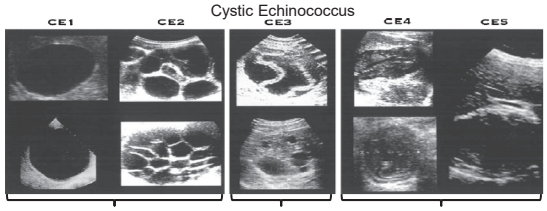
Echinococcus granulosus – treatment

Reasons for not spilling cyst contents
1. Anaphylaxis may occur
2. Spilled protoscoleces can reestablish infection

Typically treat with albendazole for several days before surgery or PAIR (usually 2d-1wk before, and 1-3 months after)

Treatment – WHO Guidelines 2010

Cystic Echinococcus



Acta Tropica 114 (2010) 1–16

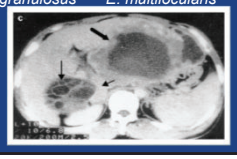
ACTIVE		TRANSITIONAL	INACTIVE
Unilocular Simply cyst Cyst wall visible	Multivesicular Multiseptated cysts	Anechoic content Detached membrane Solid matrix	Heterogenous, hypoechoic or hyperechoic No daughter cysts CE5 with thick calfied wall
---PAIR or SURGERY---	---SURGERY---	---SURGERY--- ---PAIR if no solid matrix---	---NO TREATMENT---

Echinococcus multilocularis

fox/rodent lifecycle

causes an infiltrative, tumor-like growth in liver
- → poorly demarcated
- → has a semi-solid nature (does not form large cysts)

E. granulosus *E. multilocularis*

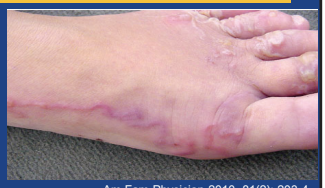


Lancet 2003 362:1295-304

Question #3

A 13 year old girl developed a pruritic rash on her foot after moving to rural northeast Florida. Which of the following helminths is the most likely cause of the rash?

A. *Enterobius vermicularis*
B. *Ascaris lumbricoides*
C. *Trichuris trichiura*
D. *Toxocara canis*
E. *Anyclostoma braziliense*



Am Fam Physician 2010, 81(2): 203-4.

Major Helminth Pathogens

TREMATODES	CESTODES	NEMATODES
Blood flukes *Schistosoma mansoni* *Schistosoma japonicum* *Schistosoma haematobium*	Intestinal tapeworms *Taenia solium* *Taenia saginata* *Diphyllobothrium latum* *(Hymenolepis nana)*	Intestinal *Ascaris lumbricoides* *Ancylostoma duodenale* *Necator americanus* *Trichuris trichiura* *Strongyloides stercoralis* *Enterobius vermicularis*
Liver flukes *Fasciola hepatica* *Clonorchis sinensis* *Opisthorchis viverrini*	Larval cysts *Taenia solium* *Echinococcus granulosus* *Echinococcus multilocularis*	Tissue Invasive *Wuchereria bancrofti* *Brugia malayi* *Onchocerca volvulus* *Loa loa* *Trichinella spiralis* *Angiostrongylus cantonensis* *Anisakis simplex* *Toxocara canis/cati* *Gnathostoma spinigerum* *(Dirofilaria repens)* *(Baylisascaris procyonis)*
Lung flukes *Paragonimus westermani*		
Intestinal flukes *Fasciolopsis buski* *Metagonimus yokagawai*		

Nematodes (roundworms)

→ Nonsegmented round worms

→ Flexible outer coating (cuticle)

→ Muscular layer under the cuticle

→ Nervous, digestive, renal, and reproductive organs.

How do people get infected with nematodes?

1. Eating eggs in fecally contaminated food or soil
   Ascaris, Trichuris, Enterobius, and Toxocara
2. Direct penetration of larvae through skin
   Hookworms, Strongyloides
3. Eating food containing infectious larvae
   Trichinella, Angiostrongylus, Anisakis
4. Vector transmission
   Wuchereria, Brugia, Oncho, Loa

Intestinal Helminths - Lifecycles

Strongyloides and Hookworms

SKIN → LUNGS → GUT

Ascaris

GUT → LIVER → LUNGS → GUT

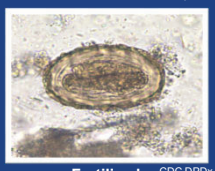
Ascaris lumbricoides

- Large numbers of worms can cause abdominal distention and pain or intestinal obstruction
- can cause "Loeffler's syndrome" - an eosinophilic pneumonitis with transient pulmonary infiltrates
- cholangitis and/or pancreatitis b/c aberrant migration

Ascaris lumbricoides - Diagnosis

Will not find eggs until 2-3 months after pulmonary symptoms occur
After 2-3 months, easy to find eggs since females make 200,000/day


Unfertilized


Fertilized

CDC DPDx

Rx: albendazole or mebendazole

HOOKWORMS
Ancylostoma duodenale and Necator americanus

- MAJOR cause of ANEMIA and protein loss (b/c plasma loss)
- pneumonitis associated with wheezing, dsypnea, dry cough (usually a few days to weeks after infection)
- urticarial rash
- mild abdominal pain

If sensitized → papulovesicular dermatitis at entry site "ground itch"

If worms migrate laterally → **cutaneous larvae migrans**
(especially dog and cat hookworms, as late as 2-8 wks after exposure to A. braziliense)

Still endemic in the U.S. → 35% of individuals from a rural community in Alabama had N. americanus in their stool samples
Am. J. Trop. Med. Hyg., 97(5), 2017, pp. 1623–1628

Trichuris trichiura (whipworm)

4cm long nematode

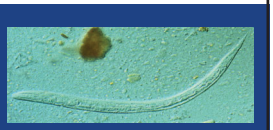
Life cycle: Fecal-oral

In heavy infections:
- loose and frequent stools
- tenesmus
- occ blood to frank blood
- in heavily infected children: rectal prolapse

Dx: eggs are football shaped with two polar plugs

CDC DPDx

Strongyloides stercoralis
(can complete lifecycle in host!)



Usual manifestations
GI: mild abdominal/epigrastric pain
Pulm: wheezing, transient infiltrates
Skin: urticarial rashes, larva currens

Hyperinfection syndrome
→immunocompromised state
steroids, TNF-inhibitors, HTLV-1, malignancy, malnutrition….NOT HIV
→large burden of parasites

GI:	Nausea, vomiting, abdominal pain, diarrhea, erosions b/c millions of larvae in intestinal mucosa
Pulmonary:	diffuse infiltrates, wheezing, dyspnea, cough
Systemic:	fever and hypotension due to gram negative sepsis

-- Often do not see eosinophilia in hyperinfection --

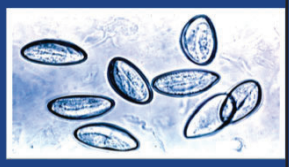
Strongyloides stercoralis

Diagnosis
- stool o/p (sensitivity is low - 30-60%)
- serology

Treatment of choice: ivermectin

Prevention in pts from endemic countries who are about to be immunosuppressed
- Empirically treat, or check serology and treat if positive.

Enterobius vermicularis
(pinworm)



- Found everywhere
- Fecal/oral
- Humans are the only hosts
- peri-anal itching in some pts

Dx: "scotch tape test" or swube, eggs with one flat side

Rx: albendazole, mebendazole, or pyrantel pamoate single dose repeat in 2 wks b/c risk reinfection.
→ treat all members of households
→ careful trimming of fingernails, handwashing, washing of bedclothes to rid house of eggs

Question #4

2020 INFECTIOUS DISEASE BOARD REVIEW — PREVIEW QUESTION

A 6 yo boy from Indiana who has a pet dog and likes to play in a sandbox presents with fever, hepatosplenomegaly, wheezing, and eosinophilia. He has never travelled outside the continental U.S.

The most likely causative agent acquired in the sandbox is:

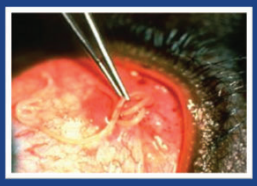
A. *Anisakis simplex*
B. *Onchocerca volvulus*
C. *Enterobius vermicularis*
D. *Toxocara canis*
E. *Anyclostoma braziliense*

Major Helminth Pathogens

TREMATODES	CESTODES	NEMATODES
Blood flukes *Schistosoma mansoni* *Schistosoma japonicum* *Schistosoma haematobium*	Intestinal tapeworms *Taenia solium* *Taenia saginata* *Diphyllobothrium latum* *(Hymenolepis nana)*	Intestinal *Ascaris lumbricoides* *Ancylostoma duodenale* *Necator americanus* *Trichuris trichiura* *Strongyloides stercoralis* *Enterobius vermicularis*
Liver flukes *Fasciola hepatica* *Clonorchis sinensis* *Opisthorchis viverrini*	Larval cysts *Taenia solium* *Echinococcus granulosus* *Echinococcus multilocularis*	Tissue Invasive *Wuchereria bancrofti* *Brugia malayi* *Onchocerca volvulus* *Loa loa* *Trichinella spiralis* *Angiostrongylus cantonensis* *Anisakis simplex* *Toxocara canis/cati* *Gnathostoma spinigerum* *(Dirofilaria repens)* *(Baylisascaris procyonis)*
Lung flukes *Paragonimus westermani*		
Intestinal flukes *Fasciolopsis buski* *Metagonimus yokagawai*		

Filariae

- Threadlike
  - (from Latin *filum* = thread)
- Tissue-invasive
- Roundworms
- Transmitted by insect vectors



Body location of filarial infections

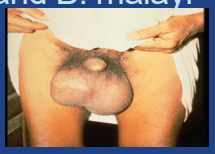
	Adults	Microfilariae
Wuchereria bancrofti *Brugia malayi* (lymphatic filariasis) --mosquitoes--	lymphatics	blood (night)
Loa loa (eyeworm) --Chrysops flies--	SQ tissues (moving)	blood (day)
Onchocerciasis (river blindness) --blackflies--	SQ tissues (nodules)	skin

Treatment of Filariasis

	Treatment	Avoid
Lymphatic filariasis	**DEC**	**-----**
Loa Loa	**DEC**	**DEC and Ivermectin if high microfilaria level**
Onchocerciasis	**ivermectin**	**DEC**

ADVERSE EFFECTS
Loa with high microfilaremia → encephalopathy and death
Onchocerciasis → severe skin inflammation and blindness

W. bancrofti and B. malayi

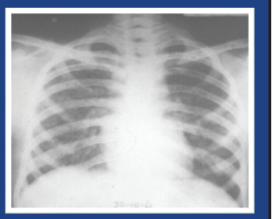


- Asymptomatic microfilaremia
- Lymphangitis
  - retrograde (filarial lymphangitis)
  - bacterial skin/soft tissue infections (dermatolymphangioadenitis)
- Lymphatic obstruction
  - Lymphedema, elephantiasis, hydrocele, chyluria

Tropical pulmonary eosinophilia

- Paroxysmal nocturnal asthma
- Pulmonary infiltrates
- Peripheral blood eosinophilia (>3,000/mm^3)
- Elevated serum IgE
- Rapid response to anti-filarial therapy

Likely due to excessive immune response to microfilariae in lung vasculature

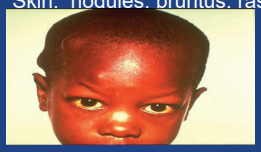
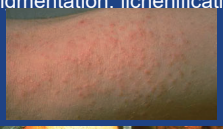
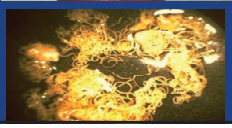
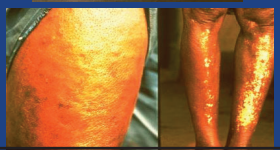


Lymphatic filariasis: diagnosis

- Definitive diagnosis
  - Identification of microfilariae in nighttime blood
  - Detection of circulating antigen in blood (only Wb)
  - Identification of adult worm (by tissue biopsy or ultrasound "filaria dance sign")
- Presumptive diagnosis
  - Compatible clinical picture + positive antifilarial antibodies
- Treatment:
  - DEC, doxycycline
  - NOTE: Triple drug therapy (DEC/albendazole/ivermectin) is now recommended by W.H.O. for eradication campaigns in areas that are NOT co-endemic for Loa loa or Onchocerca

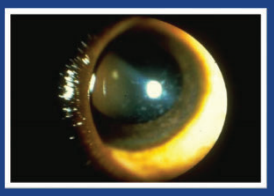
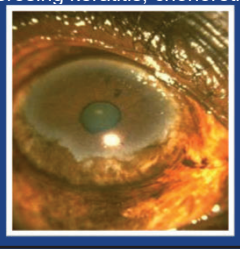
Manifestations of Onchocerciasis

Skin: nodules, pruritus, rash, depigmentation, lichenification

Manifestations of Onchocerciasis

- Eye: punctate keratitis, sclerosing keratitis, chorioretinitis

Onchocerciasis

Diagnosis
- Serology
  - anti-filarial
  - onchocerca-specific
- Parasitologic: skin snips, nodulectomy

Treatment

Ivermectin

Moxidectin (FDA approved in 2018…has much longer half-life)
→ both are primarily microfilaricidal
→ therefore need repeated treatments for many years

(alternative: **doxycycline** for 6 weeks, which kills endosymbiotic *Wolbachia* bacteria, kills adult worms)

Onchocerciasis in the U.S.?

The Emergence of Zoonotic *Onchocerca lupi* Infection in the United States – A Case-Series

Clinical Infectious Diseases® 2016;62(6):778–83

- *Onchocerca lupi → an infection of wolves*
- *as with O. volvulus, is transmitted by blackflies*
- *6 human cases reported to date*
- *3 with deep nodules near cervical spinal cord*
- *Southwestern U.S.(Arizona, New Mexico, Texas)*

Nodding syndrome

Neurological disease
- *Progressive cognitive dysfunction*
- *Nodding seizures – especially when children start to eat*
- *Growth stunting*

→ ***associated with Onchocerciasis***

Tanzania 1960s
South Sudan 1990s
Northern Uganda 2007

A child in Uganda with nodding syndrome. NPR 2/15/2017

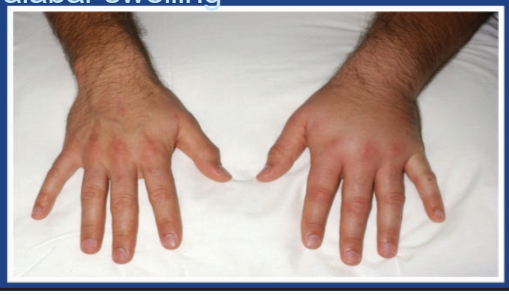
May be due to cross-reactive antibodies, triggered by Onchocerca infection, that recognize leiomodin-1 in the hippocampus

Johnson et al, Science Translational Medicine 2017 v9 issue 377

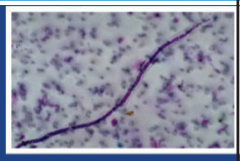
Loiasis: clinical manifestations

- Asymptomatic microfilaremia
- Non-specific symptoms
  - fatigue, urticaria, arthralgias, myalgias
- Calabar swellings
- Eyeworm
- End organ complications (rare)
  - endomyocardial fibrosis, encephalopathy, renal failure

Calabar swelling



Loiasis: Diagnosis



Definitive diagnosis
- Identification of adult worm in subconjunctiva
- Detection of Loa microfilaria in **noon blood**

Presumptive diagnosis

Compatible clinical picture + positive antifilarial antibodies

Trichinellosis

1. Eat meat containing cysts (pork, boar, horse, wild game)
2. Larvae released from cysts by gastric acid.
3. Adults invade small bowel, mature into adults over 1-2wks.
   --> ABDOMINAL CRAMPS and DIARRHEA IF HEAVY INFXN
4. Adults (who only live for about a month) make larvae.
5. Larvae migrate to striated muscle, encyst, and live in "nurse cells"
   → **SEVERE MUSCLE PAIN**
   → **PERIORBITAL EDEMA**
   → **EOSINOPHILIA**
   +/- fever and urticaria

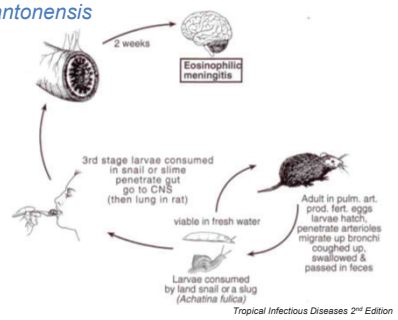
CDC DPDx

Diagnosis: serologies are supportive, + biopsy is definitive
Treatment: albendazole + steroids

Angiostrongylus cantonensis

Human acquisition by eating

- Snails or slugs (often on vegetables!!)
- Paratenic hosts (Freshwater shrimps or crabs, frogs)



Nice CDC movie on angiostrongylus:

https://www.youtube.com/watch?v=V_f1IK93ZIE

Tropical Infectious Diseases 2nd Edition

Angiostrongylus cantonensis

→ *Numerous case reports in Hawaii past two years*

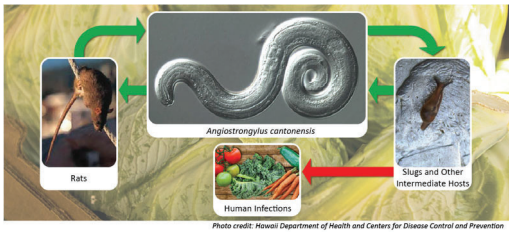


Photo credit: Hawaii Department of Health and Centers for Disease Control and Prevention

Angiostrongylus cantonensis summary (the rat lungworm)

- The most common parasitic cause of eosinophilic meningitis worldwide
- SE Asia, Pacific basin, Caribbean (Jamaica)
- Caused by
  - ingestion of parasites in snail or slugs (often on vegetables!!)
  - OR
  - ingestion of paratenic hosts (prawns, shrimps, crabs, frogs)
- In rats, develop to adults in 2-3 weeks and migrate from surface of brain through venous system to the pulmonary arteries
- In humans, develop to young adults and cause meningitis 1-2 weeks after infection

Rx: primarily supportive
corticosteroids often given…benefit unclear but some data suggests they may be helpful
anthelmintic therapy controversial as may cause exacerbation of meningitis

Anisakis

Ingestion of larvae in raw or undercooked seafood (found worldwide)

In humans, parasite buries its head into gastric mucosa. Eosinophilia common.

CDC DPDx

Symptoms
1) due to invasion of worm (pain, vomiting)
2) due to allergic rxn to worm
(mild urticaria, itchy sensation back of throat, naphylactic shock)

Treatment
→ usually simple endoscopic removal
→ for allergic symptoms, avoid contaminated fish

Toxocariasis (and Baylisascariasis)

Due to dog (*Toxocara canis*), cat (*Toxocara cati*), and raccoon (*Baylisascaris procyonis*) ascarids.

Humans acquire infection by ingestion of animal feces.
In humans → larvae hatch in intestine and migrate to liver, spleen, lungs, brain, and/or eye.

Symptoms

Visceral Larva Migrans (VLM)
usually 2-5 year olds
fever, eosinophilia, hepatomegaly
also wheezing, pneumonia, splenomegaly

Ocular Larva Migrans (OLM)
often in 10-15 year olds
retinal lesions that appear as solid tumors

***Baylisascaris* often more severe and more likely to cause CNS disease (eosinophilic meningitis)**

Toxocara larva in liver (VLM)
CDC DPDx

Toxocariasis

Dx: Clinical picture + Toxocara antibody testing
(serum and intraocular fluid by ELISA testing)

NOTE: Toxocara IgG is only supportive b/c many individuals have + Ab due to prior exposure

Rx: usually self-limited disease.
acute VLM or OLM can be Rx with albendazole and steroids

Gnathostoma spinigerum and hispidum

Undercooked freshwater fish (ceviche!), frogs, birds, reptiles
Asia (esp Thailand), Central/South America, parts of Africa

→ Disease due to migrating immature worms.
→ Often with peripheral eosinophilia

SKIN: migratory, painful subcutaneous swellings (recur every few weeks, can last for years)
creeping eruption/cutaneous larva migrans

TISSUE: visceral larva migrans
eosinophilic meningoencephalitis
radiculomyelitis
ocular disease (anterior and posterior uveitis)

Dx: empiric or by biopsy, no antibody test

Rx: can be difficult, may require 3 weeks of albendazole

Areas of focus for helminth infections

Trematodes:
- Schistosomiasis
- Paragonimus

Cestodes:
- Cysticercosis
- Echinococcus

Nematodes:
- Hookworms
- Strongyloides
- Lymphatic filariasis
- Onchocerciasis
- Trichinella
- Angiostrongylus

Possible question hints

Freshwater exposure + eosinophilia → Schistosomiasis
Crab/crayfish + pulmonary sxs + eosinophilia → Paragonimus
Cysticercosis → ANY food contaminated with tapeworm eggs
Allergic symptoms after trauma → Echinococcus
itchy feet return to tropics → ground itch due to hookworms
Gram- sepsis after TNF inhibitor → Strongyloides hyperinfection
Subcutaneous nodules → Onchocerca volvulus
Blood microfilaria night → lymphatic filariasis (day = Loa loa, skin = Ov)
Muscle pain + eosinophilia → Trichinella
Eosinophilic meningitis → Angiostrongylus
Abdominal pain after sushi → Anisakis
Eosinophilia + F + ↑ AST/ALT in child → visceral larva migrans

Caveat to today's talk – a bit simplistic

Multiple parasites can cause similar diseases

Eosinophilic meningitis

Nematodes:
- Angiostrongylus cantonensis
- Baylisascaris procyonis
- Gnathostoma species
- Toxocara canis & T. cati
- Trichinella spiralis
- Strongyloides stercoralis
- Loa loa
- Meningonema peruzzi

Trematodes:
- Schistosoma species (larvae or eggs)
- Paragonimus westermani
- Fascioliasis

Cestodes:
- Neurocysticercosis
- Echinococcus

Good Luck!

Ed Mitre
edwardmitre@gmail.com

48

Lyme Disease

Dr. Paul G. Auwaerter

48 – Lyme Disease

Speaker: Paul G. Auwaerter, MD

2020 INFECTIOUS DISEASE BOARD REVIEW

Lyme Disease

Paul G. Auwaerter, MD
Sherrilyn and Ken Fisher Professor of Medicine
Clinical Director, Division of Infectious Diseases
Johns Hopkins University School of Medicine

Disclosures of Financial Relationships with Relevant Commercial Interests

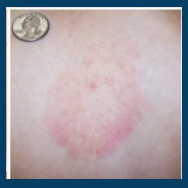
- Scientific Advisory Board – DiaSorin, Adaptive BioTherapeutics
- Grantee – MicroBplex, NIH/SBIR (Lyme disease diagnostics)
- Equity – JNJ

Question # 1

PREVIEW QUESTION

A 56 y.o man from southern Missouri
Onset in July:
- Myalgia and malaise
- Rash of two days duration
- Tick bite 1 week ago

Exam: T 37.0°C
Annular "bulls-eye" ~6 cm
(same area that engorged tick was removed earlier in the week)

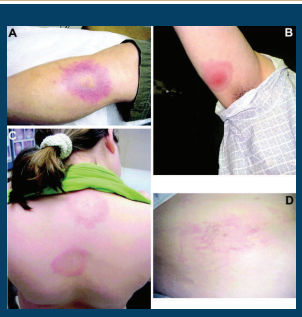


Question # 1

PREVIEW QUESTION

Which of the following is the most likely diagnosis?

A. Lyme disease due to *Borrelia burgdorferi*
B. Human Monocytic Ehrlichiosis, *Ehrlichia chaffeensis*
C. *Borrelia mayonii*
D. Southern tick-associated rash illness (STARI)
E. B. lonestari infection



STARI

Rash variable

Usually single lesion

Multiple described

Maybe Bull's eye-like

Expanding range of Lone Star Tick
(name may be obsolete?)

STARI

No infection yet convincingly documented
- B. lonestarii (single case)

Appears to occur after bite of Lone star tick

B. burgdorferi tests including serology negative
- Likely accounts for some reported Lyme disease cases in non-endemic states

Unclear if doxycycline needed

No sequelae

James AM, J Infect Dis 2001;183:1810

48 – Lyme Disease

Speaker: Paul G. Auwaerter, MD

B. burgdorferi: Vector-borne Infection

- Spirochetal infection due to *Borrelia burgdorferi* (Bb)
- Tick-borne disease
  - *Ixodes* species
  - In North America
    - *Ixodes scapularis* (mostly)
      - Black legged tick
    - *Ixodes pacificus*
      - Western black legged tick
- Not known as STD or blood-borne infection

Source: CDC

Commonly called the "deer tick"

Small-sized tick, unengorged

Adults: sesame seed

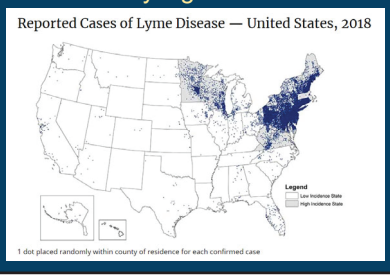
Nymphs: poppy seed

Bacterial reservoir:

Mice, other small mammals

Not: deer, humans

Most common vector-borne infection in US: A mostly regional disease



Source: CDC accessed 7/10/20

Lyme Borreliosis

USA

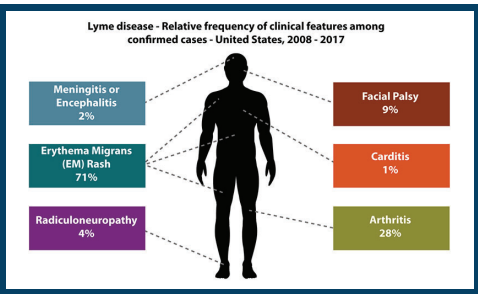
- *Borrelia burgdorferi*
  - Geographically localized
    - ~20-30,000 cases reported annually in US
      - 10x more than reported?
    - 95% cases in 14 states
    - Coastal, lake and river environs
      - New England
      - Mid-Atlantic
      - Upper Midwest

Europe

- *Borrelia afzelii & Borrelia garinii >> Borrelia burgdorferi*
- Occasionally others
- Genus name: changing to *Borreliella?*

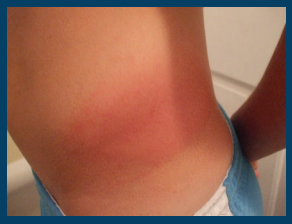
Lyme Disease Presentations

- Early, localized
  - Rash: erythema migrans
- Early, disseminated
  - Rash: multiple erythema migrans
  - Cardiac
  - Neurologic
- Late
  - Lyme arthritis
  - Neurologic (rare)
  - Dermatologic (Europe)



(based on 61% of reported cases 235,037–probably favors later presentations, Source CDC: accessed 7/21/19)
http://www.cdc.gov/lyme/stats/chartstables/casesbysymptom.html

Question # 2



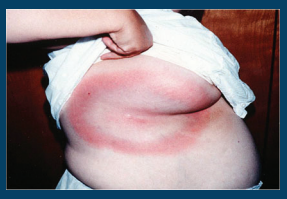
July, 18M living in suburban Maryland, with this rash growing to ~12 cm, first noted 4d, ago, asymptomatic. Landscaper, had tick bite 10d ago. PCP gave cephalexin 2d ago.

Which of the following is true

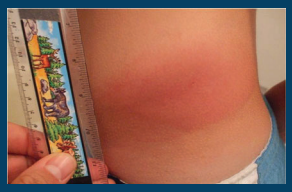
A. Lack of response to cephalexin is consistent with erythema migrans
B. Lack of systemic symptoms makes this unlikely to be Lyme disease
C. Ordering *B. burgdorferi* 2-tier serology will likely confirm Lyme disease
D. Whole blood *B. burgdorferi* PCR is superior to serology in early infection
E. Tick should be submitted for Lyme PCR

Early, localized LD: Erythema migrans

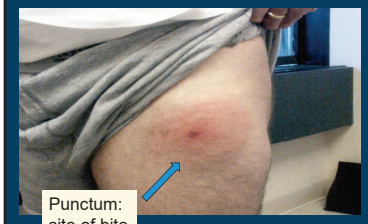
Classic: "bull's eye" with central clearing upon expansion

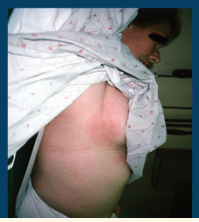


Most common: homogeneous, pink-red ovoid



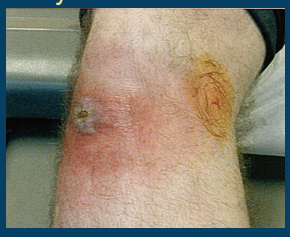
Typical Erythema Migrans

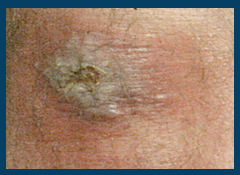




Lesions: occur typically below neck and above knees & elbows

Spider bite?: differential diagnosis may also be confused with MRSA, cellulitis



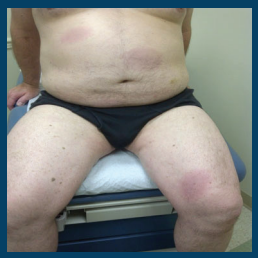


Less typical erythema migrans: skin punch biopsy *B. burgdorferi* culture positive (research labs only)

Erythema migrans

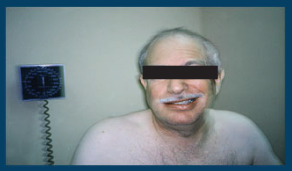
- Primary lesion: occurs 3-30d [7-14d average] @ site tick bite site
  - > 5cm = more secure diagnosis
    - Ddx: includes cellulitis, tinea, erythema marginatum, tick hypersensitivity reaction (smaller)
  - Diagnosis: characteristic rash + epidemiology
    - Serologic testing not recommended, rash sufficient
    - Acute serology negative 40-70% in early Lyme disease
- Most lesions with minimal local symptoms
  - ~70% experience flu-like problems (fever, HA, myalgia)

Early, Disseminated Lyme disease (1)



- Multiple Erythema Migrans
  - Often smaller and less red than primary lesion
  - Always ill:
    - Fever
    - Flu-like symptoms
    - Headache

Early, Disseminated Lyme disease (2)



- Neuroborreliosis
  - Aseptic meningitis
    - Lymphocytic predominance
  - Cranial nerve palsy
    - CN VII (facial)
      - Most common
      - Bilateral CN VII may occur
      - Other CN: seen less
        - e.g., III, VI, VIII
  - Radiculoneuritis
  - Mononeuritis multiplex

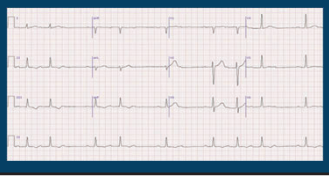
Diagnosis – Facial Palsy

- Facial Palsy: up to 25% due to *B. burgdorferi* (Long Island NY)[1]
- Serology may take 4-6 wks turn positive
  - (if untreated, recheck if negative and suspicious)
- Lumbar puncture
  - Optional
- Most would recover without antibiotic therapy[2]
  - Main role of abx: prevent later disease

[1]Neurology 1992; 41:1268.
[2]Laryngoscope 1985; 95:1341. Clin Infect Dis. 2006 Nov 1;43(9):1089

Early, Disseminated Lyme disease (3)

- 19M collapsed outside VT college cafeteria
  - Lacrosse athlete, not well for ~ 1 month



- Lyme carditis
  - 1°, 2° or 3° block
    - May be variable
    - 3° most identified since symptomatic
      - May need temporary pacer
      - Complete heart block usually resolves within several days of antibiotic, lesser block may take weeks

PA2

Question # 3

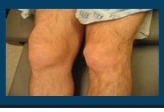
56M Long Island, NY with R knee pain and swelling x 3 weeks. Thought this was a wrenched knee from yardwork.

No fever, rash, tick bite or Lyme disease history

PMH: HTN, hyperlipidemia

PE: afebrile, mildly warm knee, moderate effusion, reduced ROM

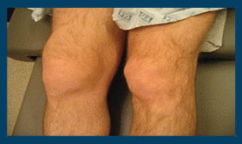
Labs: nl CBC



Which of the following is usually true for Lyme arthritis?

A. If untreated, the knee swelling will not remit
B. *B. burgdorferi* PCR synovial fluid ~ 100% sensitivity
C. Synovial fluid WBCs >50,000 cells/mL
D. Synovial fluid *B. burgdorferi* culture ~100% sensitivity
E. Serum *B. burgdorferi* 2-tier testing ~100% sensitivity

Late Lyme disease (1): Lyme arthritis



- Recurrent mono- or oligo-arthritis
  - Knee most common
    - Large, cool effusions
    - Baker's cysts may develop
  - Other large joints possible + TMJ
- Afflicts 50-60% untreated patients
- May remit, recur over period of wks to mos w/o abx rx

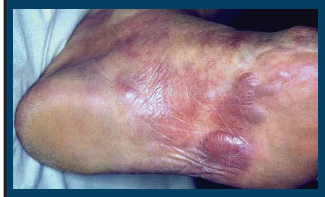
Ann Int Med 1987; 107:725

Late Lyme disease (2): Neurologic

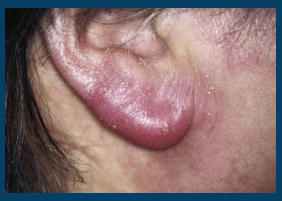
- Encephalopathy:
  - Cognitive dysfunction, objective
  - Due to systemic illness, rather than true CNS infection
- Encephalitis: rare
  - Objective neurological or cognitive dysfunction
  - White matter changes on MRI or abnormal CSF
  - CSF: (+) lymphocytic pleocytosis, Bb antibody
- Peripheral neuropathy: rare (controversial)
  - Pain or paresthesia
  - Diffuse axonal changes on EMG/NCV

Late Lyme disease (3): Dermatologic

Acrodermitis chronica atrophicans (Europe)



Borrelia Lymphocytoma (Europe)



Question # 4

- 49F complains of four years of fatigue, headache, poor sleep and joint aches since trip to London UK
  - PMH: TAH/BSO
  - Medications: hormone replacement
  - SH: Married, accountant. Lives in central Pennsylvania. Two dogs, often sleep in bed.
  - PE: normal
  - Labs: normal CBC, ESR, TSH
    - *B. burgdorferi* serology: EIA (not done), IgM WB 3/3 bands, IgG 1/10

Question # 4

- What is the best recommendation at this time?

A. Doxycycline 100 mg x 14 days
B. Doxycycline 100 mg x 28 days
C. Repeat Lyme serology (two tier: EIA w/ reflex WB)
D. Lyme C6 antibody assay
E. Neither additional Lyme disease testing or treatment

Laboratory testing

- Two tier serology: not needed for erythema migrans
  - First: total Ab screen – ELISA or EIA
  - If positive, second tier reflexes to immunoblots (IB)
    - IgM: ≥ 2/3 bands, use only if < 4 wks of symptoms
      - High rates false (+)
    - IgG: ≥ 5/10 bands, more reliable
      - Alternative criteria (different bands): less specific
  - Often negative in early infection (first 2-3 weeks)
  - May need acute/convalescent for confusing rashes or neuroborreliosis
  - Serology: may remain (+) for decades including IgM

MMWR 1995;44:590
Clin Infect Dis 2001;33(6):780-5

Diagnostics: Lyme arthritis

- Arthrocentesis
  - Synovial fluid: inflammatory
    - 10,000-25,000 WBC average (range: 500 – 100,000)
    - PMN predominant
  - Bb PCR –non standardized
    - Sensitivity 40-96% if prior to antibiotic therapy
    - Specificity 99%
- Serology: ~100% (+) in blood
  - High titer, Bb IgG immunoblot
- Culture: rarely (+)

Arvikar, Steere: Inf Dis Clin N Am 2015;29(2):269-280

Common Clinical Scenarios: Improper Use of Serology

1) EIA/ELISA only, no Western blot (WB aka immunoblot)
2) Ordering just WB -- w/o EIA/ELISA (total ab)
   - >50% population reactive to 1 or more antigens
3) Using the IgM WB alone for symptoms > 1 month
4) Serology at time of erythema migrans
5) Treating tests that "stay positive [IgM or IgG]"
6) Testing samples by WB other than serum
   --CSF or synovial fluid

Other tests

- Second generation Ab assays: C6 or VlsE (variable major protein-like sequence expressed)
- C6 Ab: more specific than first tier screen
  - Less specific than full two tier test
  - Positive, earlier in infection
  - Helpful to discriminate false (+) IgM IB
  - Better at detecting *B. garinii, B. afzelli* (Europe)
- Beware of "Lyme" specialty labs with unvalidated or poorly validated testing

Clin Infect Dis 2013;57(3):333-343.

Lyme disease: Antibiotics

- Oral
  - Doxycycline
  - Amoxicillin
  - Cefuroxime
- Parenteral
  - Ceftriaxone
  - Cefotaxime
  - Penicillin G
- Duration
  - 10d EM doxycycline
  - 14d EM amoxicillin
  - 14-21d neurologic-28d days
  - 28d arthritis (oral)
  - 14d arthritis (parenteral, usually as second course)
- Parenteral therapy
  - Neuroborreliosis
    - Not necessary, CN VII palsy
    - European data suggests oral doxycycline equivalent
  - Late Lyme arthritis (some usually after oral first course)
  - Carditis (3°, initially)
- Subjective symptoms may persist after abx
  - More common in women

Sanchez et al, JAMA. 2016;315(16):1767-77

Treatment: Late Lyme arthritis

- Initial treatment: amoxicillin or doxycycline PO x 28d
  - If lack of response: second course orals or ceftriaxone IV x 14d
- ~10% do not respond to repeated antibiotic therapy
  - Abx-refractory Lyme arthritis
    - Bb culture/PCR (-), no viable organisms
    - Autoimmune phenomenon, associated with certain HLA DR alleles binding to OspA → strong Th1 response
  - Treatment: DMARDs, intra-articular corticosteroids, synovectomy

Lyme Disease: Expectations Regarding Resolution

- Subjective problems, post-treatment
  - Prospective studies, treated erythema migrans

Time	Symptomatic
Erythema migrans (d0)	73%
3 months	24%
≥ 6 months	11.5% [0-40.8%]
15 years	Equivalent to general US population

Need to manage expectations,

No benefit from additional antibiotics

Post-infectious syndromes not unique to LD

Wormser, et al. Ann Intern Med 2003;138:697 Wormser, et al. Clin Infect Dis 2015;61(2):244
Cerar, et al. Am J Med 2010;123:79

Randomized, placebo-controlled trial scorecard for persistent symptoms attributed to Lyme disease after initial treatment

Longer-term abx v. placebo Subjective sx OR Encephalopathy after initial treatment	Antibiotics with Durable Effect and Clinically Significant Benefit	Antibiotics Not Effective
7 trials	0	7

Placebo effect: noted in up to 36%
No study yielded evidence of *B. burgdorferi* by culture or PCR in these pa

1. Klempner M, et al. NEJM 2001; 345:85 (2 studies)
2. Krupp LB, et al. Neurology 2003;60:1923
3. Oksi J, et al. Eur J Clin Micro 2007;26(8)571
4. Fallon BA, et al. Neurology 2008; 70:992
5. Söwall, BMC Infectious Diseases 2012, 12:186
6. Berende A, et al. NEJM 2016;375(13):1209-20 (PLEASE trial)

"Chronic Lyme disease"

- What is it? Originally, late Lyme disease
  - Now: vague term, often used by some to encompass broad range of symptoms
    - Objective evidence of LD not needed.
      - Lack of good clinical history
      - Often no reliable evidence of LD by laboratory testing
  - Offered as explanation for
    - Chronic—fatigue, pain, headaches, brain fog, sleep problems, depression
    - Legitimate diseases: multiple sclerosis, ALS, Alzheimer's, autism, Parkinson's

PA2

Question # 5

42M went camping with his son on Cape Cod, MA

Didn't use DEET, no tick bites known

About 4d after returning home, fever, chills, myalgia. Noted rash on thigh

PMH: none

PE: Appears ill, non-toxic, 104/60, P96 T101.7°F

Exam only notable for 3 pink ovoid rashes over trunk, R thigh (largest ~7cm)

Labs: WBC 2.2 Hg 9.6 plt 110K

Doxycycline is prescribed. What should also be performed as part of the plan?

A. PCR for *E. chaffeensis*
B. Serology for spotted fever rickettsia (RMSF)
C. Blood smear
D. Serology for *B. burgdorferi*
E. Nothing additional

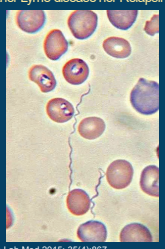
Lyme disease: co-infections

- Incidence depends on geographic acquisition
  - *B. microti:* 2-40%
  - HGA: *2-11.7%*
  - Uncommon to rare
    - *B. miyamotoi*
    - *B. mayonii*
    - *Ehrlichia eauclairensis*
    - Powassan virus (Deer Tick virus)
- Disease severity
  - Lyme + HGA:
    - Data mixed on effect
  - Lyme + Babesia:
    - Increases severity of Lyme disease presentation
    - Converse: Lyme doesn't appear to affect Babesia presentations

IDSA/AAN/ACR Lyme disease Guideline (submitted) 2020

B. miyamotoi--Ixodes spp. Vector

Neither Lyme disease nor Relapsing Fever



Telford, et al. Clin Lab Med 2015; 35(4):867

- Serosurvey New England: 0.8-4.0%
- Likely underdiagnosed
- Sx: HA, fever, chills, myalgia
- Not like relapsing fever:
  - No rigor, ↓ BP
  - May resemble HGA
    - Leukopenia, thrombocytopenia, LFT abnl
  - Opportunistic pathogen?
- Dx: not widely available
  - rGlpQ EIA
  - PCR
  - Doesn't appear to frequently cross-react with B burgdorferi Ab
- Treatment: likely identical as for LD

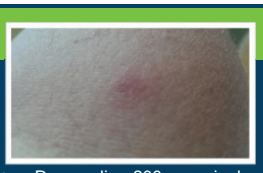
PA2

Question # 5

42M just returned from a hiking trip Colorado, removing a tick on his arm 2d earlier. He is now heading out of town again on a beach vacation.

There is some intense itching and redness at the site he thinks may be larger (~1cm) than yesterday. He is otherwise well.

The best course of action would be:



A. Doxycycline 200mg x single dose
B. Doxycycline x 14d
C. Doxycycline x 30d
D. Cefuroxime x 14d
E. Observation

I. scapularis tick bite prophylaxis

B. burgdorferi transmittal

- Tick attachment time
  - < 24 h: 0/58 (0%)
  - < 48 h: 4/50 (8%)
  - < 72 h: 36/52 (69%)

JID 2001; 183:773-8

Infection risk in highly endemic areas

Intervention	Risk	95% CI
No tick found	20%	
Removing tick	2.2%	[1.2-3.9%]
Single 200mg dose doxycycline*	0.4%	[0.02-2.1%]
10d doxy	0%	[0-0.97%]

*200 mg given with 72h of tick bite

J Antimicrob Chemother 2010;65:1137-1144
N Engl J Med 2001; 345:79-84

Lyme disease: some pearls

- No need for serology if diagnosing erythema migrans
- *B. burgdorferi* IgM immunoblot most common cause of misdiagnosis
- Late Lyme arthritis: always seropositive
  - No evidence that seronegative Lyme exists in patients with long-term symptoms
- Lab evidence of LD essential unless hx of EM exists
- Prolonged antibiotic treatment doesn't improve resolution of subjective symptoms

49

Lots of Protozoa

Dr. Edward Mitre

49 – Lots of Protozoa

Speaker: Edward Mitre, MD

2020 INFECTIOUS DISEASE BOARD REVIEW

Lots of Protozoa

Edward Mitre, MD
Professor, Department of Microbiology and Immunology
Uniformed Services University of the Health Sciences

Disclosures of Financial Relationships with Relevant Commercial Interests

- None

Protozoa

Protozoa - Extraintestinal	Protozoa - Intestinal
Apicomplexa	**Apicomplexa**
Plasmodium	Cryptosporidium
Babesia	Cyclospora
(Toxoplasma)	Cystoisospora
Flagellates	**Flagellates**
Leishmania	Giardia
Trypanosomes	Dientamoeba
(Trichomonas)	**Amoebae**
Amoebae	Entamoeba
Naegleria	**Ciliates**
Acanthamoeba	Balantidium
Balamuthia	

Not Protozoa **Kingdom Fungi:** Microsporidiosis agents
Kingdom Chromista: Blastocystis

Protozoa

Protozoa - Extraintestinal	Protozoa - Intestinal
Apicomplexa	**Apicomplexa**
Plasmodium	Cryptosporidium
Babesia	Cyclospora
(Toxoplasma)	Cystoisospora
Flagellates	**Flagellates**
Leishmania	Giardia
Trypanosomes	Dientamoeba
(Trichomonas)	**Amoebae**
Amoebae	Entamoeba
Naegleria	**Ciliates**
Acanthamoeba	Balantidium
Balamuthia	

Not Protozoa **Kingdom Fungi:** Microsporidiosis agents
Kingdom Chromista: Blastocystis

INFECTIOUS DISEASE BOARD REVIEW **PREVIEW QUESTION**

Question 1: A 54 yo woman presents with fever, chills, and oliguria one week after travel to Malaysia.

Vitals: 39.0° C, HR 96/min, RR 24/min, BP 86/50

Notable labs: Hct 31%, platelets14,000/μl, Cr of 3.2 mg/dL.

Peripheral blood smear has intraerythrocytic forms that are morphologically consistent with *Plasmodium malariae*.

The most likely infectious agent causing the patient's illness is:

A. **Plasmodium malariae**
B. **Plasmodium knowlesi**
C. **Plasmodium vivax**
D. **Plasmodium falciparum**
E. **Babesia microti**

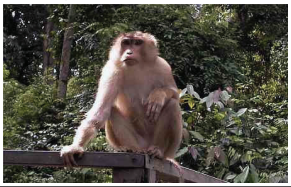
P. knowlesi

diagnosed in over 120 people in Malaysian Borneo

Lancet 2004;363:1017-24.

morphologically similar to *P. malariae*

usually a parasite of long-tailed macaques



increasingly recognized in Myanmar, Phillipines, Indonesia, and Thailand.

causes high parasitemia

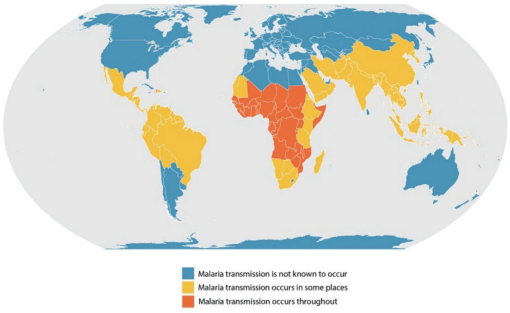
highly morbid and can be lethal

MALARIA

one of the most important pathogens in the history of the world

In 1775 the Continental Congress bought quinine for George Washington's troops

MALARIA EPIDEMIOLOGY



This map shows an approximation of the parts of the world where malaria transmission occurs.

https://www.cdc.gov/malaria/about/distribution.html

In non-immune patients, falciparum malaria is a medical emergency!!

→most studies find it to be the #1 cause of fever in a returned traveler

→ infected individuals can rapidly progress from clinically appearing well to being critically ill

Family Feud: The Three Most Common Causes of Fever in a Returned Traveler.

1.
2.
3.

Family Feud: The Three Most Common Causes of Fever in a Returned Traveler.

1. Malaria
2. Malaria
3. Malaria

49 – Lots of Protozoa

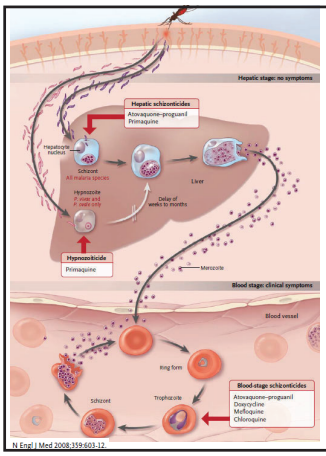
Speaker: Edward Mitre, MD

---Some helpful heuristics---

If patient has	make sure patient doesn't have
Fever and freshwater contact	
Fever and unpasteurized milk	
Fever and undercooked meat	
Fever and raw vegetables	
Fever and untreated water	
Fever and wild dog bite	
Fever and abdominal pain	
Fever and headache	
Fever and diarrhea	
Fever and cough	
Fever and dysuria	

---Some helpful heuristics---

If patient has	make sure patient doesn't have
Fever and freshwater contact	Malaria
Fever and unpasteurized milk	Malaria
Fever and undercooked meat	Malaria
Fever and raw vegetables	Malaria
Fever and untreated water	Malaria
Fever and wild dog bite	Malaria
Fever and abdominal pain	Malaria
Fever and headache	Malaria
Fever and diarrhea	Malaria
Fever and cough	Malaria
Fever and dysuria	Malaria



N Engl J Med 2008;359:603-12.

Sporozoites
- Infective stage
- Come from mosquito

Liver schizont
- Asymptomatic replicative stage
- Become 10,000 to 30,000 merozoites

Hypnozoite
- Dormant liver stage in vivax and ovale
- Release merozoites weeks to months after primary infection

Merozoites
- Infect RBCs and develop into ring-stage trophozoites
- Mature into schizonts, which release merozoites which infect more RBCs

Gametocytes
- Infective stage for mosquitoes

characteristics of human malaria species

	P. falciparum	P. knowlesi	P. vivax	P. ovale	P. malariae
incubation	8 - 25 d	prob 8-25 d	~ 2 wks	~ 2 wks	~ 3-4 wks
hypnozoite	no	no	yes	yes	no
RBC age	any	any	young	young	old
parasitemia	high	high	< 2%	< 2%	< 1%
morbidity	high	high	high	moderate	low
mortality	high	moderate	low	low	low

Possible evolutionary defenses against malaria

Duffy antigen negative (P. vivax uses Duffy Ag to enter RBCs)

Sickle cell trait (increases survival during *P. falciparum* infection, perhaps by selective sickling of infected RBCs)

Glucose-6-phosphate dehydrogenase deficiency

(malaria parasites grow poorly in G6PD deficient RBCs, perhaps b/c this results in an overall increase in reactive oxygen species in RBCs)

Uncomplicated (mild) malaria

Symptoms: fevers, chills, headache, fatigue

***NOTE: abdominal pain presenting symptom in 20%**

→ ***periodicity of fevers not common when patients seen acutely***

Labs: Thrombocytopenia in 50%
mild anemia in 30%
typically no leukocytosis
may see evidence of hemolysis with mild increase T bili and LDH

Complicated (severe) malaria

- Cerebral malaria (altered mental status, seizures)
- Respiratory distress/pulmonary edema
- Severe anemia (hct <15% in children, <20% in adults)

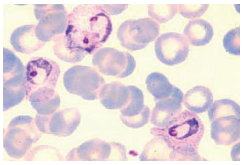
} Often seen in children of endemic countries. Adults more often get multiorgan failure.

- Renal failure
- Hypoglycemia
- Shock (SBP < 80 mm Hg or capillary refill > 3 seconds)
- Acidosis (often lactic acidosis)
- Jaundice (total bilirubin > 3 mg/dL)
- Bleeding disorder (spontaneous bleeding or evidence of DIC)

These complications primarily occur with *Plasmodium falciparum,* usually when parasitemia >2%.

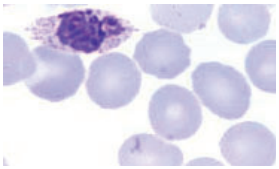
NOTE: in the absence of end organ damage, parasitemia >10% is often used as the cut-off to treat for severe malaria

P. vivax or ovale



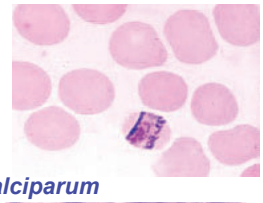
-Schüffner's dots
-enlarged infected cells

P. ovale



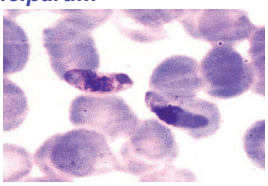
-mature schizont
-elongated or oval
-6-12 merozoites

P. malariae



-band form
(also seen in *P. knowlesi*)

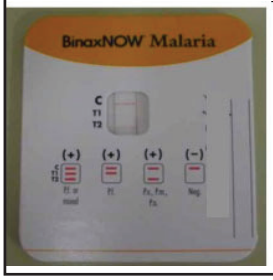
P. falciparum



Banana shaped gametocyte

Malaria: Diagnosis

antigen capture
→ sensitivity 95% for P. falciparum (about 85% for other species)



Binax Now® ICT assay for the detection of *Plasmodium falciparum* malaria according to the level of parasitemia

Parasitemia (no. of parasites/μL of whole blood)	Microscopy (no. positive)	NOW ICT (no. positive)	Sensitivity (%)
1–100	4	3	75.0
101–1,000	26	25	96.2
1,001–10,000	37	36	97.3
>10,000	34	33	97.1

Am. J. Trop. Med. Hyg., 69(6), 2003, pp. 589–592

IDBR PREVIEW QUESTION

Question 2: A 33-year-old woman is traveling to Uganda to do field studies in anthropology. She is two months pregnant. Which of the following do you prescribe for malaria prophylaxis?

A. Doxycycline
B. Chloroquine
C. Mefloquine
D. Atovaquone/progruanil
E. No prophylaxis

Malaria Chemoprophylaxis

no vax for travelers - RTS,S about 40% efficacy, starting large scale in Africa

CENTRAL AMERICA and MIDDLE EAST

	Pre-Exposure	During	Post-Travel
Chloroquine 500mg tabs	1 tab/wk x 2 wks	1 tab/wk	4 weeks
EVERYWHERE			
Atovaquone/proguanil 250/100mg	1 tab daily x 2 d	1 daily	7 days
Doxycycline 100mg tabs	none	1 daily	4 weeks
Tafenoquine 100mg tabs	2 tab daily x 3 d	2 tab/wk	2 tab after 1 wk
Mefloquine (not SE Asia) 250mg tabs	1tab/wk x 2-3 wks	1 tab/wk	4 weeks

**FDA black box warning in 2013 that mefloquine can cause neurologic symptoms, hallucinations, and feelings of anxiety, mistrust, and depression mefloquine. Thus, many U.S. practitioners now reserve mefloquine for pregnant travelers to areas with chloroquine resistance*

Treatment of *P. falciparum*

Uncomplicated (no organ dysfunction, low parasitemia, able to take po)

if chloroquine sensitive area → chloroquine

if chloroquine resistant area

→ artemether/lumefantrine (Coartem) x 3 days
→ atovaquone/proguanil (Malarone) x 3 days
→ 2nd line: quinine x 3 days + doxycycline x 7 days

Severe

→ IV artesunate **FDA approved since May 2020**
(CDC malaria hotline: 770-488-7788 or -7100)

(note: IV quinidine unavailable in U.S. since 3/2019)

***NOTE: there is increasing artemisinin resistance in SE Asia but it has not yet emerged in Africa*

Treatment of *P. vivax*

chloroquine x 3 days
THEN primaquine (30 mg base) x 14 days
OR tafenoquine (two 150 mg tabs) FDA-approved 7/2018!

→ Need to check G6PD status before administering primaquine OR tafenoquine as both can cause severe hemolysis in patients with G6PD deficiency

→ Primaquine requires cytochrome P-450 2D6 to be effective. Therefore, clinical failure to cure *P. vivax* can be due to low host levels of CYP450-2D6. *N Engl J Med 2013; 369:1381-1382*

* Suggestions for all ID practitioners *

1) Make sure the facility where one works has the means to rapidly test for malaria

2) Ensure that hospital pharmacy has access to appropriate medications for treatment of malaria

Babesia

Transmission

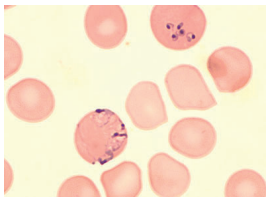
- Ixodes ticks in Northeast and upper midwest
  →co-infection with Lyme and Anaplasma
- Transfusion (approx. 1/20k in NE if un unscreened…Ab screening tests approved by FDA in 2018)

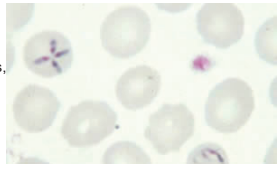
Symptoms: fever, headache, chills, myalgias
less common: nausea, dry cough, neck stiffness, vomiting, diarrhea, arthralgias
→ severe disease: in HIV, asplenia

Labs: anemia, thrombocytopenia, mild increase LFTs, normal/low/high WBC

Diagnosis: small ring forms in RBCs, PCR, Ab
merozoites can make tetrad ("Maltese cross")

Treatment: azithromycin + atovaquone
(clindamycin + quinine is alternative)
→ Exchange transfusion for severe disease





CDC DpDx

Protozoa

Protozoa - Extraintestinal

Apicomplexa
Plasmodium
Babesia
(Toxoplasma)

Flagellates
Leishmania
Trypanosomes
(Trichomonas)

Amoebae
Naegleria
Acanthamoeba
Balamuthia

Protozoa - Intestinal

Apicomplexa
Cryptosporidium
Cyclospora
Cystoisospora

Flagellates
Giardia
Dientamoeba

Amoebae
Entamoeba

Ciliates
Balantidium

Not Protozoa **Kingdom Fungi:** Microsporidiosis agents
Kingdom Chromista: Blastocystis

Leishmaniasis

→**obligate intracellular protozoan infection**
→**transmitted by sand flies** (noiseless, active in evenings)

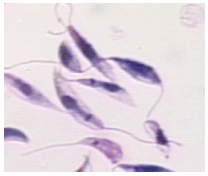
Lutzomyia
New world leishmaniasis

Phlebotomus
Old world leishmaniasis

Leishmania life cycle – Two stages

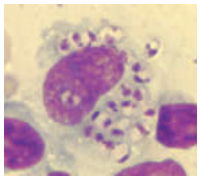
Promastigote

extracellular, in sand fly
2µm wide x 20µm long
+ flagella
large central nucleus
band shaped kinetoplast



Amastigote

Intracellular (macrophages)
Round or oval
Wright-Giemsa:
dark-purple nucleus
small rod shaped kinetoplast



CDC DpDx

Question 3: A 42 yo man from Bolivia presents with nasal stuffiness and is found to have nasal septal perforation. Biopsy demonstrates intracellular amastigotes consistent with Leishmania.

Which is the most likely species?

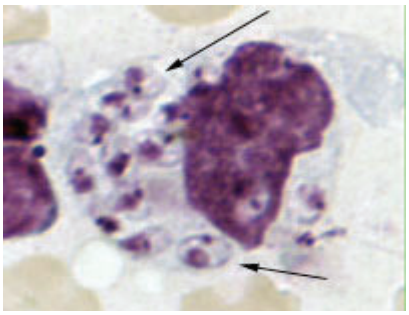
A. L. mexicana
B. L. braziliensis
C. L. peruviana
D. L. infantum chagasi
E. L. major

Leishmania taxonomy and disease simplified

	Cutaneous	Mucosal	Visceral
NEW WORLD			
L. mexicana complex	X		
L. braziliensis	X	X	
L. Infantum chagasi			X
OLD WORLD			
L. tropica	X		
L. major	X		
L. donovani			X
L. infantum chagasi			X

*note: *L. braziliensis* is in the Viannia subgenus. *L. V. guyanensis* and *L. V. panamensis* also cause mucosal disease. *L. peruviana* DOES NOT

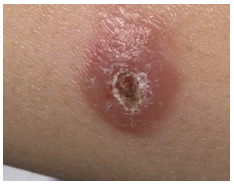
Here are some very clear amastigotes
→ intracellular organisms with nucleus and kinetoplast



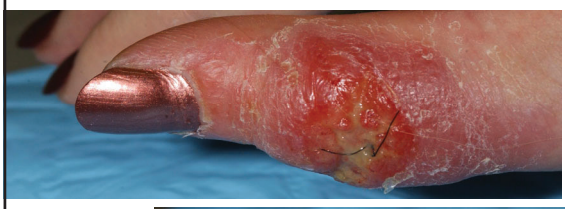
http://www.dpd.cdc.gov/dpdx/HTML/Leishmaniasis.htm

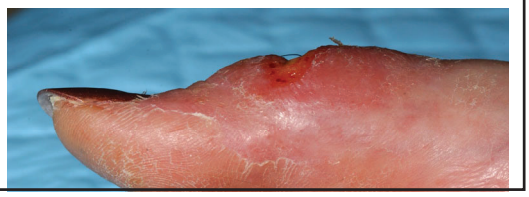
Cutaneous Leishmaniasis – Clinical Presentation

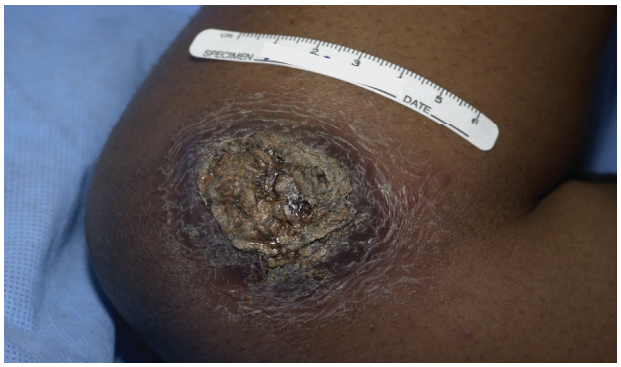
- **papule → nodule →ulcerative lesion → atrophic scar**
  - **ulcerative lesion may have:**
    - **induration,**
    - **scaliness**
    - **central depression**
    - **raised border**

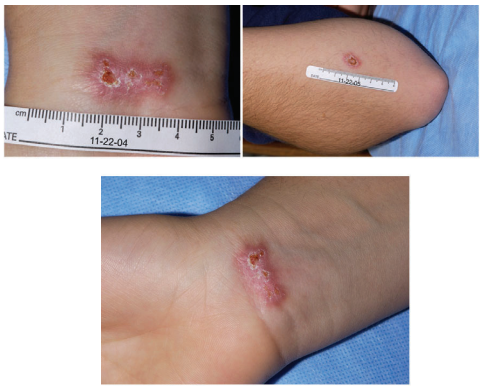


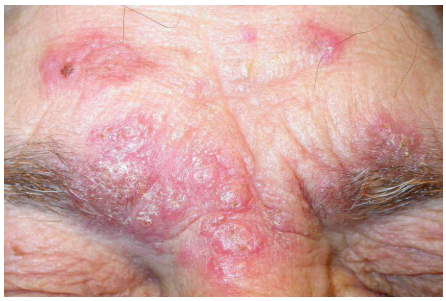
- **takes weeks to months to develop**
- **usually painless, unless superinfected**
- **most lesions will eventually resolve on their own**











Cutaneous Leishmaniasis – Diagnosis

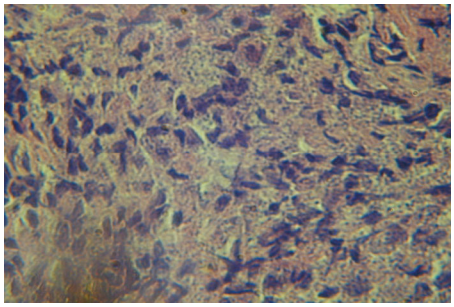
Definitive diagnosis is very helpful because

1. **Allows you to rule out other possibilities**
2. **May help in deciding whether and how to treat**

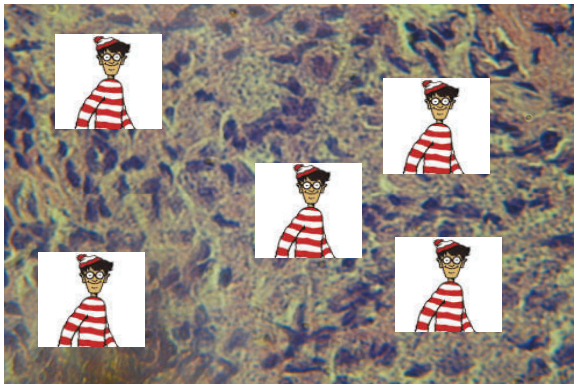
Diagnostic Tools (edge of ulcer skin: scraping, aspirate, punch)

Touch prep with examination under oil looking for amastigotes
Culture on triple N media (may take weeks to grow)
(Nicolle's modification of Novy and MacNeal's medium – biphasic)
Histology
PCR

Amastigotes in tissue sample



Amastigotes in tissue sample



Cutaneous Leishmaniasis – Treatment Recommendations

→ **Treat systemically if *L. (V.) braziliensis, guyanensis, panamensis***

→ **If not, ok to observe if there are:**
few lesions, they are < 5 cm, not on face/fingers/toes/genitals, normal host, no subcutaneous nodules

Treatment Options

local: heat (FDA approved), cryotherapy, other
systemic
oral: miltefosine for certain species (2014 FDA approved)
ketoconazole, fluconazole (not FDA approved)
IV: pentavalent antimony (stibogluconate, IND)
liposomal amphotericin B (not FDA approved)

*****2016 IDSA GUIDELINES FOR TREATMENT OF LEISHMANIA*****
http://www.idsociety.org/Guidelines/Patient_Care/IDSA_Practice_Guidelines/Infections_by_Organism/Parasites/Leishmaniasis/

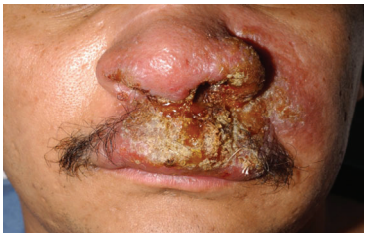
Mucosal leishmaniasis

Leishmania (Viannia) braziliensis *dissemination* to nasal mucosa

also *L. (V.) guyanensis* and *L. (V.) panamensis*

Slow, progressive, destructive

Can occur months or years following cutaneous ulcer



Treatment:
IV antimony (stibogluconate) (IND)
IV liposomal amphotericin (off-label)
oral miltefosine

Note: infection of Leishmania organisms with Leishmaniavirus, a double-stranded RNA virus, may be associated with increased risk of mucocutaneous disease
J Infect Dis. 2016 Jan 1;213(1):112-21

Visceral Leishmaniasis

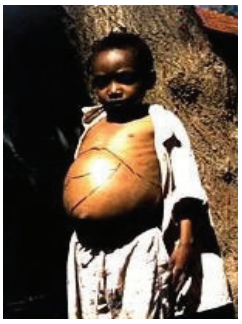
L. donovani, L. infantum chagasi

amastigotes in macrophages go to local LNs then hematogenously to liver, spleen, bone marrow

A peristent disease that can reactivate
TNF blockade,
HIV CD4 < 200

Weeks/months: fevers, chills, fatigue
hepatosplenomegaly

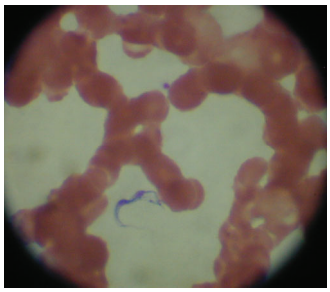
pancytopenia & hypergammaglobulinemia



Diagnosis: intracellular amastigotes in bone marrow or splenic aspirate
antibody to rK39 recombinant Ag (dipstick test)

Treatment: liposomal ampho B (miltefosine for *L. donovani*)

Question 4: A 41 yo woman presented to a local emergency department with a one day history of fever associated with swelling and redness in her groin four days after returning from safari in Tanzania. Peripheral blood smear is obtained.



What is the most likely diagnosis?

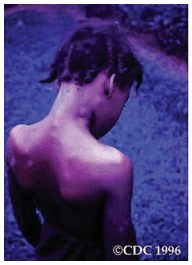
A. Leishmania donovani
B. Plasmodium vivax
C. Trypanosoma brucei
D. Wuchereria bancrofti
E. Leptospira interrogans

African Trypanosomiasis (sleeping sickness)

Vector = tse tse fly (Glossina sp)

Trypanosoma brucei gambiense (W. Africa)
- humans as reservoirs
- progression over many months

Trypanosoma brucei rhodesiense (E. Africa)
- cattle and game park animals as reservoirs
- progression over weeks



DISEASE
within 5 days: chancre at Tse Tse fly bite
regional lymphadenopathy

for weeks: fever, hepatosplenomegaly, lymphadenopathy, faint rash, headache

late: mental status changes, terminal somnolent state

African Trypanosomiasis – Lab findings

Non-specific lab findings
- anemia
- thrombocytopenia
- elevated IgM
- hypergammaglobulinemia

Diagnostic lab findings
- detection of parasite in lymph node, circulating blood, or CSF

-->do FNA of lymph node while massaging node, then push out the aspirate onto a slide and immediately inspect under 400x power. Trypanosomes can be seen moving for 15-20minutes, usually at edge of the coverslip

- a card agglutination test that detects T.b.gambiense sp. antibodies.
-->V. sensitive (94-98%), but poor specificity
--> can get false +s in pts with Schisto, filaria, toxo, malaria

African Trypanosomiasis - Life Cycle

Q. Why are Trypanosoma brucei infections associated with persistently elevated IgM levels?

African Trypanosomiasis - Life Cycle

Q. Why are Trypanosoma brucei infections associated with persistently elevated IgM levels?

A. because they keep changing their outer surface protein

- T. brucei contains as many as 1000 genes encoding different VSGs (VSG = variant surface glycoprotein)
- each trypanosome expresses one, and only one, VSG at a time
- individual parasites can spontaneously switch the VSG they express

African Trypanosomes – The Lady Gaga of the Microbial World

African Trypanosomiasis –Treatment

→ **must do CSF analysis to decide on Rx!!!**

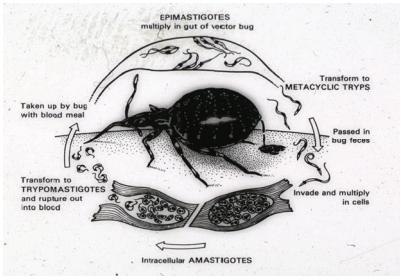
If > 5 WBC/mm^3, treat as if in late stage

	West African	East African
Early	pentamidine	suramin
Late (CNS)	eflornithine+nifurtimox	melarsoprol

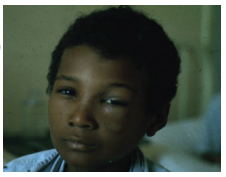
Notes: 1) Melarsoprol associated with ~5% death rate due to reactive encephalopathy.
2) This is reduced by co-administration of corticosteroids.
3) Oral fexinidizole promising for T. b. gambiense infection (Lancet 2018;391, 10116).

Chagas disease

- transmitted by *Trypanosoma cruzi* (also blood transfusion and congenitally)
- vector: reduviid (triatomine) bugs
- reservoirs: opossums, rats, armadillos, raccoons, dogs, cats



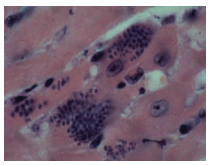
Chagas – Clinical Disease



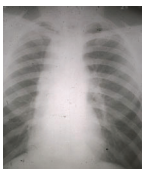
Acute (starts 1 week after infection, can persist for 8 weeks)
- fever
- local lymphadenopathy
- unilateral, painless periorbital edema

Indeterminate stage
- serology positive, no evidence of disease

Chronic



dilated cardiomyopathy, R>L (CHF, syncope, arrythmia)

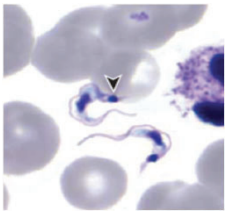


megaesophagus

49 – Lots of Protozoa

Speaker: Edward Mitre, MD

Chagas Diagnosis & Rx



Acute disease

- identification of parasites in blood

Chronic disease

- *T. cruzi* specific IgG antibodies in serum
  → **two tests recommended for diagnosis**

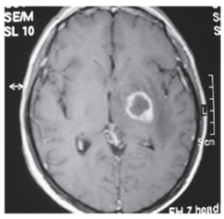
(research: xenodiagnosis, hemoculture, PCR)

NOTE: U.S. blood supply being screened

Treatment: Benznidazole (FDA approved in 2017) or Nifurtimox (from CDC on IND)

Always offer: acute infection, congenital, < 18 yo, reactivation disease
Usually offer: 19-50 years old and no advanced cardiac disease
Individual decision: > 50 years old and no advanced cardiac disease

Chagas in immunosuppressed patients



2008 Int J Infectious Diseases

T. cruzi and AIDS

Primarily reactivation neurologic disease

→ acute,diffuse, necrotic meningoencephalitis
→ focal CNS lesions (similar to Toxo)**

T. cruzi and solid organ transplant

→ recipient of infected organ:
fevers, hepatosplenomegaly, myocarditis
→ disease often does not occur until months after transplant

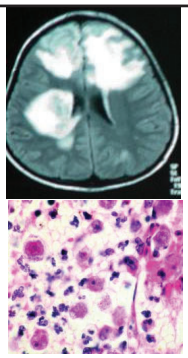
ALSO…. reactivation myocarditis occurs in ~40% of patients that receive heart transplant because of Chagas cardiomyopathy

Protozoa

Protozoa - Extraintestinal	Protozoa - Intestinal
Apicomplexa Plasmodium Babesia (Toxoplasma)	**Apicomplexa** Cryptosporidium Cyclospora Cystoisospora
Flagellates Leishmania Trypanosomes (Trichomonas)	**Flagellates** Giardia Dientamoeba
Amoebae Naegleria Acanthamoeba Balamuthia	**Amoebae** Entamoeba
	Ciliates Balantidium

Not Protozoa **Kingdom Fungi:** Microsporidiosis agents
Kingdom Chromista: Blastocystis

Free-living amoebae



Naegleria fowleri

- warm freshwater exposure
- enters through olfactory neuroepithelium
- fulminant meningoencephalitis
- immunocompetent children/young adults

Acanthamoeba

- found in soil and water
- enter through lower respiratory tract or broken skin
- subacute granulomatous encephalitis
- immunocompromised hosts
- chronic granulomatous keratitis (contact lens, LASIK)

Balamuthia mandrillaris

- likely enters through lower respiratory tract or broken skin
- transmission by solid organ transplantion has been reported
- subacute granulomatous encephalitis
- normal and immunocompromised hosts

Outcome → often fatal (amphotericin B, azoles, pentamidine, others tried)

Protozoa

Protozoa - Extraintestinal	Protozoa - Intestinal
Apicomplexa Plasmodium Babesia (Toxoplasma)	**Apicomplexa** Cryptosporidium Cyclospora Cystoisospora
Flagellates Leishmania Trypanosomes (Trichomonas)	**Flagellates** Giardia Dientamoeba
Amoebae Naegleria Acanthamoeba Balamuthia	**Amoebae** Entamoeba
	Ciliates Balantidium

Not Protozoa **Kingdom Fungi:** Microsporidiosis agents
Kingdom Chromista: Blastocystis

When to suspect an intestinal protozoan infection:

Patient has: Protracted watery diarrhea (weeks to months)

AND/OR:

- **history of travel [domestic (esp. camping) or foreign]**
- **recreational water activities**
- **altered immunity (HIV infection)**
- **exposure to group care (daycare)**

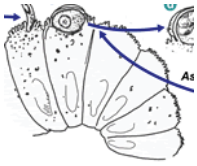
Note: discussion will focus on intestinal protozoa as they occur in patients seen in the U.S. These are leading causes of diarrhea, morbidity, and mortality worldwide, especially in young children.

Intestinal Apicomplexa parasites

Cryptosporidium
- *C. parvum:* cows
- *C. hominis:* humans

Cyclospora cayetanensis

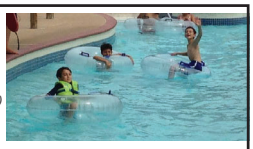
Cystoisospora belli



Cryptosporidium in enterocyte. CDC DpDx

- all have worldwide distribution
- all transmitted by water or food contaminated with oocysts
- organisms invade enterocytes
- all cause watery diarrhea that can be prolonged & severe in immunocompromised

Intestinal Apicomplexa: clinical clues



Cryptosporidium *(2013 GEMS study: major burden of childhood diarrhea)*
- watery diarrhea of several weeks
- cattle workers and daycare outbreaks
- cysts are resistant to chlorine (water supply outbreaks)
  --> #1 cause of water park/swimming pool outbreaks

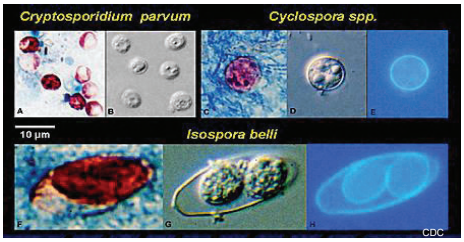
Cyclospora cayetanensis - self-limited immunocompetent BUT can last up to 10 weeks!

- abrupt onset with nausea, vomiting, and fever early
- anorexia, weight loss, fatigue late in course
- food associated outbreaks: raspberries, lettuce, herbs
- esp. Nepal, Peru, Guatemala

Cytoisospora belli
- no animal reservoirs known
- watery diarrhea
- may be associated with a peripheral eosinophlia!
  (the ONLY intestinal protozoa that does this)

Intestinal Coccidia characteristics

Pathogen	Size	Stain	Treatment
Cryptosporidium	4 μm	m acid-fast	(none) nitazoxanide or paromomycin
Cyclospora	10 μm	m acid-fast	TMP/SMX
Cytoisospora	20 μm	m acid-fast	TMP/SMX



note: stool Ag tests commercially available for cryptosporidium
recently FDA-approved stool multiplex PCR detects cryptosporidium

Morbidity and Mortality Weekly Report

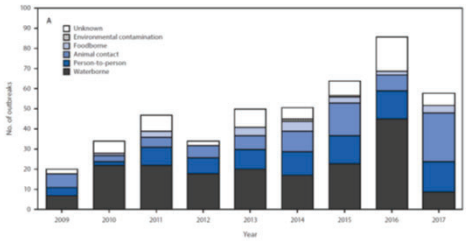
Cryptosporidiosis Outbreaks — United States, 2009–2017

MMWR / June 28, 2019 / Vol. 68 / No. 25

Morbidity and Mortality Weekly Report

Cryptosporidiosis Outbreaks — United States, 2009–2017

MMWR / June 28, 2019 / Vol. 68 / No. 25



"The number of reported outbreaks has increased an average of approximately 13% per year."

49 – Lots of Protozoa

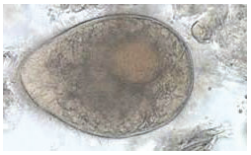
Speaker: Edward Mitre, MD

Question 5: A 28 year old woman returns after studying mosquito breeding habits in Honduras for one year. She reports intermittent abdominal pain and diarrhea for several months. Stool ova and parasite exam is positive for the presence of a ciliated single cell organism.

What is the most likely diagnosis?

A. Balantidium coli
B. Entamoeba histolytica
C. Giardia lamblia
D. Dientamoeba fragilis
E. Endolimax nana

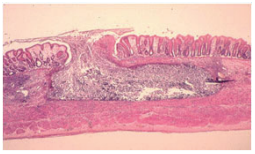
Balantidium coli

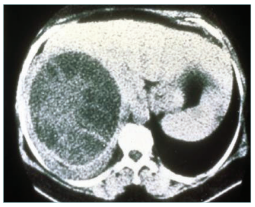

CDC DpDx

- the only ciliated pathogen of humans!
- largest protozoan pathogen of humans!
  (about 70 μm wide and up to 200 μm long)
- found worldwide, especially Central and S. America, S.E. Asia, and Papua New Guinea
- associated with eating food/water contaminated with pig feces
- Symptoms: most people asymptomatic
  can cause colitis with abdominal pain, weight loss, +/- diarrhea
  (especially in malnourished and immunocompromised)
- Treatment: tetracycline (!) or metronidazole

Entamoeba histolytica

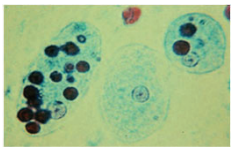
- strictly human pathogen – therefore acquired by food/water contaminated with human feces
- kill cells by small bites (trogocytosis)!!
  Nature 2014, 508, 526





wide range of clinical presentations
- asymptomatic
- traveler's diarrhea (a common cause)
- colitis (can be lethal)
  sharp abdominal pain
  bloody diarrhea
  fever
  flask-shaped ulcerations
  →onset can occurs weeks to months after travel
- ameboma
- extraintestinal (liver, brain abscess) in young men
  hepatic tenderness
  crackles at the right base

Entamoeba histolytica


E. histolytica trophozoites with ingested RBCs.

Diagnosis

Stool O/P
- only 50% sensitive for colitis and abscess
- poor specificity b/c unable to differentiate *E.histolytica* from non-pathogenic *E. dispar* and the diarrhea-only causing *E. moshkovskii*
  (note: ingested RBCs suggestive of Eh, but not 100%)

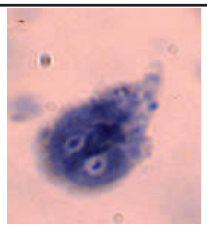
Stool antigen testing > 90% sensitive for intestinal disease

Serology
- very helpful in amebic liver abscess (95% sensitive)
- helpful (about 85% sensitive) in intestinal amebiasis

Treatment
tinidazole or metronidazole followed by intraluminal agent (paromomycin)

Giardia intestinalis

(prior G. lamblia, G. duodenalis)



Flagellated protozoan
- fecal/oral via ingestion of cyst form in food/water
- cyst is chlorine resistant
- cysts from humans (beavers, muskrats)

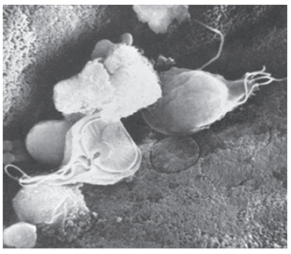
Disease in U.S.
- most common parasitic infection in the U.S (20k cases reported/year, likely 2M)
  → U.S-acquired cases peak in the late summer/early fall
  → a leading cause of traveler's diarrhea

Symptoms
- intermittent watery diarrhea weeks to months
- foul smelling stools, flatulence, "sulfur burps"

49 – Lots of Protozoa
Speaker: Edward Mitre, MD

Giardia

At risk populations
- international travelers
- swimming in lakes/streams, outdoor survival/camping
- infants in daycare
- child care workers
- immunoglobulin deficiencies (esp CVID)
- HIV when CD4 < 100



Diagnosis
- stool antigen test
- recently approved stool multiplex PCR

Treatment

tinidazole, metronidazole (off-label), nitazoxanide, and albendazole (off label)

Other intestinal protozoa

Non-pathogens

amoebae
- *Entamoeba dispar*
- *Entamoeba hartmanni*
- *Entamoeba coli*
- *Endolimax nana*
- *Iodamoeba bütschlii*

flagellates
- *Chilomastix mesnili*
- *Trichomonas hominis*

Treat if symptomatic: *Dientamoeba fragilis* (implicated in IBS)

Protozoa

Protozoa - Extraintestinal

Apicomplexa
- Plasmodium
- Babesia
- (Toxoplasma)

Flagellates
- Leishmania
- Trypanosomes
- (Trichomonas)

Amoebae
- Naegleria
- Acanthamoeba
- Balamuthia

Protozoa - Intestinal

Apicomplexa
- Cryptosporidium
- Cyclospora
- Cystoisospora

Flagellates
- Giardia
- Dientamoeba

Amoebae
- Entamoeba

Ciliates
- Balantidium

Not Protozoa

Kingdom Fungi: Microsporidiosis agents
Kingdom Chromista: Blastocystis

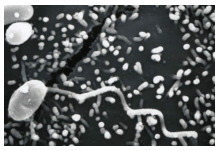
Microsporidia – obligate intracellular fungi!

→Produce extracellular, 1-2 micron, infective spores
→Spores have a coiled organelle called a polar tubule
→After ingestion, the spore germinates and the polar tubule is used to inject sporoplasm into a host cell

Spores of *E. hellem* bursting out of a cell (CDC DpDx)

Enterocytozoon bieneusi
- watery diarrhea
- biliary disease (cholangitis, acalculous cholecystitis)

Encephalitozoon intestinalis
- watery diarrhea
- biliary disease
- disseminated disease (liver, kidney, lung, sinuses)



Polar tubule inserted into a eukaryotic cell (CDC DpDx)

Encephalitozoon cuniculi, hellem
- can cause disseminated disease of multiple organs, plus eye

Many species (including *Vittaforma corneae*): punctate keratoconjunctivitis (contact lens use, after eye surgery, bathing in hot springs)

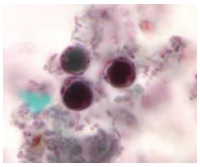
DIAGNOSIS: modified trichrome stain, Calcofluor white, IFA
TREATMENT: albendazole (not effective for *E. bieneusi*)

Blastocystis

What is it?

Nobody really knows!!

It may be part of a new kingdom (Chromista!), with kelp and diatoms!



Blastocystis cyst-like forms , trichrome (CDC DpDx)

Forms are 5-40 microns wide. Anaerobic. Eukaryotic.
→ cystic, ameboid, granular, and vacuolar forms

Does it cause disease?
That's a good question!! Maybe.
Associated with watery diarrhea, abdominal discomfort, nausea, and flatulence.

Diagnosis: light microscopy

Treatment?
metronidazole, TMP/SMX, or nitazoxanide (none FDA-approved)

Protozoan infections that can reactivate in the severely immunocompromised
- Toxoplasmosis
  - encephalitis with mass lesions
  - pneumonitis
  - retinitis
- Leishmania
  - reactivation of visceral and cutaneous reported
  - visceral with fever, hepatosplenomegaly, pancytopenia
- Chagas
  - encephalitis with mass lesions
  - hepatosplenomegaly and fevers
  - myocarditis in 40% that receive heart transplant b/c Chagas disease
- Malaria

Some other protozoa that can cause severe disease in immunocompromised
- Cryptosporidium
- Giardia
- Microsporidia
- Babesia
- Acanthamoeba

49 – Lots of Protozoa

Speaker: Edward Mitre, MD

NOAA photo library

Edward Mitre, M.D.
edwardmitre@gmail.com

2020 INFECTIOUS DISEASE BOARD REVIEW

GW | Office of Continuing Education in the Health Professions

25th Annual

COMPREHENSIVE REVIEW *for* INFECTIOUS DISEASE BOARD PREPARATION

DAY 5

COURSE DIRECTORS:
John E. Bennett, MD
Henry Masur, MD

COURSE CO-DIRECTORS:
Paul Auwaerter, MD
David N. Gilbert, MD
Roy M. Gulick, MD, MPH
Andrew Pavia, MD
Richard J. Whitley, MD

www.IDBoardReview.com

WEDNESDAY, AUGUST 26, 2020

#	Start		End	Presentation	Speaker
50	9:45 AM	-	10:15 AM	**Daily Question Preview 5**	*Drs. Gilbert (Moderator), Aronoff, Bennett, Boucher, Masur, and Patel*
51	10:15 AM	-	10:30 AM	**How to Prepare for the Certification, Recertification, or Check-in Exam**	*Helen Boucher, MD*
52	10:30 AM	-	11:15 AM	**Nocardiosis, Rhodococcus, Meliodosis and Actinomycosis**	*David Aronoff, MD*
53	11:15 AM	-	12:15 PM	**Microbiology: What You Need to Know for the Exam**	*Robin Patel, MD*
	12:15 PM	-	12:30 PM	***BREAK***	
54	12:30 PM	-	1:15 PM	**Zoonoses**	*David Aronoff, MD*
55	1:15 PM	-	2:00 PM	**Antibacterial Drugs I**	*Helen Boucher, MD*
56	2:00 PM	-	2:30 PM	**Helicobacter and Clostridioides Difficile**	*David Aronoff, MD*
57	2:30 PM	-	3:15 PM	**Fungal Disease in Normal Abnormal Hosts**	*John Bennett, MD*
	3:15 PM	-	3:30 PM	***BREAK***	
58	3:30 PM	-	4:15 PM	**Tuberculosis in Immunocompetent and Immunosuppressed Hosts**	*Susan Dorman, MD*
59	4:15 PM	-	5:00 PM	**Management of HIV-Related Opportunistic Infections II**	*Henry Masur, MD*
60	5:00 PM	-	5:30 PM	**Skin and Soft Tissue Infections**	*Helen Boucher, MD*
61	5:30 PM	-	6:30 PM	**Antibacterial Drugs II**	*David Gilbert, MD*

50

Board Review Session 5

Drs. Gilbert (Moderator), Aronoff, Bennett, Boucher, Masur, and Patel

50 – Board Review Session 5

Drs. Gilbert (Moderator), Aronoff, Bennett, Boucher, Masur, and Patel

2020 INFECTIOUS DISEASE BOARD REVIEW

Board Review Session 5

Moderator: David Gilbert, MD
Faculty: Drs. Aronoff, Bennett, Boucher, Masur, and Patel

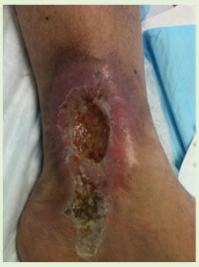
2020 INFECTIOUS DISEASE BOARD REVIEW

Answer Keys with Rationales

The answer key, including rationales, will be posted tomorrow to the "Board Review Answer Keys" section on the online materials site.

#1

This otherwise healthy patient, who has never left the Midwestern United States, has a chronic leg ulcer. He has had a negative stains and cultures for fungi, mycobacteria, Nocardia, or viral inclusions.



#1

This otherwise healthy patient with a chronic leg ulcer is most likely to have:

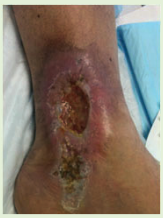
A) Common variable immunoglobulin deficiency

B) Lupus erythematosus

C) Hepatitis C

D) Ulcerative colitis

E) Mycobacterium ulcerans



#2

A 52 year old man has been in the ICU following a cocaine related stroke.

He was intubated following his stroke, developed staph epidermidis bacteremia from a PICC line (peripherally inserted central catheter), and is now off antibiotics (7 day course of daptomycin has been completed) ready to move to the rehabilitation floor. He has a Foley catheter and a peripheral IV line.

The patient is alert and oriented and has no new complaints.

#2

The resident preparing to transfer the patient calls an ID consult because the urine in the Foley bag is cloudy. The patient is afebrile with normal vital signs, no new physical findings, and he does not have pain over his bladder and no flank pain.

The medical resident has obtained a urinalysis on fresh urine from the Foley catheter. there are 50-75 WBC per high power field and 5-10 RBCs with 2+ bacteria but a negative leukocyte esterase. Culture is sent.

There are no changes in his complete blood count or chemistry profile.

The patient has no known antibiotic allergies.

#2

What would you suggest?

A) No change in regimen: follow for 48 hours with Foley in place, pending urine culture result and treat with antibiotic according to culture.

B) Replace the Foley, and treat with antibiotics if urine culture is positive according to urine isolate susceptibility pattern

C) Replace the Foley and treat empirically with ciprofloxacin

D) Remove the Foley and do a voiding test to determine if Foley is necessary; no antibiotic therapy

E) Remove the Foley and do a voiding test to determine if Foley is necessary; treat empirically with ciprofloxacin

#3

A 55 year old male undergoes emergency surgery for a ruptured appendix with severe bacterial peritonitis and septic shock.
He has no antibiotic allergy or intolerances.

Which one of the following antibiotics requires concomitant metronidazole IV?

A) Piperacillin-tazobactam

B) Ampicillin-sulbactam

C) Ceftolozane-tazobactam

D) Imipenem-cilastatin-relebactam

E) Eravacycline

#3

A 55 year old male undergoes emergency surgery for a ruptured appendix with severe bacterial peritonitis and septic shock.
He has no antibiotic allergy or intolerances.

Which one of the following antibiotics requires concomitant metronidazole IV?

A) Piperacillin-tazobactam

B) Ampicillin-sulbactam

C) Ceftolozane-tazobactam

D) Imipenem-cilastatin-relebactam

E) Eravacycline

#4

An 86-year-old man is admitted to the hospital for treatment of community-acquired pneumonia and receives IV ceftriaxone followed by oral moxifloxacin.

By day 4, his temperature is normal and he is ready for discharge when he develops loose stools with some abdominal cramping.

He is having 6-8 watery bowel movements a day. There is no blood in the stool. His albumin is 3.0, creatinine 1.9, and white blood cell count is 18,000/mm3. A stool specimen is submitted and is positive for Clostridium difficile toxin using PCR for the toxin B gene.

#4

Which of the following drugs would you use to treat this patient assuming you were choosing monotherapy?

A) IV Metronidazole

B) PO Metronidazole

C) IV Fidaxomicin

D) PO Rifaxamin

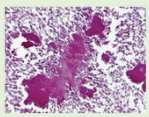
E) PO Vancomycin

#5

A 42-year-old woman was referred for management of an incarcerated, indirect, inguinal hernia on the right side. She had used an IUD for many years.

Her peripheral blood white cell count, C-reactive protein and erythrocyte sedimentation rate were normal. The patient was afebrile.

During operation on the hernial sac, a putrid, inflammatory, tumorous formation associated with the right ovary was found. The histopathologic picture of the resected ovary showed a highly active zone of abscess formation, with granular conglomerates of a filamentous microorganism (Figure).



#5

In addition to surgical resection, treatment should involve which of the following medications?

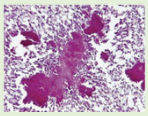
A) Penicillin

B) Voriconazole

C) Trimethoprim-sulfamethoxazole

D) Weekly amphotericin B

E) Ciprofloxacin



#6

A 27-year-old woman calls to say, "I've got another urinary tract infection." In the past six months, she was seen twice for complaints of dysuria and frequency.

The first time, a urine dipstick test was consistent with a UTI, and she responded to three days of antibiotics. The second time, which was two months ago, a culture was sent that grew a highly susceptible E. coli, and again her symptoms went away with three days of antibiotic treatment.

She is otherwise healthy, sexually active and never had any urinary symptoms before the current year.

#6

Which one of the following is the most appropriate approach to this patient's complaint?

A) Culture her urine

B) Image her urinary tract

C) Perform a bladder emptying study

D) Prescribe antibiotics for three days

E) Prescribe antibiotics for 2 weeks.

#7

A patient with HIV infection (CD4=25 cells/μL and VL 1 million c/ml) has cryptococcal meningitis (positive serum and CSF crypt antigen) with severe headaches and blurred vision.

The opening pressure on the initial LP was not measured.

Papilledema is seen on funduscopic exam. A CT scan shows no mass lesion or signs of herniation. The patient was started on Liposomal Amphotericin plus 5FC.

#7

Which of the following would you recommend in response to her persistent severe headache and blurred vision on day 2 of therapy:

A) Immediate institution of acetazolamide and monitor for first 6 hours before adding another intervention

B) Immediate institution of dexamethasone and monitor for 24 hours

C) Initiate daily lumbar punctures to reduce intracranial pressure

D) Double the dose of Liposomal amphotericin B to 1.2 mg/kg/day

E) Add Fluconazole 1200 mg to the antifungal regimen

#8

A 67-year-old patient on methadone for chronic pain (5 mg q 8 H) for several years due to severe low back pain is admitted for pneumococcal pneumonia and an empyema.
A chest tube is inserted and he is treated for pneumococcal pneumonia with bacteremia and empyema: vancomycin plus ceftriaxone is his initial regimen.

The day after his chest tube is inserted, the patient has considerable pain at the chest tube site. Acetaminophen and ketorolac are given in addition to has baseline methadone, but after 24 hours of this analgesic regimen the patient cannot sleep due to considerable, constant pain which he states in 10/10 in severity.

#8

What would you recommend for pain relief?

A) Stopping the methadone and administering increasing doses of codeine starting at 5 mg q4h

B) Maintaining the methadone dose and adding codeine at 5 mg q4h with increasing doses as needed

C) Stopping the methadone and prescribing fentanyl by patient controlled analgesia (PCA)

D) Continue current regimen of methadone, acetaminophen and ketorolac for 48 hrs. more before switching the regimen

#9

A 22-year-old university student was in his usual state of health until the evening prior to hospital admission when he went to bed with a headache. He told his roommate that he felt feverish; the following morning his roommate found him in bed, moaning and lethargic, and brought him to the Emergency Department.

In the Emergency Department, he appeared toxic and drowsy but was oriented. His temperature was 40°C, heart rate 124/min, and blood pressure 98/60 mm Hg.

His neck was stiff and he had a purpuric non-blanching rash most prominent on the trunk, legs, and wrists.
A lumbar puncture is performed revealing 5000 cells/l (10% lymphocytes, 90% neutrophils), a protein of 275 mg/dL and a glucose of 15 mg/dL.

#9 **Gram stain of spinal fluid shows Gram negative cocci in pairs. Bacterial cultures are pending.**

His cerebrospinal fluid was submitted to testing with a multiplex PCR panel, and returned the results below.

Viruses	Bacteria	Fungi
Cytomegalovirus NEGATIVE	Escherichia coli K1 NEGATIVE	Cryptococcus neoformans/gattii NEGATIVE
Enterovirus NEGATIVE	Haemophilus influenzae NEGATIVE	
Herpes simplex virus 1 NEGATIVE	Listeria monocytogenes NEGATIVE	
Herpes simplex virus 2 NEGATIVE	Neisseria meningitidis POSITIVE	
Human herpes virus 6 POSITIVE	Streptococcus agalactiae NEGATIVE	
Human parechovirus NEGATIVE	Streptococcus pneumoniae NEGATIVE	
Varicella zoster virus NEGATIVE		

#9

Which of the following is the most appropriate antimicrobial regimen for this patient?

A) Vancomycin and cefepime

B) Vancomycin and cefepime and acyclovir

C) C. Ceftriaxone and ganciclovir

D) Ceftriaxone and acyclovir

E) Ceftriaxone alone

#10 **A 34 year old man who underwent renal transplantation for end stage renal disease due to focal sclerosing glomerulonephritis two months prior to presentation, presents to the Emergency Department in January with headache and fever of five days duration.**

His post-transplant course was uncomplicated and he is receiving prednisone, tacrolimus, mycophenylate mofetil and trimethoprim-sulfamethoxazole.
He and his donor were cytomegalovirus and Epstein-Barr virus seropositive.

He lives in Minnesota and has been at home since the transplant. He has no personal history of or exposure to tuberculosis.
There is no history of travel to the desert Southwest of the United States, or outside of the United States and no animal exposure

#10 **A lumbar puncture is performed revealing 50 cells/ml (90% lymphocytes, 10% neutrophils), a protein of 75 mg/dL and a glucose of 35 mg/dL. Gram stain of spinal fluid is negative and bacterial cultures are in progress.**

His spinal fluid is submitted to testing with a multiplex PCR panel, and returns the results shown below.

Viruses	Bacteria	Fungi
Cytomegalovirus NEGATIVE	Escherichia coli K1 NEGATIVE	Cryptococcus neoformans/gattii NEGATIVE
Enterovirus NEGATIVE	Haemophilus influenzae NEGATIVE	
Herpes simplex virus 1 NEGATIVE	Listeria monocytogenes NEGATIVE	
Herpes simplex virus 2 NEGATIVE	Neisseria meningitidis Negative	
Human herpes virus 6 NEGATIVE	Streptococcus agalactiae NEGATIVE	
Human parechovirus NEGATIVE	Streptococcus pneumoniae NEGATIVE	
Varicella zoster virus NEGATIVE		

#9

Which test is most urgent to perform on his cerebrospinal fluid next?

A) Mycobacterial culture

B) West Nile virus PCR

C) Zika virus PCR

D) Cryptococcal antigen

E) Examination for Naegleria fowleri

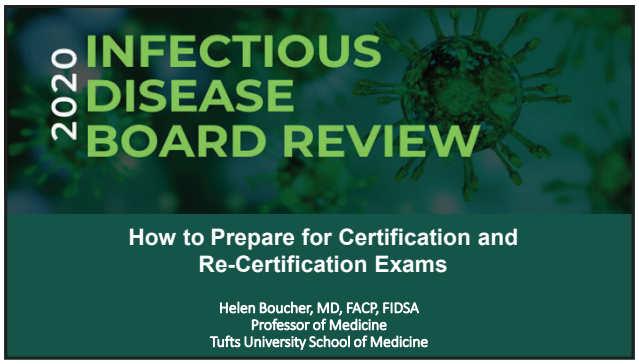
51

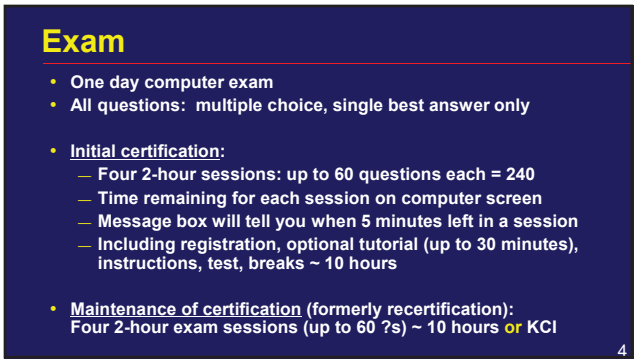
How to Prepare for the Certification, Recertification, or Check-in Exam

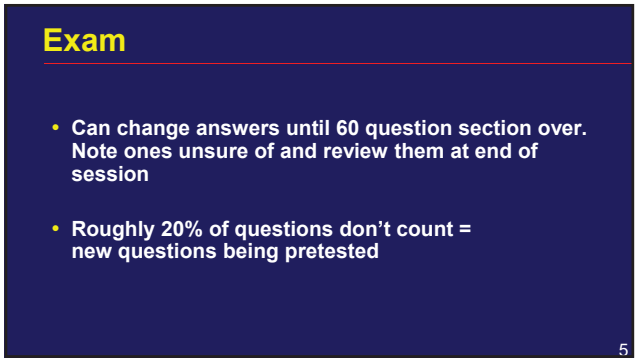
Dr. Helen Boucher

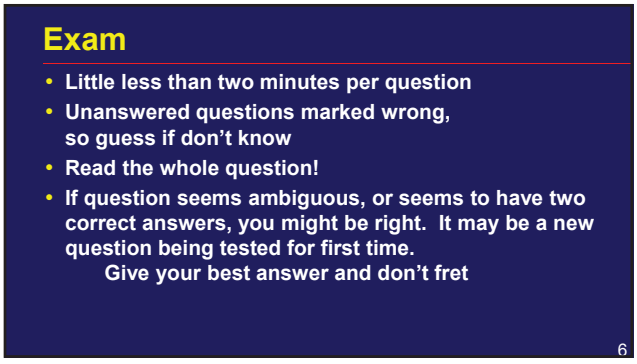
51 – How to Prepare for Certification and Re-Certification Exams

Speaker: Helen Boucher, MD









51 – How to Prepare for Certification and Re-Certification Exams

Speaker: Helen Boucher, MD

Breaks

- Breaks are optional. Take them!
- 3 breaks during day: total 100 minutes
- 1 break after each of first 3 test sessions
- Can use some or all of break time
- Amount of break time used after each session subtracted from total time
  - For example: if take 10 minute break after session one, amount of break time remaining for exam is 90 minutes
- 100 minutes break time for MOC exam (3 breaks)

7

Exam

- Confirmation email will specify appointment time and give driving directions to test center
- Check out site before exam:
  - Where is it? Where to park? Where to eat?
- Arrive ½ hour early
- Each testing center has 8 - 25 workstations
- An administrator will be present
- At start of exam: see several screens reviewing instructions about taking exam, and asked to agree to a Pledge of Honesty

8

Exam

- You will need personal ID (2 types): government-issued ID with photo and signature (driver's license, passport, etc.)

  And

  another form of ID with signature or photo (Social Security card, credit card, ATM card, etc.)
- Not allowed to take exam with expired ID
- Palm vein scan, security wanding, signature and photograph will be taken

9

Exam

- Short orientation then taken to computer workstation
- May request left-handed mouse
- May request instructions adjust height and contrast of computer
- Erasable notepads provided and can type and save notes in pop-up box that accompanies each question
- Can request headphones or earplugs; cannot bring your own
- Any problem: Don't get up! Raise your hand
- Electronic fingerprint each time enter and exit testing room - allow 10 min to check back in

10

Disabled Test Takers

- ABIM complies with the Americans with Disabilities Act (ADA)
  - They will make reasonable modifications to exam procedures as necessary, but there are limits
- Each request individually evaluated
- For more info see Forms of Accommodation on ABIM website

11

Not allowed in test room (small storage locker provided)

- Electronic devices: cell phone, PDA, pager, beeper
- Calculator, calipers, camera
- Watch – clock is in testing room
- Wallet, purse
- Briefcase, backpack
- Jacket, coat (sweater OK)
- Books, scratch paper, pens, pencils (noteboards provided)
- Medications require prior approval (contact us feature on website)
- Food and drink
- (Bring drinks for breaks to keep in locker; can bring lunch, but no refrigeration)

12

51 – How to Prepare for Certification and Re-Certification Exams

Speaker: Helen Boucher, MD

Questions about exam day

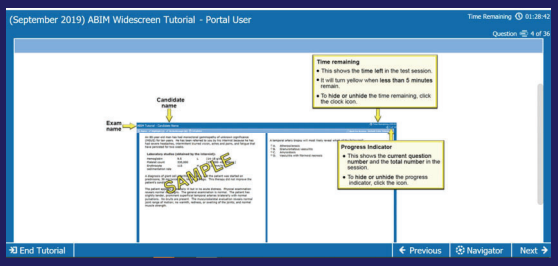
- Call ABIM 1-800-441-ABIM (2246)
  Mon-Fri: 8:30AM – 6PM
  Saturday: 9AM – 12PM

13

Exam Tutorial

- Examples of the exam question formats are available in a tutorial at the ABIM website:
  - https://www.abim.org/certification/exam-information/infectious-disease/exam-tutorial.aspx

14



15

Exam Format

Exam is composed of multiple-choice questions with a single best answer, predominantly describing patient scenarios

- Questions ask about the work done (that is, tasks performed) by physicians in the course of practice: Making a diagnosis
- Ordering and interpreting results of tests
- Recommending treatment or other patient care
- Assessing risk, determining prognosis, and applying principles from epidemiologic studies
- Understanding the underlying pathophysiology of disease and basic science knowledge applicable to patient care

16

- >75% patient case presentations
  - not trying to trick you
- Normal lab values provided
- Pediatric questions not likely
- Very little basic science:
  - mechanisms of resistance - ESBL, KPC
- Very little clinical microbiology (occasional clues):
  - things you could do to help lab
    - e.g. oil on media for lipophilic yeast
      Iron and 30° incubation for *M. haemophilum*

17

Exam Content

- Exam content determined by a pre-established blueprint
  - Different for initial certification and MOC
- Primary medical content categories are ….

18

51 – How to Prepare for Certification and Re-Certification Exams

Speaker: Helen Boucher, MD

2019 Exam Blueprint

Medical Content Category	% of Exam
Bacterial Diseases	27%
Human Immunodeficiency Virus (HIV) Infection	15%
Antimicrobial Therapy	9%
Viral Diseases	7%
Travel and Tropical Medicine	5%
Fungi	5%
Immunocompromised Host (Non-HIV Infection)	5%
Vaccinations	4%
Infection Prevention and Control	5%
General Internal Medicine, Critical Care, and Surgery	18%
	100%

19

Clinical Syndromes

- Pleuropulmonary infections
- Infections of the head and neck
- Infections and other complications in HIV/AIDS
- Cardiovascular infections
- Central nervous system infections
- Gastrointestinal and intra-abdominal infections
- Liver and biliary tract infections
- Skin and soft tissue infections
- Bone and joint infections

20

Clinical Syndromes (con't.)

- Infections of prosthetic devices
- Infections related to trauma
- Bloodstream infections and sepsis syndromes
- Nosocomial infections
- Urinary tract infections
- Sexually-transmitted diseases and reproductive tract infections
- Fever (infectious and non-infectious) and hyperthermia

21

Patient Populations

- Patients who are neutropenic
- Patients with:
  - Leukemia, Lymphoma, or other malignancies
- Patients following solid organ or bone marrow transplantation/HSCT
- Patients with HIV/AIDS or patients immunocompromised by other disease or medical therapies
- Pregnant women
- Travelers and immigrants

22

Exam Content

- More specific details of content can be found on ABIM website.

For example……

23

Bacterial Diseases (27%)*

	Approximate % of total exam
Gram-positive cocci	4.5%
Gram-positive rods	<2%
Gram-negative cocci/bacilli	2%
Gram-negative rods	2.5%
Anaerobes	2.5%
Actinomycetes	<2%
Mycobacteria	5% etc.

* percentages describe content of typical exam and are approximate

24

51 – How to Prepare for Certification and Re-Certification Exams

Speaker: Helen Boucher, MD

Bacterial Diseases (27%)
more details on website, e.g.

	Approximate % of total exam
• Gram-positive rods	<2%

Which may include:
- Listeria
- Corynebacterium
- Bacillus
- Erysipelothrix

25

Bacterial Diseases (27%)
more details on website, e.g.

	% of total exam
• Syndromes with bacterial pathogens	3%

Which may include:

Head and neck, Respiratory, Gastrointestinal, Ophthalmologic, Genitourinary, Dermatologic (including skin and soft tissue infections), Musculoskeletal, Neurologic, Cardiovascular

26

HIV Infection (15%)

	Approximate % of exam
• Epidemiology	<2%
• Pathogenesis	<2%
• Laboratory testing	<2%
• HIV treatment regimens	4.5%
• Opportunistic conditions	5%
• Malignancies	<2%
• Immune reconstitution (IRIS)	<2%
• Other complications of HIV	2%
• Related issues	<2%

27

HIV Infection (15%)
more details on website, e.g.

	Approximate % of exam
• Other complications of HIV	2%

Which may include:
- Thrombocytopenic disorders
- Hypercoagulability, Castelman's disease
- HIV infection of specific organs
- Endocrine manifestations

• Related issues	<2%

Which may include:

Substance abuse, Organ transplantation, Primary care, Non-HIV-related complications more common in HIV

28

Viral Diseases (7%)

	Approximate % of exam
• DNA Viruses	4%
• RNA Viruses	2.5%
• Prions	<2%

29

General Medicine, Critical Care and Surgery (18%)

	Approximate % of exam
• General Internal Medicine:	7.5%

Malignancies, Hemophagocytic Syndrome, Collagen vascular and autoimmune disorders, Dermatologic disorders, , Bites, stings and toxins, Non-infectious central nervous system disease, Drug fever, Ethical and legal decision making.

• Critical Care Medicine:	8%

SIRS and sepsis, Ventilator-assoc. pneumonias, Non-infectious pneumonias (ARDS), Hyperthermia and hypothermia, Near drowning and Scedosporium and Pseudallescheria infection

30

51 – How to Prepare for Certification and Re-Certification Exams

Speaker: Helen Boucher, MD

Infection Prevention and Control (5%) More details on website, e.g.

	Approximate % of exam
• Applied epidemiology and biostatistics Outbreak investigation, Healthcare quality improvement, Informatics	<2%
• Prevention of HAIs in special patients Obstetrics, Spinal cord injury, Neoplastic diseases, Organ transplant, Stem cell transplant.	<2%

31

Fungi (5%)

	Approximate % of total exam
• Yeasts, Endemic mycoses, Molds	<2% each
• Superficial / subcutaneous mycoses Mycetoma, Chromoblastomycosis, Malassezia, Dermatophytes	<2%
• Therapy	<2%
• Pneumocystis	<2%
• Therapy	<2%
• Diagnostic testing*	<2%
• Syndromes	<2%

*histopathology, culture, nonculture methods

32

- Pharm and OPAT 2.5%
- Note:
  <2% of 240 = about 5 questions

33

- **Note:**

I recommend you take a look at the website and review the lists.

……..as an example

34

Rickettsia (2.5%)

- R. rickettsii (Rocky Mountain Spotted Fever)
- R. akari (rickettsial pox)
- R. prowazekii (epidemic typhus)
- R. typhi
- Orientia tsutsugamushi (scrub typhus)
- R. conorii
- R. parkeri
- R. africae
- Coxiella burnetii

35

Exam

- Takes couple of years for new question to appear on exam and count. So new developments in last 2 years less likely to be on exam and count.
  - e.g. new Ebola treatment, COVID-19
- Things that were hot and now not, are unlikely to appear:
  - anthrax
  - monkeypox
- Effort made not to have "look up" questions:
  - e.g. Treatments for uncommon parasitic diseases
    - Malaria - yes
    - Filariasis – no

36

51 – How to Prepare for Certification and Re-Certification Exams

Speaker: Helen Boucher, MD

Pass rates

First-time Takers- Initial certification

Year	# of Examinees	Pass Rate
2008		86%
2009		93%
2010	359	91%
2011	348	96%
2012	342	95%
2013	364	87%
2014	361	86%
2015	347	94%
2016	348	98%
2017	339	97%
2018	338	98%
2019	362	98%

37

Pass rate

- Maintenance of Certification (recert.):
  - Questions were from same pool as initial exam – now different blueprint
  - 2015: 301 took; 89% passed
  - 2016: 467 took; 94% passed
  - 2017: 360 took; 90% passed
  - 2018: 367 took; 93% passed
  - 2019: 296 took; 91% passed

38

What to do from now to exam

- Know that this Board Review Course is excellent preparation
- Review questions and images from IDBR website.
- Go to ABIM website (www.abim.org) and:
  - take the tutorial
  - read about Exam Day: What to expect
  - see details about ID exam (blueprints, etc.)

39

What to do from now to exam

- From binders/on line presentations for this course, pull out the "handouts" covering your weak areas and make a little "binder" (e.g. parasites, fungi, mimic syndromes)
- Review your "little binder" just before exam

40

MOC Knowledge Check-In Exam

- Every 2 years
- Shorter – approximately 3 ½ hours
- Can be taken at home/work or in a Test Center
- "Open Book" with UpToDate®
- Uses the same MOC blueprint
- Faster results

41

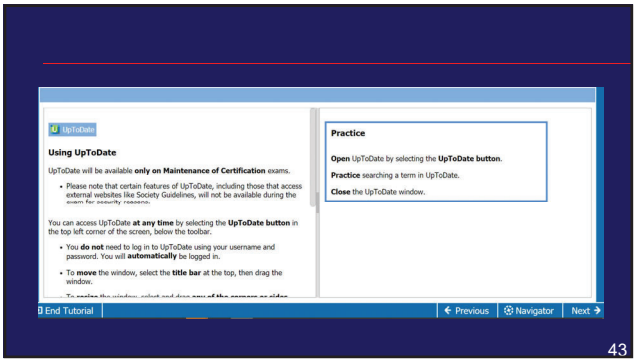
Knowledge Check-In Details

- Two sessions with 45 multiple-choice questions
- 90 minutes/session
- Open-book with UpToDate® access
- Resources:
  - ABIM exam tutorial
  - UpToDate User Academy for ABIM Exam
  - NB: some features of UpToDate, including those that access external websites like IDSA Guidelines, will not be available

42

51 – How to Prepare for Certification and Re-Certification Exams

Speaker: Helen Boucher, MD



43

Preparation Tips

- Take the exam tutorial
- Practice using UpToDate®
- Review the exam blueprint
- Sign in to your Physician Portal and review your appointment time
- Familiarize yourself with the exam day schedule

44

On the Exam Day – Home/Office

- Sign in to your Physician Portal and start your exam 30 minutes early
- Make sure you are using the same computer you used to complete the system check
- Prepare your testing space: desk cleared, door closed and webcam/microphone functioning
- Have a valid ID ready
- Use a hardwired internet connection instead of WiFi (better connection)
- Get familiar with the help link

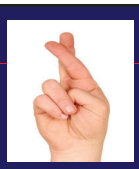
45

Last Tips

- Watch the time
  - 2 mins/question seems long but it's tempting to search and search
- Remember that some ?s are experimental – don't get bogged down
- If you clearly pass, you will receive your exam results immediately (this is great)
- If you're close or fail, it takes 3-4 weeks
- NO Stakes this year
- More changes coming!

46

Thank You: Bennett Lorber, MD



Good Luck
To You All !

47

52

Nocardiosis, Rhodococcus, Meliodosis and Actinomycosis

Dr. David Aronoff

52 – Nocardiosis Rhodococcus equi Melioidosis & Actinomycosis

Speaker: David M. Aronoff, MD, FIDSA, FAAM

2020 INFECTIOUS DISEASE BOARD REVIEW

Nocardiosis, Rhodococcus, Melioidosis, and Actinomycosis

David M. Aronoff, MD, FIDSA, FAAM
Professor of Medicine
Addison B. Scoville Jr. Chair in Medicine
Director, Division of Infectious Diseases
Vanderbilt University Medical Center

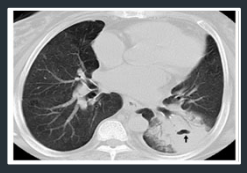
Disclosures of Financial Relationships with Relevant Commercial Interests

- None

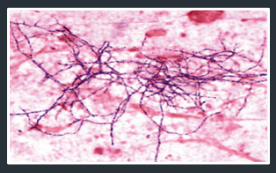
Case

54 year old man with 4 weeks of cough, low grade fevers, & left-sided chest pain. Received a liver transplant 11 months ago, complicated by rejection, requiring high dose steroids 4 months ago. He receives TMP/SMX three times a week. On exam, he is stable, chronically-ill appearing, febrile (101.1ºF), has clear lungs and benign abdomen. Labs reveal a normal white blood cell count, slight anemia, & normal creatinine. Chest radiograph reveals hazy opacity in left lower lung zone. Chest CT reveals nodular air-space consolidation in the left lower lobe with central cavitation (image). Gram strain of bronchoalveolar lavage fluid reveals beaded gram positive filamentous organisms (image).

Chest CT



BAL



CT Image from J. Bargehr, *et al. Clinical Radiology*, 2013-05-01, Volume 68, Issue 5, Pages e266-e271.
Gram stain image from Murray, *et al.* Medical Microbiology, 7E. 2013 Saunders, Elsevier.

What is the most likely cause of this patient's pneumonia?

A. Cryptococcus neoformans
B. Histoplasma capsulatum
C. Actinomyces israellii
D. Nocardia farcinica
E. Aspergillus fumigatus

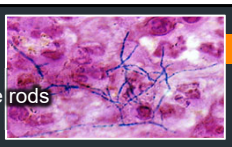
What are the most appropriate next steps in this patient's care?

A. Initiate therapy with intravenous TMP/SMX
B. Obtain a needle biopsy of the lung nodule to confirm the diagnosis
C. Obtain a brain MRI & start amikacin, imipenem, & TMP/SMX
D. Defer therapy until antimicrobial susceptibilities return

52 – Nocardiosis Rhodococcus equi Melioidosis & Actinomycosis

Speaker: David M. Aronoff, MD, FIDSA, FAAM

Nocardia Infections

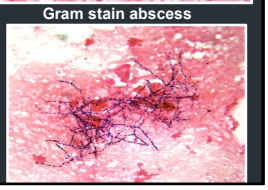


- **Microbiology:**
  - Beaded & branching gram-positive rods
  - Partially acid-fast
  - Aerobic (unlike anaerobic Actinomyces)
  - More than 80 species & >40 cause disease in humans
    - New phylogeny based on DNA sequence (*formerly*, *N. asteroides* complex): **species names are *lookups***.
- **Pathogenesis:**
  - **Inhalation** (most common)
  - **Direct inoculation** through the skin

Photo: http://path.upmc.edu/cases/case226/dx.html; Good reference: Restrepo A & Clark NM. *Clinical Transplantation*. 2019:e13509.

Images of *Nocardia*

- **Beaded**
- **Branching**
- **Gram positive**
- **Partially acid-fast**



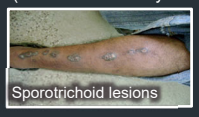
Images from http://thunderhoused.wur.blogspot.com/2010/06/nocardia-species.html

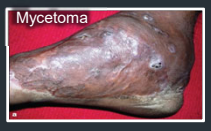
Clinical Features of *Nocardia*

- **Immunocompromised**
  - **Solid organ transplant**, hematopoietic transplant, chronic steroids, alcoholism, diabetes, CGD, CF, anti-TNF therapy, AIDS (less common)
    - *PJP prophylaxis may not prevent nocardiosis*
  - Months to years after transplantation
- **90%**: **slowly progressive pneumonia** with cough, dyspnea, & fever
  - *Aspergillus* similar; co-infections occur
  - Similar to cryptococcal disease & actinomycosis
  - Can disseminate to any organ (**brain** in particular: get MRI)

Clinical Features of *Nocardia*

- **10%**: Skin infections from direct inoculation:
  - Immunocompetent host in tropical region (*N. brasiliensis*)
  - Immunocompromised patient who gardens or walks barefoot
  - **Sporotrichoid** lesions
  - **Mycetomas**: chronic, progressive, lower limbs, draining sinuses (similar to Actinomycetes)



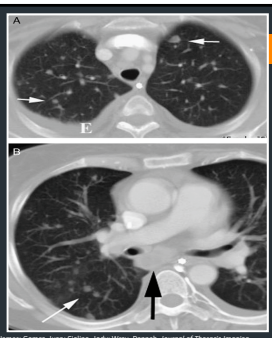


Baradkar V P, *et al. Indian J Pathol Microbiol* 2008;51:432-4 Sharma NL, *et al. Indian J Dermatol Venereol Leprol* 2008;74:635-40

Nocardia Diagnosis

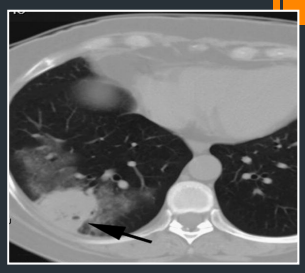
- **Diagnosis**:
  - Suggestive **radiology**
    - Chest imaging: **nodules**, cavities, infiltrates with consolidation, effusions, ground-glass opacities
    - MRI brain: single or multiple **abscesses**
  - Blood **culture**, BAL, biopsy
    - Gram stain, modified acid-fast stain, culture
  - Species identification with nucleic acid sequencing or MALDI: **predictive of drug susceptibility**

- 56-year-old woman post kidney-pancreas transplant & *N. brasiliense*s
- Small lung nodules (white arrows), small right pleural effusion & subcarinal lymphadenopathy (black arrow)



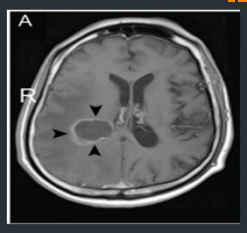
Pulmonary Nocardiosis: Computed Tomography Features at Diagnosis. Blackmon, Kevin; Ravenel, James; Gomez, Juan; Ciolino, Jody; Wray, Dannah. *Journal of Thoracic Imaging*. 26(3):224-229, August 2011. DOI: 10.1097/RTI.0b013e3181f45dd5

- 55-year-old woman with acute myelogenous leukemia & *N. nova*
- Axial CT image without contrast = solitary RLL **mass** with single focus of **cavitation** (arrow) & surrounding **ground-glass opacity**



Pulmonary Nocardiosis: Computed Tomography Features at Diagnosis. Blackmon, Kevin; Ravenel, James; Gomez, Juan; Ciolino, Jody; Wray, Dannah. *Journal of Thoracic Imaging*. 26(3):224-229, August 2011. DOI: 10.1097/RTI.0b013e3181f45dd5

- Right frontoparietal subcortical ring lesion with a central dark signal & bright peripheral contrast enhancement (black arrowheads) in postcontrast T1-weighted image.



Nandhagopal, Ramachandiran, Zakariya Al-Muharrmi, and Abdullah Balkhair. "Nocardia brain abscess." *QJM* 107.12 (2014): 1041-1042.

Nocardia Treatment

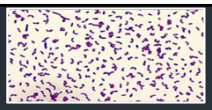
- **Susceptibility testing**
  - Important because of drug resistance
- **TMP/SMX** is mainstay (skin = monotherapy)
- Empiric combination therapy:
  - Amikacin + imipenem/meropenem + TMP/SMX
  - Ceftriaxone & linezolid as alternate agents

Restrepo A & Clark NM. *Clinical Transplantation*. 2019:e13509.

Nocardia **Buzzwords**

- **B**eaded
- **B**ranching
- **B**rain (+ lung)
- **B**actrim

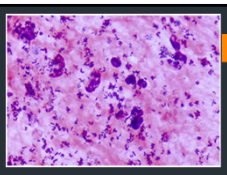
Rhodococcus



- **Clinical findings**:
  - Indolent pneumonia (80%) in **immunocompromised** host
  - **Fever, cough, hemoptysis**, fatigue, subacute, pleuritic CP
  - Nodules, thick-walled **cavities**, infiltrates, effusions possible
  - Extrapulmonary dissemination possible (**skin & brain**)
  - Mimic of TB, NTM, *Aspergillus*, *Nocardia*

Photo: microbe canvas

Rhodococcus



- **Typical patient**:
  - T cell immunosuppressed
    - HIV+ & CD4<100; organ transplant
  - Inhalation or ingestion
  - Farm, soil, manure or horse exposure in some patients
- **Microbiology**: *R. equi* is the most common
  - Gram positive, **aerobe**, **coccobacillary**
  - Colonies can be **salmon pink**
  - Weakly acid fast: can be mistaken for *Nocardia* but **no branching**

Image from W.V. Lin *et al. / Clinical Microbiology and Infection* (2019)

Rhodococcus

33 year-old HIV+ male (CD4 = 20) who lived on a cattle & horse farm

Presented to hospital with 1 month of fever, dry cough, 13# weight loss, sweats & anorexia

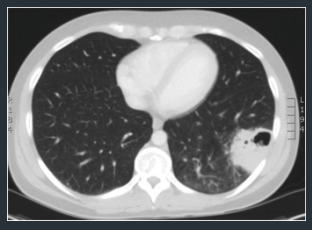


Image from Stewart A., *et al. IDCases.* (2019)

Rhodococcus

- **Diagnosis:**
  - **Culture** followed by 16S rRNA, MALDI-TOF
  - Tissue: gram stain, **necrotizing granulomatous** reaction; microabscess
  - Blood cultures may be positive (>25%)
- **Treatment:**
  - Combination therapy
  - 2 or 3 drug regimens: vancomycin + imipenem/meropenem + fluoroquinolone or rifampin 2-3 wks then oral FQ + azithro/clari or rifampin
    - Linezolid an alternative

Lin WV, *et al. Clin Micro Infect* (2019), Stewart A., *et al. IDCases.* (2019)

Rhodococcus Buzzwords

- **Short** Gram positive rod (coccobacillus)
- **Cavitary** pneumonia (hemoptysis)
- **Salmon pink** colonies
- Advanced **HIV**
- **Horse** / manure exposure

Case

- A 62 yr old sheep rancher from Northern Australia was referred to a West Coast hospital because of refractory pneumonia that had failed to respond completely to multiple, prolonged courses of antibiotics over 3 months, leaving him with continued low grade fever, productive cough & asthenia
- Gram negative rods noted in moderate abundance on Gram stain of sputum & in sputum culture. Identification by automated system failed & isolate sent to referral lab

Question

- Which of the following would have been a likely source of this infection?

A. Hospital nebulizer while hospitalized in Australia (nosocomial superinfection)
B. Water or soil from his ranch
C. Coughing worker on his ranch
D. Sick sheep on his ranch.

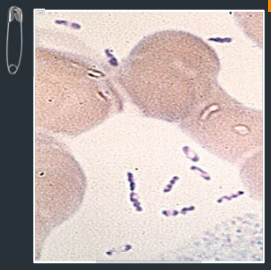
Melioidosis Take-Aways

- Microbiology lab:
  - Facultative intracellular gram-negative rod, *Burkholderia pseudomallei*
  - Oxidase positive
  - Characteristic bipolar staining with a "safety pin" appearance
- Typical patient:
  - SE Asia, northern Australia, South Asia (+ India), & China
    - *Esp.* Northeastern Thailand & northern Australia

Chakravorty A, Heath CH. *Australian Journal of General Practice* (2019)

Bacteria with "safety pin" appearance

- *Yersinia pestis*
- *Vibrio parahemolyticus*
- *Burkholderia mallei & pseudomallei*
- *Haemophilus ducreyi* (chancroid)
- *Klebsiella granulomatis* (granuloma inguinale)



Y. pestis

Melioidosis Take-Aways

- **Clinical findings:**
  - **Acute** or chronic pneumonia or sepsis
  - Transmission via percutaneous inoculation, **inhalation**
  - Risk factors = **diabetes**, alcoholism, chronic renal & lung disease
  - Acute infection more common than chronic infection

Chakravorty A, Heath CH. *Australian Journal of General Practice* (2019)

Melioidosis Take-Aways

- **Clinical findings:**
  - Acute infection can present with **pneumonia, bacteremia & septic shock**
  - Metastatic abscesses: skin ulcers or abscesses more common than bone, spleen, brain, prostate
  - Chronic infection presents like TB (cough, hemoptysis, night sweats)
  - Can become latent & reactivate like TB (rare)

Wiersinga WJ, *et al. Nat Rev Dis Primers.* 2018

Melioidosis Take-Aways

- **Diagnosis: Culture**
- **Treatment: Treat all cases**
  - Mild disease: initial intensive **IV therapy for two weeks** followed by eradication therapy **orally for 3-6 months**
  - *B. pseudomallei* resistant to penicillin, ampicillin, 1st/2nd generation cephalosporins, polymyxin, aminoglycosides
  - **Meropenem or ceftazidime** then **tmp/smx for 3-6 months**

Wiersinga WJ, *et al. Nat Rev Dis Primers.* 2018

For the most up-to-date recommendations by the International Melioidosis Society: http://www.melioidosis.info

Melioidosis: **Buzzwords**

- **SE Asia** (Thailand)/Australia
- **Soil/water exposure** (inhalation/inoculation/rainy season; post-tsunami injury)
- Pneumonia + **severe sepsis**/shock or multiple abscesses
- Can be **years after exposure** (not usually)
- **Safety pins** on Gram stain; Gram negative rods

Le Tohic, s., *et al. European Journal of Clinical Microbiology & Infectious Diseases* (2019)

Glanders

- Caused by *Burkholderia mallei* & is rare in humans
- Requires close contact w/ infected animals (horses, donkeys, mules)
- Bacteria enter through the eyes, nose, mouth, or skin wounds
- *B. mallei* is an obligate mammalian pathogen & must cause the disease to be transmitted between hosts
- Africa, Asia, Middle East, Central America, South America
- Similar presentation to melioidosis

Smith ME, Gossman WG. Glanders And Melioidosis. [Updated 2017 Oct 6]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2018 Jan.

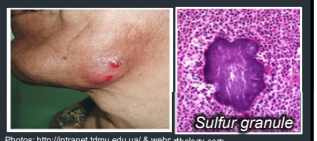
Glanders

- Incubation period usually 1 to 21 days but can be months or years
- 1st symptom usually fever, followed by pneumonia, pustules & abscesses
- The acute form is highly lethal without treatment
- Treatment = imipenem + doxycycline for 2 weeks, then azithromycin + doxycycline for 6 months

Smith ME, Gossman WG. Glanders And Melioidosis. [Updated 2017 Oct 6]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2018 Jan.

Actinomyces Take-Aways

- Microbiology lab:
  - Gram-positive, **anaerobic**, non–spore-forming bacteria
  - Part of the normal mucosal flora of the oral, gastrointestinal, respiratory, & genital tracts
  - *Actinomyces israelii* most common species
  - Produce **sulfur granules**
- Typical patient:
  - Recent dental procedures
  - Aspiration (thoracic)
  - IUD (pelvic)



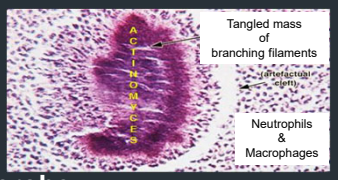
Photos: http://intranet.tdmu.edu.ua/ & webpathology.com

Actinomyces Take-Aways

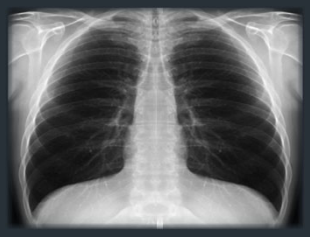
- Clinical findings:
  - Oral-cervicofacial more common>abdominal & thoracic infection
  - **Lumpy jaw**
  - Slow growing mass, **ignores tissue planes**, can necessitate, form sinuses, fistulas
  - DDx: Cancer, TB, Nocardia
- Diagnosis:
  - Culture, histopathology (sulfur granules)
- Treatment:
  - **Penicillins** (PCN, ampicillin) x weeks to months

Actinomyces: **Buzzwords**

- **Sulfur granules**
- **Dental work**
- **IUD**
- **Erosive mass**
- **Filamentous anaerobe**

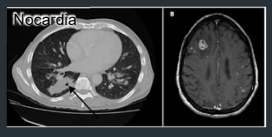


If you see this CXR think of which infection?

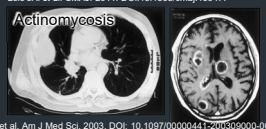


Lesions in the Lungs & Brain

- Actinomycosis
- *Aspergillus, Zygomycetes*
- *Blastomyces, Coccidioides, Cryptococcus, Histoplasma*
- *Mycobacterium tuberculosis*
- *Nocardia*
- Infectious emboli (SBE)
- Lemierre syndrome (*Fusobacterium*)
- *Toxoplasma*
- Tumors



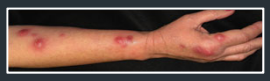
Leis JA. *et al. CMAJ.* 2011. DOI:10.1503/cmaj.100477



Colmegna I, et al. Am J Med Sci, 2003. DOI: 10.1097/00000441-200309000-00010

Causes of Sporotrichoid Lesions

Nodular lymphangitis



Organism	Exposure
Sporothrix schenckii	Gardening, soil, splinters, animal bites/scratches
Nocardia brasiliensis	Gardening, soil, splinters
Mycobacterium marinum	Aquarium, fish handling, water exposure
Leishmania brasiliensis	Living/traveling in endemic regions

Photo: eScholarship

THANK YOU

d.aronoff@vanderbilt.edu
@DMAronoff

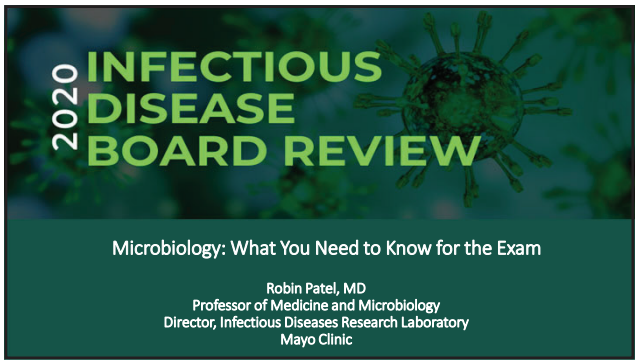
53

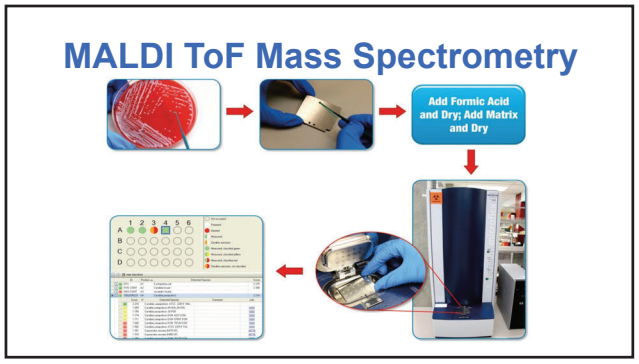
Microbiology: What You Need to Know for The Exam

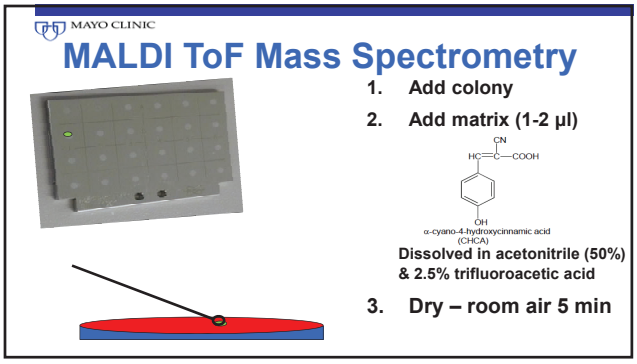
Dr. Robin Patel

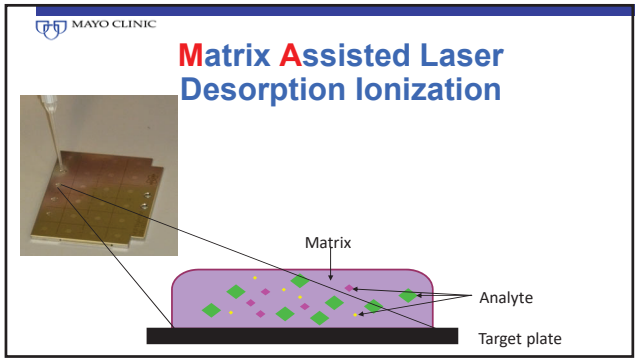
53 - Microbiology: What You Need to Know for The Exam

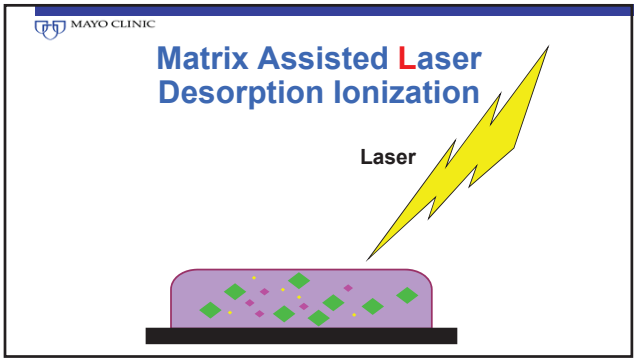
Speaker: Robin Patel, MD





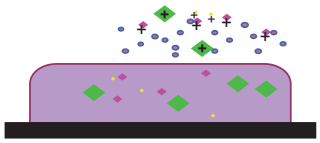






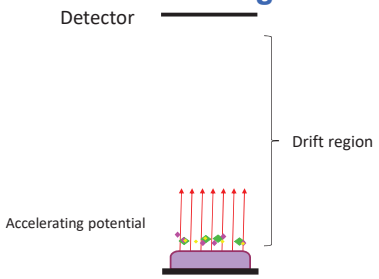
MAYO CLINIC

Matrix Assisted Laser Desorption Ionization



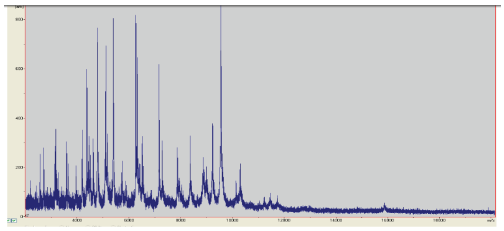
MAYO CLINIC

Time of Flight



MAYO CLINIC

Mass Spectrum Generated Compared with Library (Database)



QUESTION #1

Which of the following will not grow on sheep blood, chocolate and/or MacConkey agar?

A. ***Granulicatella adiacens***
B. ***Bordetella pertussis***
C. ***Brucella melitensis***
D. ***Vibrio cholerae***
E. ***Abiotrophia defectiva***

BACTERIA REQUIRING SPECIALIZED MEDIA

- *Bordetella pertussis*
- *Brucella* species (+/-)
- *Burkholdheria pseudomallei* (+/-)
- *Campylobacter* species
- *Francisella tularensis* (+/-)
- *Helicobacter pylori*
- *Legionella* species
- *Mycoplasma* species (+/-)
- *Ureaplasma* species

QUESTION #2

Which of the following bacteria may stain acid-fast positive?

A. ***Rhodococcus* species**
B. ***Cutibacterium* species**
C. ***Finegoldia* species**
D. ***Microbacterium* species**
E. ***Wolbachia* species**

ACID-FAST BACTERIA (MYCOLIC ACIDS)

- *Mycobacterium* species
- "Modified" acid fast stain positive
  - Weaker decolorizing agent (0.5-1% sulfuric acid in place of 3% acid-alcohol); do not stain well with Ziehl-Neelsen or Kinyoun stain
    - *Nocardia* species
    - *Rhodococcus* species
    - *Gordonia* species
    - *Tsukamurella* species
    - *Dietzia* species
- *Tatlockia* (*Legionella*) *micdadei* and some *Corynebacterium* species
  - [But not *Cutibacterium* (or *Propionibacterium*) species]

QUESTION #3

A laboratory technologist who has a longstanding history of diabetes mellitus inadvertently opens the lid of an agar plate growing an organism which is subsequently determined to be *Burkholdheria pseudomallei*.

You are asked to make a recommendation regarding postexposure prophylaxis.

QUESTION #3

Which of the following would you recommend?

A. Trimethoprim-sulfamethoxazole
B. Amoxicillin
C. Streptomycin
D. Cephalexin
E. None

Burkholderia pseudomallei Laboratory Exposure

Low risk Events	Inadvertent opening of the lid of an agar plate growing *B. pseudomallei* outside a biologic safety cabinet
	Inadvertent sniffing of agar plate growing *B. pseudomallei* in the absence of contact between worker and bacterium
	Splash event leading to visible contact of *B. pseudomallei* with gloved hand or protected body, in the absence of any evidence of aerosol
	Spillage of small volume of liquid culture (<1mL) within a functioning biologic safety cabinet
	Contamination of intact skin with culture
High risk Events	The presence of any predisposing condition without proper personal protective equipment (PPE): diabetes mellitus; chronic liver or kidney disease; alcohol abuse; long-term steroid use; hematologic malignancy; neutropenia or neutrophil dysfunction; chronic lung disease (including cystic fibrosis); thalassemia; any other form of immunosuppression
	Needlestick or other penetrating injury with implement contaminated with *B. pseudomallei*
	Bite or scratch by experimental animal infected with *B. pseudomallei*
	Splash event leading to contamination of mouth or eyes
	Generation of aerosol outside biologic safety cabinet (e.g., sonication, centrifuge incident)

Peacock SJ et al. Emerg Infect Dis. 2008 Jul http://wwwnc.cdc.gov/eid/article/14/7/07-1501

Burkholderia pseudomallei Postexposure Antimicrobial Drug Prophylaxis

Antimicrobial Drug	Dosage	Frequency
Trimethoprim-sulfamethoxazole (TMP-SMX)	2 × 160–800 mg (960 mg) tablets if >60 kg, 3 × 80–400 (480 mg) tablets if 40 kg-60 kg, and 1 × 160–800 mg (960 mg) or 2 × 80–400 (480 mg) tablets if adult <40 kg plus folate 5 mg/d	Every 12 h
Doxycycline	2.5 mg/kg/dose up to 100 mg orally	Every 12 h
Amoxicillin–clavulanic acid	20/5 mg/kg/dose. Equates to 3 × 500/125 tabs if >60 kg, and 2 × 500/125 tabs if ≤60kg	Every 8 h

Peacock SJ et al. Emerg Infect Dis. 2008 Jul http://wwwnc.cdc.gov/eid/article/14/7/07-1501

QUESTION #4

Which of the following, if present in a clinical specimen, poses a hazard for laboratory personnel?

a. Entamoeba histolytica
b. Trichuris trichiura
c. Enterobius vermicularis
d. Strongyloides stercoralis
e. Babesia microti

Strongyloides stercoralis

- Larvae - two forms
  1. Rhabditiform (in stool)
  2. Filariform

  Infectious stage that develops in soil and occasionally in patient (leads to autoinfection and is hazardous to laboratory personnel)
- Larvae detected
  - Microscopically (top) or
  - By placing feces on plate and detecting migrating larvae where they leave a trail of bacterial colonies (bottom)

LABORATORY- ACQUIRED BACTERIAL, FUNGAL AND PARASITIC INFECTIONS (SELECTED)

- *Bacillus anthracis*
- *Brucella* species
- *Burkholderia pseudomallei*
  - (*Burkholderia mallei*)
- *Coxiella burnetii*
- *Coccidioides immitis/posadasii* (*Blastomyces dermatitidis*, *Histoplasma capsulatum*)
- Dermatophytes
- Enteric pathogens
- *Francisella tularensis*
- *Mycobacterium tuberculosis*
- *Neisseria meningitidis*
- *Salmonella enterica* subsp. *enterica* serovar Typhi
- *Staphylococcus aureus*
- *Strongyloides stercoralis*
- *Yersinia pestis*

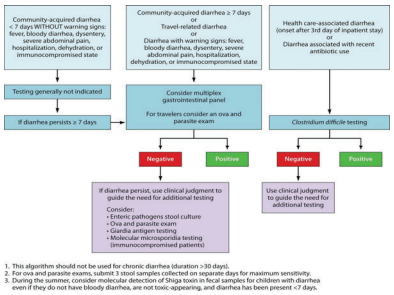
ORGANISMS ABOUT WHICH THE LABORATORY SHOULD BE NOTIFIED IF SUSPECTED

- Avian influenza
- *Bacillus anthracis*
- *Brucella* species
- *Burkholderia pseudomallei*
- *Burkholderia mallei*
- *Clostridium botulinum*
- *Coxiella burnetii*
- *Coccidioides immitis/posadasii*
- Hemorrhagic fever viruses (e.g., Eboia, Marburg, Chapare, Crimean-Congo, Guanarito, Hanta, Junin, Kayasnur Forest Disease, Lassa fever, Lujo, Machupo, Omsk Hemorrhagic Fever, Sabia)
- *Francisella tularensis*
- Measles
- MERS, SARS-CoV
- Nipah virus, Hendra virus
- Smallpox
- *Yersinia pestis*

FDA-APPROVED/CLEARED MULTIPLEX PANELS FOR GASTROINTESTINAL PATHOGENS IN STOOL

	Verigene EP	Luminex GPP	BioFire GIP
Number of targets	8	14	22
Campylobacter species	✓	✓	✓
Salmonella species	✓	✓	✓
Shigella species/Enteroinvasive *E. coli*	✓	✓	✓
Vibrio species	✓	✓	✓
Yersinia enterocolitica	✓		✓
Escherichia coli 0157		✓	✓
Enterotoxigenic *E. coli*		✓	✓
Enteropathogenic *E. coli*			✓
Enteroaggregative *E. coli*			✓
Plesiomonas shigelloides			✓
Shiga toxin-producing *E. coli*	✓	✓	✓
Clostridioides difficile		✓	✓
Norovirus GI/GII	✓	✓	✓
Rotavirus A	✓	✓	✓
Astrovirus			✓
Adenovirus 40/41		✓	✓
Sapovirus			✓
Cryptosporidium species		✓	✓
Entamoeba histolytica		✓	✓
Giardia lamblia		✓	✓
Cyclospora cayetanensis			✓

TESTING ALGORITHM FOR ACUTE GASTROENTERITIS



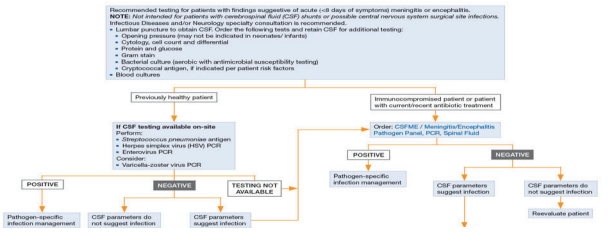
1. This algorithm should not be used for chronic diarrhea (duration >30 days).
2. For ova and parasite exams, submit 3 stool samples collected on separate days for maximum sensitivity.
3. During the summer, consider molecular detection of Shiga toxin in fecal samples for children with diarrhea even if they do not have bloody diarrhea, are not toxic-appearing, and diarrhea has been present <7 days.

BIOFIRE FILMARRAY MENINGITIS/ENCEPHALITIS PANEL

Viruses	Bacteria	Fungi
Cytomegalovirus	*Escherichia coli* K1	*Cryptococcus neoformans/gattii*
Enterovirus	*Haemophilus influenzae*	
Herpes simplex virus 1	*Listeria monocytogenes*	
Herpes simplex virus 2	*Neisseria meningitidis*	
Human herpes virus 6	*Streptococcus agalactiae*	
Human parechovirus	*Streptococcus pneumoniae*	
Varicella zoster virus		

MAYO CLINIC

Meningitis/Encephalitis Panel Algorithm



MAYO CLINIC

FDA-Approved Multiplex Respiratory Panels

Parameter	FilmArray	Verigene	x-TAG RVP	x-TAG RVP FAST	NxTAG-RPP	eSensor RVP	ePlex
Analysis platform	FilmArray system or FilmArrayTorch	Verigene system	Luminex 100/200	Luminex 100/200	Luminex MAGPIX	eSensor	ePlex system
Acceptable specimens	NP swab	NP swab	NP swab	NP swab	NP swab	NP swab	NP swab
Number of targets	20	16	12	8	20	14	17
Pathogens							
Viruses							
Adenovirus	✓	✓	✓	✓	✓	✓(differentiates B/E from C)	✓
Coronavirus							✓
Coronavirus HKU1	✓				✓		
Coronavirus NL63	✓				✓		
Coronavirus 229E	✓				✓		
Coronavirus OC43	✓				✓		
SARS-CoV-2	✓						
Human bocavirus					✓		
Human metapneumovirus	✓	✓	✓	✓	✓	✓	✓
Influenza A	✓	✓	✓	✓	✓	✓	✓
Subtype H1	✓	✓	✓	✓	✓	✓	✓
Subtype H3	✓	✓	✓	✓	✓	✓	✓
Subtype 2009 H1N1	✓					✓	✓
Influenza B	✓	✓	✓	✓	✓	✓	✓
Parainfluenza 1	✓	✓	✓		✓	✓	✓
Parainfluenza 2	✓	✓	✓		✓	✓	✓
Parainfluenza 3	✓	✓	✓		✓	✓	✓
Parainfluenza 4	✓	✓			✓		✓
Respiratory syncytial virus	✓			✓			
Respiratory syncytial virus A		✓	✓		✓	✓	✓
Respiratory syncytial virus B		✓	✓		✓	✓	✓
Rhinovirus/enterovirus	✓	✓	✓	✓	✓	✓	✓
Bacteria							
Chlamydophila pneumoniae	✓				✓		✓
Mycoplasma pneumoniae	✓				✓		✓
Bordetella pertussis	✓	✓					
Bordetella parapertussis	✓						
B. parapertussis/Bordetella bronchiseptica		✓					
Bordetella holmesii		✓					
Throughput	Scalable	Low	Medium	Medium	High	Medium	Scalable
Time to result	~1 hour	~2.3 hours	~8 hours	~6 hours	~4 hours	~6 hours	~1.5 hours

The acceptable specimen type for all panels is nasopharyngeal swab. RVP, respiratory virus panel; RPP, respiratory pathogen panel. Ramanan et al. Clin Microbiol Rev 2018;31:1-28

MAYO CLINIC

FilmArray® Respiratory Panel EZ (RP EZ)

- VIRUSES:
  - Adenovirus, Coronavirus, Human Metapneumovirus, Human Rhinovirus/Enterovirus, Influenza A, Influenza A/H1, Influenza A/H3, Influenza A/H1-2009, Influenza B, Parainfluenza Virus, Respiratory Syncytial Virus
- BACTERIA:
  - *Bordetella pertussis, Chlamydophila pneumoniae, Mycoplasma pneumoniae*

MAYO CLINIC

Lower Respiratory Tract Panels

	Curetis Unyvero	BioFire
Bacteria		
Acinetobacter spp.	✓	
Acinetobacter calcoaceticus-baumannii complex		✓
Chlamydia pneumoniae	✓	✓
Citrobacter freundii complex	✓	
Enterobacter aerogenes		✓
Enterobacter cloacae		✓
Enterobacter cloacae complex	✓	
Escherichia coli	✓	✓
Haemophilus influenzae	✓	✓
Klebsiella oxytoca	✓	✓
Klebsiella pneumoniae	✓	
Klebsiella pneumoniae group		✓
Klebsiella variicola	✓	
Legionella pneumophila	✓	✓
Moraxella catarrhalis	✓	✓
Morganella morganii	✓	
Mycoplasma pneumoniae	✓	✓
Proteus spp.	✓	✓
Pseudomonas aeruginosa	✓	✓
Serratia marcescens	✓	✓
Staphylococcus aureus	✓	✓
Stenotrophomonas maltophilia	✓	
Streptococcus agalactiae		✓
Streptococcus pneumoniae	✓	✓
Streptococcus pyogenes		✓

	Curetis Unyvero	BioFire
Viruses		
Influenza A		✓
Influenza B		✓
Respiratory Syncytial Virus		✓
Human Rhinovirus/Enterovirus		✓
Human Metapneumovirus		✓
Parainfluenza virus		✓
Adenovirus		✓
Coronavirus (non-SARS-CoV)		✓
Resistance genes		
bla_{KPC}	✓	✓
bla_{NDM}	✓	✓
bla_{IMP}		✓
bla_{OXA-23}	✓	
bla_{OXA-48}	✓	
$bla_{VIM/GES}$	✓	
$bla_{VIM/GES-like}$		✓
bla_{SME}	✓	✓
bla_{CTX-M}	✓	✓
bla_{TEM}	✓	
mecA	✓	
mecA/C and *MREJ*		✓

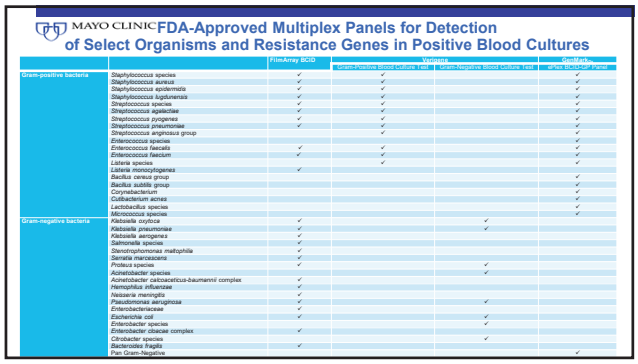
QUESTION #5

- You are asked to see a 62 year old man with a positive blood culture to advise on management.
- Gram stain of the positive blood culture bottle shows Gram positive cocci in clusters.
- A rapid PCR panel performed on the positive blood culture bottle contents detects *Staphylococcus* species as well as *mecA*.

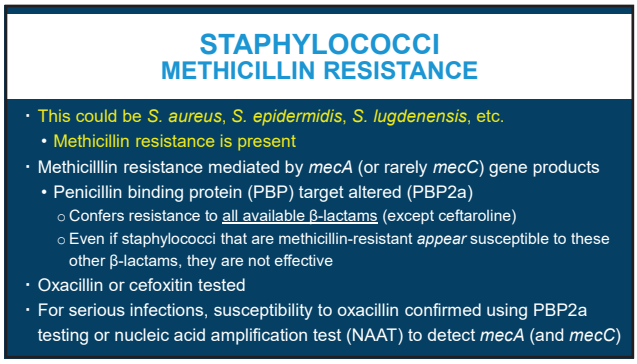
QUESTION #5

Which of the following is the interpretation of this finding?

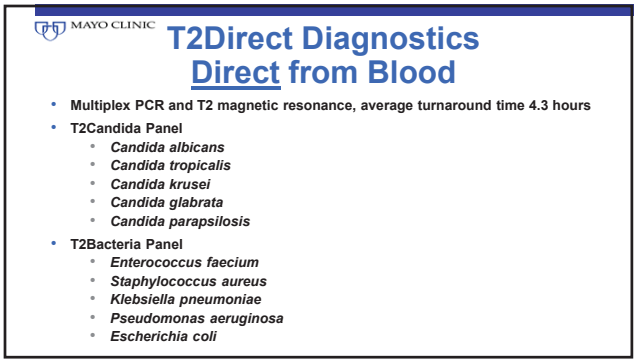
A. The patient has methicillin-resistant *Staphylococcus aureus* bacteremia
B. The patient has methicillin-susceptible *S. aureus* bacteremia
C. The patient has methicillin-resistant *Staphylococcus epidermidis* bacteremia
D. The patient has methicillin-susceptible *Staphylococcus lugdunensis* bacteremia
E. The patient has a methicillin-resistant staphylococcal bacteremia that could be due to *S. aureus*, *S. epidermidis*, *S. lugdenensis* or another *Staphylococcus* species


MAYO CLINIC FDA-Approved Multiplex Panels for Detection of Select Organisms and Resistance Genes in Positive Blood Cultures

		FilmArray BCID	Verigene		GenMark
			Gram-Positive Blood Culture Test	Gram-Negative Blood Culture Test	ePlex BCID-GP Panel
Gram-positive bacteria	Staphylococcus species	✓	✓		✓
	Staphylococcus aureus	✓	✓		✓
	Staphylococcus epidermidis	✓	✓		✓
	Staphylococcus lugdunensis	✓	✓		✓
	Streptococcus species	✓	✓		✓
	Streptococcus agalactiae	✓	✓		✓
	Streptococcus pyogenes	✓	✓		✓
	Streptococcus pneumoniae	✓	✓		✓
	Streptococcus anginosus group		✓		✓
	Enterococcus species				✓
	Enterococcus faecalis	✓	✓		✓
	Enterococcus faecium	✓	✓		✓
	Listeria species		✓		✓
	Listeria monocytogenes	✓			
	Bacillus cereus group				✓
	Bacillus subtilis group				✓
	Corynebacterium				✓
	Cutibacterium acnes				✓
	Lactobacillus species				✓
	Micrococcus species				✓
Gram-negative bacteria	Klebsiella oxytoca	✓		✓	
	Klebsiella pneumoniae	✓		✓	
	Klebsiella aerogenes	✓			
	Salmonella species	✓			
	Stenotrophomonas maltophilia	✓			
	Serratia marcescens	✓			
	Proteus species	✓		✓	
	Acinetobacter species	✓		✓	
	Acinetobacter calcoaceticus-baumannii complex	✓			
	Haemophilus influenzae	✓			
	Neisseria meningitis	✓			
	Pseudomonas aeruginosa	✓		✓	
	Enterobacteriaceae	✓			
	Escherichia coli	✓		✓	
	Enterobacter species	✓		✓	
	Enterobacter cloacae complex	✓			
	Citrobacter species	✓		✓	
	Bacteroides fragilis	✓			
	Pan Gram-Negative				✓

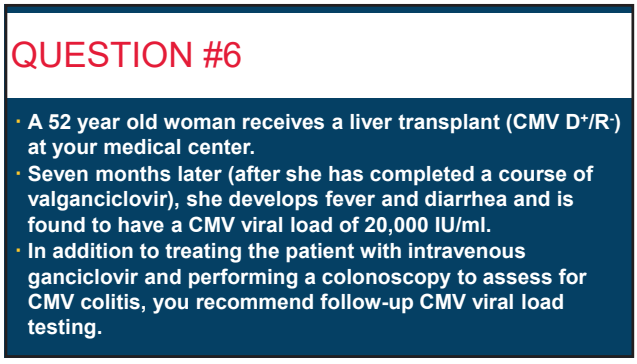

STAPHYLOCOCCI
METHICILLIN RESISTANCE

- This could be *S. aureus*, *S. epidermidis*, *S. lugdenensis*, etc.
  - Methicillin resistance is present
- Methicilllin resistance mediated by *mecA* (or rarely *mecC*) gene products
  - Penicillin binding protein (PBP) target altered (PBP2a)
    - Confers resistance to all available β-lactams (except ceftaroline)
    - Even if staphylococci that are methicillin-resistant *appear* susceptible to these other β-lactams, they are not effective
- Oxacillin or cefoxitin tested
- For serious infections, susceptibility to oxacillin confirmed using PBP2a testing or nucleic acid amplification test (NAAT) to detect *mecA* (and *mecC*)

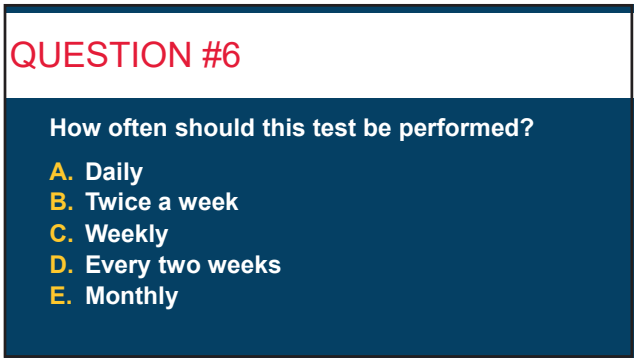

MAYO CLINIC

T2Direct Diagnostics
Direct from Blood

- **Multiplex PCR and T2 magnetic resonance, average turnaround time 4.3 hours**
- **T2Candida Panel**
  - ***Candida albicans***
  - ***Candida tropicalis***
  - ***Candida krusei***
  - ***Candida glabrata***
  - ***Candida parapsilosis***
- **T2Bacteria Panel**
  - ***Enterococcus faecium***
  - ***Staphylococcus aureus***
  - ***Klebsiella pneumoniae***
  - ***Pseudomonas aeruginosa***
  - ***Escherichia coli***


QUESTION #6

- **A 52 year old woman receives a liver transplant (CMV D^+/R^-) at your medical center.**
- **Seven months later (after she has completed a course of valganciclovir), she develops fever and diarrhea and is found to have a CMV viral load of 20,000 IU/ml.**
- **In addition to treating the patient with intravenous ganciclovir and performing a colonoscopy to assess for CMV colitis, you recommend follow-up CMV viral load testing.**


QUESTION #6

How often should this test be performed?

A. Daily
B. Twice a week
C. Weekly
D. Every two weeks
E. Monthly

OPTIMAL FREQUENCY CMV VIRAL LOAD TESTING

- Weekly viral load testing sufficient to document antiviral response, antiviral resistance emergence
  - $T_{1/2}$ virus ~5-8 days
  - May rise 1st few days on therapy
  - Obtain baseline viral load day therapy started
- Treatment
  - Until viral clearance, symptom resolution and 2 week minimum
- Changes >3-fold (>0.5 log)
  - Biologically important changes in viral replication
- Preemptive treatment → weekly viral load testing

QUESTION #7

You are consulted to advise on the course of action for a 57 year old female liver transplant recipient (transplant for alcoholic steatohepatitis; CMV D^+/R^+) who has a whole blood HHV-6 viral load of $3.6x10^6$ copies/ml at three months post-transplant. The test was performed because of a report of subjective fever of four days' duration. She has no other new symptoms. The patient received one month of acyclovir prophylaxis post-transplant and is currently receiving mycophenolate mofetil, prednisone and trimethoprim-sulfamethoxazole. Her post-transplant course was complicated by one episode of treated rejection on day 30 post transplant. Physical examination is unremarkable and she is afebrile.

QUESTION #7

Which of the following would you recommend?

A. Intravenous ganciclovir
B. Oral valganciclovir
C. Oral acyclovir
D. Intravenous foscarnet
E. No antiviral therapy is indicated

CHROMOSOMALLY INTEGRATED HUMAN HERPESVIRUS-6

- High HHV-6 levels in whole blood
  - (>5.5 $\log_{10}$ copies/ml)
  - Suggest chromosomally integrated HHV-6
- 1:1 ratio of viral to human genomes

Pellett et al. Rev Med Virol. 2012;22:144-55

QUESTION #8

A 65 year old man has multiple blood cultures positive for *Pseudomonas aeruginosa* resistant to amikacin, gentamicin, tobramycin, aztreonam, cefepime, ceftazidime, meropenem, piperacillin-tazobactam, ciprofloxacin, and levofloxacin. You call the clinical microbiology laboratory to request susceptibility testing of an additional antimicrobial.

Which of the following is most appropriate?

A. Dalbavancin
B. Tedizolid
C. Ceftolozane/tazobactam
D. Oritavancin

QUESTION #9

You are asked to see a 43 year old woman to advise on management of a positive blood culture.

- Gram stain of her blood culture bottle shows Gram-negative bacilli.
- A rapid PCR panel performed on the positive blood culture bottle contents detects *Enterobacteriaceae* and bla_{KPC}.

QUESTION #9

The *bla*$_{KPC}$ gene product would be expected to confer resistance to which of the following?

A. Cefepime
B. Plazomicin
C. Colistin
D. Ceftazidime/avibactam

TYPICAL SUSCEPTIBILITY OF A KPC-PRODUCER

Klebsiella pneumoniae carbapenemase producer

Ampicillin	>16 R	Ampicillin/Sulbactam	>16/8 R	Piperacillin/Tazobactam	64/4 R
Cefazolin	>16 R	Oral cephalosporins	R	Cefepime	>16 R
Ceftazidime	>16 R	Ceftriaxone	>32 R	Ertapenem	>1 R
Meropenem	>8 R	Aztreonam	>16 R	Ciprofloxacin	>2 R
Levofloxacin	4 I	Amikacin	>32 R	Gentamicin	>8 R
Tobramycin	4 S	Tigecycline	2 S	TMP/SMX	>2/38 R

TYPICAL SUSCEPTIBILITY OF AN ESBL-PRODUCER

Escherichia coli

– Extended spectrum beta-lactamase producer

Ampicillin	>16 R	Ampicillin/Sulbactam	>16/8 R	Piperacillin/Tazobactam	16/4 S
Cefazolin	>16 R	Oral cephalosporins	R	Cefepime	>16 R
Ceftazidime	>16 R	Ceftriaxone	>32 R	Ertapenem	≤0.5 S
Meropenem	≤1 S	Aztreonam	>16 R	Ciprofloxacin	≤1 S
Levofloxacin	≤2 S	Amikacin	≤8 S	Gentamicin	≤1 S
Tobramycin	4 S	Tigecycline	2 S	TMP/SMX	>2/38 R

QUESTION #10

Which of the following susceptibility patterns would be typical for an *Escherichia coli* isolate carrying a New Delhi metallo-β-lactamase (NDM)?

	Cefazolin	Cefotaxime	Ceftazidime	Piperacillin/ tazobactam	Imipenem	Aztreonam
a)	R	S	S	S	S	S
b)	R	R	R	S	S	R
c)	R	R	R	R	S	R
d)	R	R	R	R	R	R

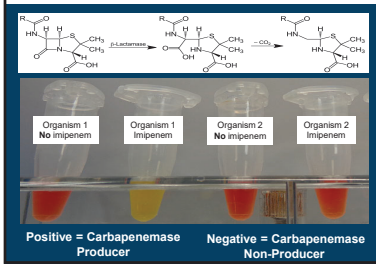
QUESTION #11

Which of the following tests for carbapenemase production?

A. PBP2a test
B. D-test
C. Carba NP test
D. Polymerase chain reaction assay

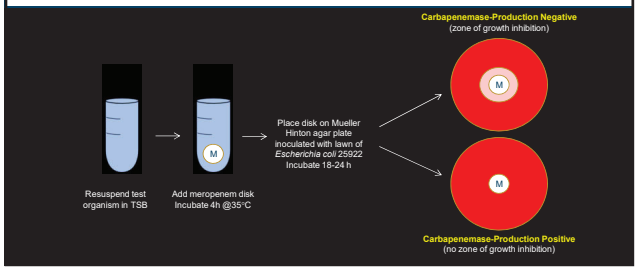
CARBAPENEMASE PRODUCTION TEST

Carba NP TEST



- **β-lactam ring hydrolyzed by carbapenemase**
- **↓pH (detected by indicator dye color change red → yellow)**
- **Rapid (2 hours)**

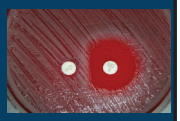
CARBAPENEMASE PRODUCTION TEST MODIFIED CARBAPENEM INACTIVATION



QUESTION #12

The image shows *Staphylococcus aureus* grown with an erythromycin disc (left) and a clindamycin disc (right).

Which of the following is the correct interpretation of these results?



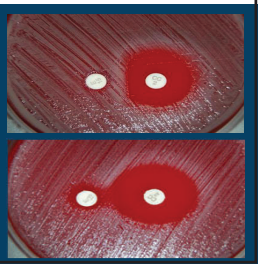
A. **Erythromycin susceptibility, inducible clindamycin resistance**
B. **Erythromycin resistance, constitutive clindamycin resistance**
C. **Erythromycin resistance, inducible clindamycin resistance**
D. **Erythromycin susceptibility, constitutive clindamycin resistance**

INDUCIBLE CLINDAMYCIN RESISTANCE (D-TEST)

- Macrolide resistance from alteration in ribosomal target → co-resistance to clindamycin; constitutive or inducible
  - Constitutive, erythromycin & clindamycin test resistant
  - Inducible, erythromycin tests resistant but clindamycin tests falsely susceptible
- (Macrolide resistance due to efflux → no effect on clindamycin)

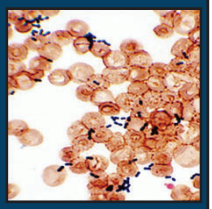
INDUCIBLE CLINDAMYCIN RESISTANCE (D-TEST)

- Erythromycin & clindamycin disks incubated on plate
  - Flattening of zone of inhibited growth between disks = inducible clindamycin resistance (top)
  - If erythromycin does not influence zone around clindamycin disk, clindamycin susceptible (bottom)



QUESTION #13

- **You are asked to see a 95 year old woman who is a resident of a long-term care facility to advise on therapy for bacteremia associated with a urinary tract infection.**
- **She has had two sets of blood cultures collected, both of which signaled positive after 17 hours of incubation.**
- **Gram stain of the bottles is shown.**
- **A rapid PCR panel performed on the positive blood culture bottle detects *Enterococcus* species as well as *vanA/vanB*.**



QUESTION #13

Which of the following is the most likely identity of the blood culture isolate?

A. ***Enterococcus gallinarum***
B. ***Enterococcus faecium***
C. ***Enterococcus faecalis***
D. ***Enterococcus casseliflavus***
E. ***Enterococcus avium***

ENTEROCOCCI
VANCOMYCIN SUSCEPTIBILITY TESTING

- **Vancomycin MICs ≥32 µg/ml**
  - Typically VanA or VanB mediated resistance
  - Typically *E. faecium*
  - Epidemiologically significant
- **Vancomycin MICs, 8-16 µg/ml (intermediate)**
  - VanC
  - *E. gallinarum* or *E. casseliflavus/flavescens*
  - Not epidemiologically significant

QUESTION #14

A 44 year old man who underwent bilateral lung transplantation for pulmonary hypertension develops a sternal wound infection with sternal dehiscence 15 days post-transplant.

Blood cultures are negative. He undergoes sternal debridement with the finding of purulence and negative Gram and KOH stains.

After three days of incubation, pinpoint, clear colonies are visualized on cultures on sheep blood agar, however Gram stain of these colonies is negative.

QUESTION #14

Which of the following is the most appropriate empiric antibiotic to treat this patient?

a) Cefepime
b) Ceftriaxone
c) Trimethoprim-sulfamethoxazole
d) Azithromycin
e) Doxycycline

Mycoplasma hominis

- Post-cardiothoracic transplant
  - Pleuritis, surgical site infection and/or mediastinitis
- Treatment
  - Inactive
    - Cell wall active antibiotics
    - Trimethoprim/sulfamethoxazole
    - Aminoglycosides
    - Erythromycin and azithromycin
  - Active
    - Tetracyclines (doxycycline preferred)
    - Fluoroquinolones
    - Clindamycin

Sampath, R., et al. EBioMedicine (2017), http://dx.doi.org/10.1016/j.ebiom.2017.04.026

QUESTION #15

A transplant hepatologist calls to inquire about ganciclovir resistance testing on a liver transplant patient with CMV colitis and the following CMV viral loads:

7/01/16: 26,000 IU/ml (day of diagnosis)
7/11/16: 25,000 IU/ml
7/20/16: 22,000 IU/ml
7/31/16: 27,000 IU/ml

- The patient is CMV D^+/R^-, received 3 months of valganciclovir prophylaxis, and now has CMV disease after discontinuing valganciclovir.
- He has been receiving full dose intravenous ganciclovir since July 1st and his diarrhea is unchanged.

QUESTION #15

A plasma test for mutations in which of the following genes is most appropriate?

A. UL51
B. UL54
C. UL89
D. UL97
E. Testing is unlikely to be helpful given the patient's viral load

QUESTION #16

Results of testing show a M460V UL97 mutation. This mutation would be expected to confer resistance to:

A. Cidofovir
B. Foscarnet
C. Ganciclovir
D. Ganciclovir and foscarnet
E. Ganciclovir and cidofovir

CYTOMEGALOVIRUS ANTIVIRAL RESISTANCE

- **Risk factors**
  - **Prolonged drug exposure**
  - **D^+R^-, lung transplant recipient**
- **Amplify and sequence directly from plasma**
  - **(viral load ~1,000 IU/ml required)**
- **≥6 weeks antiviral drug exposure**
  - **Should include ≥2 weeks full-dose therapy before testing**
  - **Accelerated schedule: Poor host factors, extreme viral loads**

Gene	Drug(s) affected
UL97	Ganciclovir
UL54	Ganciclovir and cidofovir (if selected for by these agents); foscarnet (if selected for by foscarnet)

Kotton CN et al. Transplantation 2013;96:333 and Chou S. Curr Opin Infect Dis 2015;28:293

54

Zoonoses

Dr. David Aronoff

54 – Zoonoses

Speaker: David M. Aronoff, MD, FIDSA, FAAM

2020 INFECTIOUS DISEASE BOARD REVIEW

Zoonoses

David M. Aronoff, MD, FIDSA, FAAM
Professor of Medicine
Addison B. Scoville Jr. Chair in Medicine
Director, Division of Infectious Diseases
Vanderbilt University Medical Center

Disclosures of Financial Relationships with Relevant Commercial Interests

- None

Zoonoses: major infection route from animals in USA

- **Direct contact with animal or animal tissue**
  - Cat scratch disease, anthrax, tularemia, monkeypox
- **Contact with insect vector**
  - Tularemia, plague
- **Intact skin contact with animal urine**
  - Leptospirosis
- **Ingestion of animal product**
  - Brucellosis
- **Inhalation of animal product**
  - Q Fever

THERE ARE MANY

TABLE 1. Bacterial zoonoses by transmission mechanism and causative agent(s)

Bacterial zoonoses transmitted by direct contact with animals or infected animal materials	**Causative agent(s)**
Anthrax	*Bacillus anthracis*
Brucellosis	*Brucella* spp.
Cat scratch disease	*Bartonella* spp.
Erysipelothrix infections	*Erysipelothrix rhusiopathiae*
Glanders and melioidosis	*Burkholderia mallei* and *Burkholderia pseudomallei*
Leptospirosis	*Leptospira interrogans* spp.
Mycobacterioses	*Mycobacteria* spp.
Q fever	*Coxiella burnetii*
Bacterial zoonoses transmitted principally by animal bites or scratches	
Pasteurellosis	*Pasteurella multocida* and other spp.
Capnocytophaga infections	*Capnocytophaga canimorsus*
Cat scratch disease	*Bartonella henselae*
Rat bite fever	*Spirillum minus* and *Streptobacillus moniliformis*
Vector-borne bacterial zoonoses	
Lyme borreliosis	*Borrelia burgdorferi* sensu lato (incl. *Borrelia garinii*, *Borrelia afzelii*)
Tick- and louse-borne relapsing fever borreliosis	*Borrelia recurrentis*, *Borrelia turicatae*, *Borrelia hermsii*, others
Plague	*Yersinia pestis*
Tularaemia	*Francisella tularensis*
Rickettsioses	Spotted fever and typhus group *Rickettsia* species
Ehrlichiosis and Anaplasmosis	*Ehrlichia chaffeensis*, *Anaplasma phagocytophilum*
Scrub typhus	*Orientia tsutsugamushi*
Foodborne bacterial zoonoses and intoxications	
Salmonellosis	*Salmonella enteritidis*
Campylobacteriosis	*Campylobacter* spp.
Listeriosis	*Listeria monocytogenes*
Escherichia coli O157:H7 infections	*Escherichia coli* STEC
Yersinia enterocolitica infections	*Yersinia enterocolitica*
Clostridium perfringens gastroenteritis	*Clostridium perfringens*
Botulism	*Clostridium botulinum*
Staphylococcal food poisoning	*Staphylococcus aureus*

Chikeka & Dumler *Clin Microbiol Infect* 2015; 21: 404–415

CATS
- *Bartonella henselae*
- *Pasteurella multocida*

BIRDS
- *Chlamydia*
- *Chlamydophila psitacci*

FARM ANIMALS (sheep, cows, goats, chicken, *etc*)
- *Bacillus anthracis*
- *Brucella*
- *Coxiella burnetii*
- *Campylobacter*
- *E. coli* (Shiga toxin+)
- *Erysipelothrix rhusiopathiae*
- *Hepatitis E*
- *Leptospira*
- *Salmonella*

FISH
- *E. rhusiopathiae*
- *Mycobacterium marinum*
- *Streptococcus iniae*
- *Vibrio*

DOGS
- *Campylobacter*
- *Capnocytophaga*
- *Leptospira*
- *Pasteurella multocida*
- *Staph intermedius/pseudintermedius*

Adapted from *Comprehensive Review of Infectious Diseases* (2020), Elsevier.

LEECHES
- *Aeromonas hydrophila*

RABBITS
- *Francisella tularensis*

REPTILES
- *Salmonella*

RODENTS
- *Leptospira*
- *Monkeypox*
- *Salmonella*
- *Spirillum minus*
- *Streptobacillus moniliformis*
- *Yersinia pestis*

Adapted from *Comprehensive Review of Infectious Diseases* (2020), Elsevier.

Direct contact with animal or animal tissue

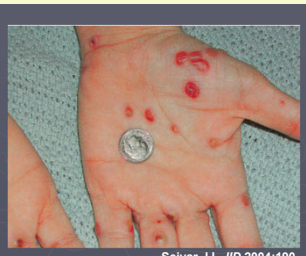
Question #1

19 yr woman presented with several days of headache, fever, chills, myalgias, cough & a rash

On exam she had generalized adenopathy & a vesiculopustular rash with focal areas of hemorrhage progressing in a uniform manner including the entire body, most prominently on the trunk, palms & soles

She reported her new pet prairie dog was also ill (lethargy, wasting, not eating)

Question #1



Sejvar JJ, *JID* 2004:190

Question #1

What is the most likely infection?

A. *Erysipelothrix rhusiopathiae*
B. Smallpox
C. Gambian cutaneous ulcerans
D. Monkeypox
E. Yaws (*Treponema pallidum pertenue*)

Question #2

25 yr WM presented in July with painful right inguinal mass of one week's duration. He is otherwise well. Married. Monogamous. No hx penile or skin lesion. Fishing last week in Northern Virginia creek, hiked through wooded area. Picked ticks off legs & neck. Has kitten & dog. Exam: T37°C, 5 cm tender red mass in right midinguinal area, fixed to skin. Genitalia normal. Aspiration of soft center: 5 cc yellow pus. Gm stain neg. Keflex 250 mg qid. One week later: mass unchanged. Culture neg. Syphilis FTA & HIV neg.

Question #2

Most likely dx:

A. Bartonella henselae
B. Treponema pallidum
C. Haemophilus ducreyi
D. Francisella tularensis
E. Klebsiella (Calymmatobacterium) granulomatis

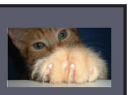
Purulent inguinal node

- *Bartonella henselae*: young cats
  - **Stellate abscess** on bx. **Warthin Starry** stain positive early
  - Dx: serology, PCR, or DFA on pus
- Tick borne tularemia ("glandular"): this case *could be* tularemia
  - Exposure to wild animals or their ticks
  - Gram stain, routine culture negative
  - But: he should be **systemically ill** (fevers, chills, malaise common)
  - Uncommon: 100-200 cases per year in the USA
- Chancroid: painful genital ulcer
- No suppurative lymph nodes in syphilis or granuloma inguinale (*Klebsiella granulomatis*) (painless ulcers)

Suppurative inguinal lymph nodes (continued)

- *Staphylococcus aureus*. Gram stain of pus & culture positive. Distal lesion may be present.
- Lymphogranuloma venereum (LGV)-
  - *Chlamydia trachomatis* L1-L3: genital lesion usually inapparent
  - "Stellate abscesses" on bx
  - (+) Nucleic acid amplification test on urine or wound

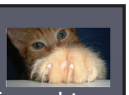
Cat Scratch Disease



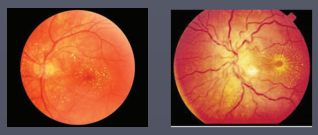
- *B. henselae* causes most cases
- >13,000 cases in the USA per year[1]
- Clinical findings:
  - 80% <21 yrs old, acute suppurative lymphadenitis proximal to bite, scratch, lick of young cat
  - Cats have chronic bacteremia but seem healthy
- Cat fleas may transmit between cats & occasionally to humans

1. Nelson CA, *at al. Emerging Infectious Diseases* 22 (2016); Photo from http://www.catscratchmed.com

Cat Scratch Disease



- Papule or pustule often at inoculation site if sought
- Often self-limited
- Encephalitis, **stellate retinitis**, uveitis rare



Lipid exudates forming a macular star

Photos from http://www.catscratchmed.com, http://imagebank.asrs.org/file/1173/cat-scratch-retinitis-with-macular-lipid, http://www.nejm.org/doi/full/10.1056/ENEJMicm010038#t=article

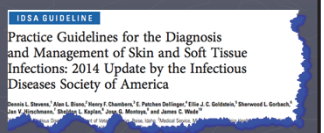
Cat Scratch Disease

Rx: 10% drain spontaneously

If not, node aspiration improves pain & helps exclude *Staph. aureus*

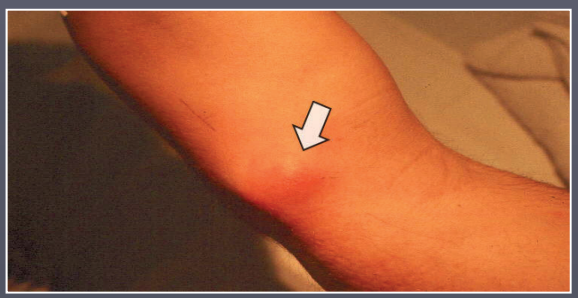
Treatment = AZITHROMYCIN (a bit better than no Rx)

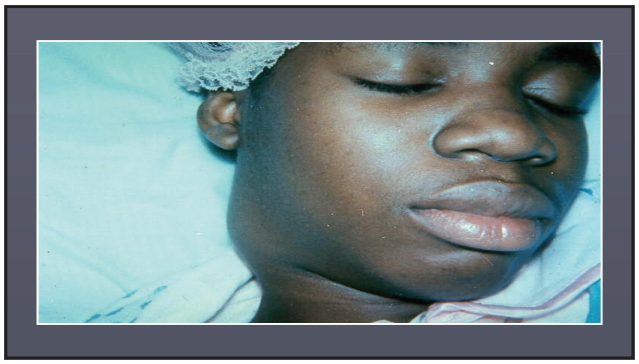
(TMP/SMX alternative)

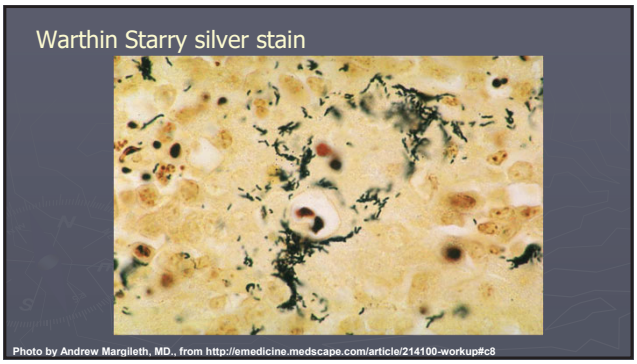

IDSA GUIDELINE

Practice Guidelines for the Diagnosis and Management of Skin and Soft Tissue Infections: 2014 Update by the Infectious Diseases Society of America

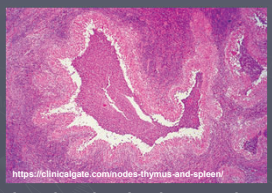
Shorbatli LA, *et al. Int J Clin Pharm.* (2018)



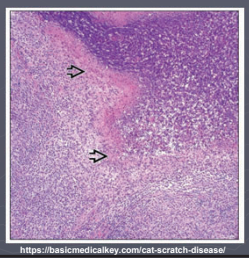




Cat Scratch Lymphadenopathy
Stellate abscesses, necrotizing granulomas
Necrotic area with neutrophils surrounded by **palisading histiocytes**



Lymph nodes showing central abscess formation surrounded by palisaded histiocytes

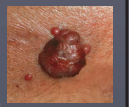


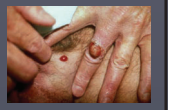
Major Syndromes due to *Bartonella* species

- *Bartonella*: **Slow growing** weakly Gram (-) rod
- *B. henselae*- cat scratch disease, peliosis
- *B. bacilliformis*- **Andes, Peru** & **sand fly** bite; Carrion's disease
  - Oroya fever (acute phase: fever + anemia) → verruga peruana (later; hemangioma-like nodules in the skin & mucous membranes); Treatment = ciprofloxacin (Oroya); azithromycin (vp)
- *B. quintana*
  - Human **body louse** *Pediculus humanus var. corporis* = vector
  - Bacteremia in the **homeless**, trench fever
  - **Endocarditis**

Major Syndromes due to *Bartonella* species

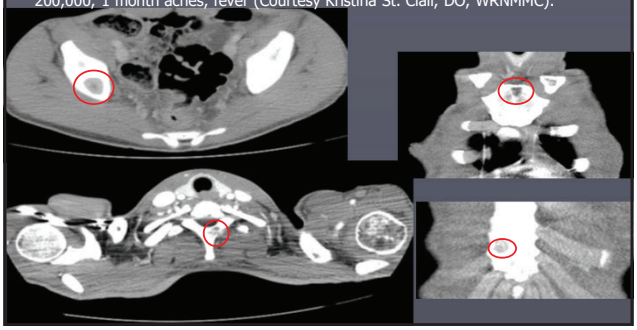
- HIV-associated (CD4<<100)
  - **Bacillary angiomatosis** (cutaneous)
    - Caused by either *B. henselae* or *B. quintana*
    - Lesions bleed easily
    - Biopsy: vascular proliferation, plump endothelial cells, bacilli
    - DDx = Kaposi sarcoma
  - Bacillary **peliosis** (*B. henselae*)
  - Osteomyelitis (lytic; *B. quintana*)
  - Chronic bacteremia/endocarditis





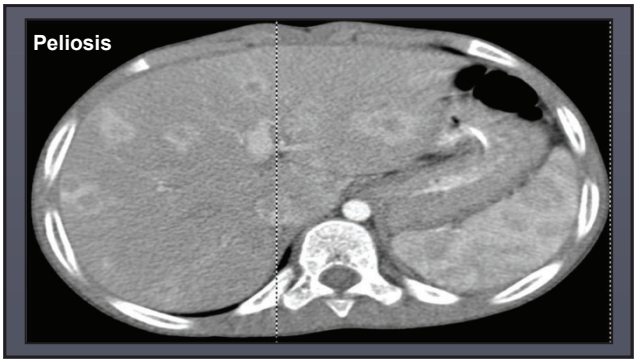
Images from http://mddk.com/bacillary-angiomatosis.html

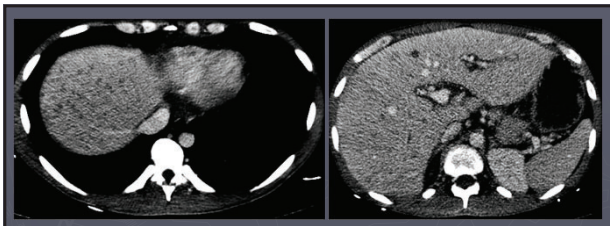
Bartonella osteomyelitis: 30 yr old man with HIV, CD 4=3, viral load 200,000, 1 month aches, fever (Courtesy Kristina St. Clair, DO, WRNMMC).



Bacillary peliosis

- *B. henselae*
- Hepatosplenic bacillary peliosis
- Fever, chills, hepatosplenomegaly
- CT: Hypodense dense center +/- contrast enhancing rim
- Ultrasound, MRI = masses
- Blood filled spaces. Numerous bacilli on Warthin Starry stain or immunostaining





29 year old male with longstanding HIV (CD4 < 10) with 3 months of fevers & weight loss. + hepatosplenomegaly & mild transaminitis, elevated Alk phos. CT showed innumerable hepatic & splenic hypodensities.
IgG (+) *Bartonella* 1:512 & serum *Bartonella henselae* PCR (+).
He had rescued a kitten 6 months prior & reported scratches & bites.

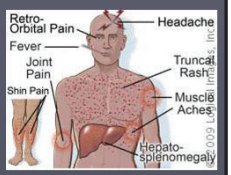
Case courtesy of Dr. Sam Bailin (Vanderbilt)

Solid Organ Transplantation

- SOT, like AIDS, can predispose to ALL the manifestations of bartonellosis
  - Lymphadenitis
  - Skin lesions (bacillary angiomatosis)
  - Bone lesions
  - Liver lesions

Bartonella quintana

- Transmitted by human body **lice**
- Crowded, unsanitary conditions: "trench fever" in WW1
- Splenomegaly, fever, arthropathy & arthritis, leg pains, rash, & severe weakness, thrombocytopenia
- Bacteremia, endocarditis in AIDS, **homeless** +/- alcoholics



Brouqui P, *et al. NEJM* (1999)

Bartonella endocarditis

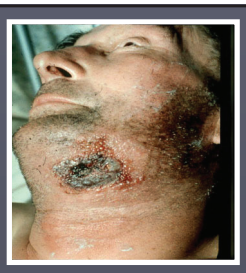
- <5% of all bacterial endocarditis
- Consider *B. quintana* or *B. henselae* in **homeless** pt. with **culture negative** endocarditis
- Insidious or acute onset of fever, weight loss, anorexia.
- Serology: IgG>1:800 highly suggestive (not species specific)
- **PCR** of serum, valve tissue
- Lysis-centrifugation blood cult.
  - 35ºC, fresh chocolate agar, hold 2-4 weeks
- Rx: gentamicin + doxycycline x 6 weeks

ANTHRAX

Images from https://www.dermnetnz.org/topics/anthrax

ANTHRAX

- Skin (95%): pruritic papule on skin exposed to goat hair, animal hides. Small **vesicles around an ulcer**. +/- pain. **Edema**. Mild systemic symptoms.
- DX: *Aerobic*, encapsulated, sporulating **Gram positive** bacillus seen on smear, culture of vesicle fluid
- RX: Penicillin but "weaponized" strains resistant to multiple antibiotics
- Inhalation (5%), ingestion (<1%)
- Anthrax rare in USA. Bioterrorism: see online lecture

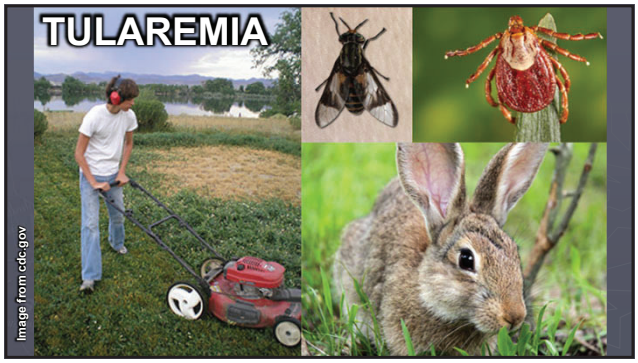


http://www.pcds.org.uk/clinical-guidance/anthrax

Edema
Vesicles
Necrotic ulcer

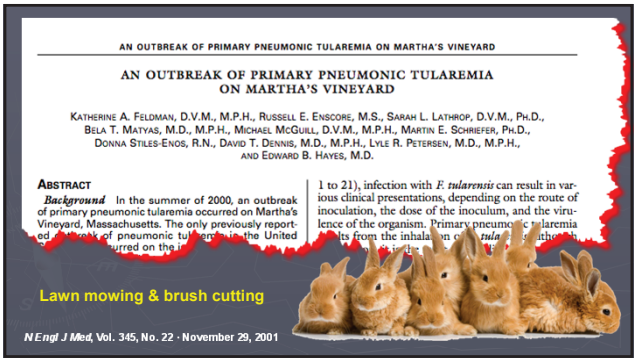
https://www.nejm.org/doi/full/10.1056/NEJMicm0802093

TULAREMIA



TULAREMIA

- Highly infectious gram-negative **coccobacillus** *Francisella tularensis*
- Vectors = **Ticks** (*Dermacentor variabilis* > *Amblyomma americanum*) & **Deerflies**
- Direct inoculation = rabbits, squirrels, muskrats, beavers, cats
- Hunters **skinning animals** (old days); farmers, veterinarians
- Red tender local lymph node inoculation site may form ulcer
- **Ulceroglandular >** glandular >> oculoglandular, pharyngeal, typhoidal, pneumonic = Bioterrorism, landscapers, mowers



AN OUTBREAK OF PRIMARY PNEUMONIC TULAREMIA ON MARTHA'S VINEYARD

AN OUTBREAK OF PRIMARY PNEUMONIC TULAREMIA ON MARTHA'S VINEYARD

KATHERINE A. FELDMAN, D.V.M., M.P.H., RUSSELL E. ENSCORE, M.S., SARAH L. LATHROP, D.V.M., PH.D., BELA T. MATYAS, M.D., M.P.H., MICHAEL MCGUILL, D.V.M., M.P.H., MARTIN E. SCHRIEFER, PH.D., DONNA STILES-ENOS, R.N., DAVID T. DENNIS, M.D., M.P.H., LYLE R. PETERSEN, M.D., M.P.H., AND EDWARD B. HAYES, M.D.

ABSTRACT

Background In the summer of 2000, an outbreak of primary pneumonic tularemia occurred on Martha's Vineyard, Massachusetts. The only previously report-

1 to 21), infection with *F. tularensis* can result in various clinical presentations, depending on the route of inoculation, the dose of the inoculum, and the virulence of the organism. Primary pneumonic tularemia

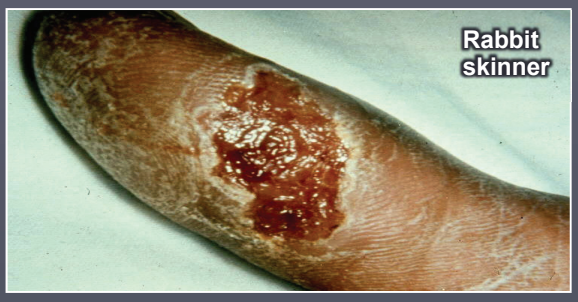
Lawn mowing & brush cutting

N Engl J Med, Vol. 345, No. 22 · November 29, 2001

TULAREMIA

- Incubation period: 3-5 days but up to 3 weeks
- DX: Serology; PCR
- Culture of *F. tularensis* is lab hazard. Neg routine culture, needs chocolate agar
- RX: **gentamicin** (or streptomycin), **FQs**, **doxycycline**
- Prophylaxis (bioterrorism) doxycycline

Maurin & Gyuranecz. *Lancet* (2016)



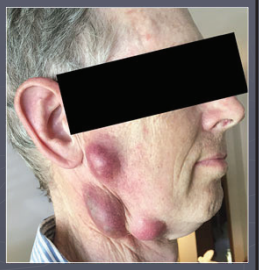
Glandular Tularemia

68-year-old with 1 wk fever then 2 mo progressive, painful swelling on R. side of neck

Exposure to a sick cat

Diagnosis made by + IgM (1:1280)

Improved with 4 wk doxycycline



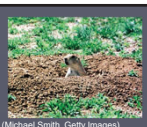
Marks, Laura, and Andrej Spec. "Glandular Tularemia." *New England Journal of Medicine* 379.10 (2018): 967-967.

Contact with insect vector

PLAGUE

PLAGUE

- *Yersinia pestis*
- New Mexico, California, Arizona & Colorado
  - Rodent **flea bite**
  - **Prairie dogs**
- Fever, nausea & swollen, painful lymph nodes
- Sepsis, pneumonia-hematogenous or aerosol in crowded conditions

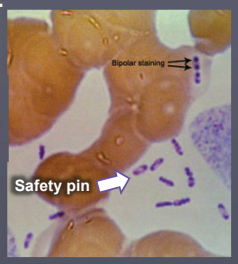


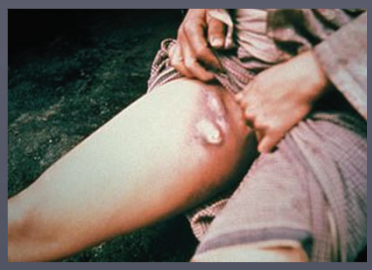
(Michael Smith, Getty Images)

(Eye of Science/Science Source)

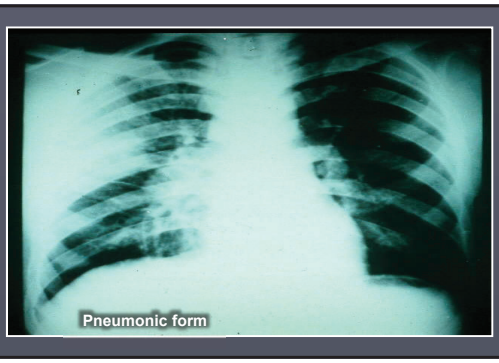
PLAGUE

- Gram negative coccobacillus
- **Bipolar-staining** bacilli
- **Safety pin** appearance
  - *Yersinia pestis*: lab hazard
- Treatment: **Streptomycin** >> doxy, cipro





Wikipedia image



Large Outbreak in Madagascar

Plague is an endemic disease in **Madagascar**

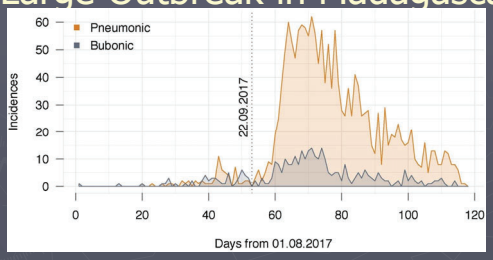
Each year there is a seasonal upsurge between September – April

In **2017**, an unprecedented **pneumonic plague** outbreak hit the main island

Nearly 2,500 reported or suspected cases (78% pneumonic)

https://www.sciencedaily.com/releases/2019/04/190416132101.htm
Randremanana R, *et al. Lancet ID*, 19(5) (2019)
Majumder MS, *et al. PLoS Curr*. (2018)

Large Outbreak in Madagascar



Nguyen VK, *et al. Epidemics* (2018)

2019

Mongolian Couple Die of Plague after Eating Raw Marmot

THE INCIDENT SPARKED A QUARANTINE, STRANDING TOURISTS FOR DAYS

May 17, 2019

By Jonny Lupsha, News Writer

A couple in Western Mongolia have died of bubonic plague after eating raw marmot, *The Guardian* reported. There are people who believe eating the innards of the rodent is good for their health. Although people ignore health warnings not to eat uncooked meat, raw marmot can carry the plague germ *Yersinia pestis*. Plague is known for causing the Black Death in the 14th century—but was it that simple?

Intact skin contact with animal urine

Question #3

- 28 yr old male presents with temp 39ºC, diffuse myalgia, headache, malaise. Returned 2 days ago from "Iron Man" race with running, biking, swimming in lake, climbing in Hawaii. Numerous mosquito bites. Exam: Conjunctival suffusion but no other localizing findings.
- WBC 14,500 with 80%PMN, no eos or bands. Platelets 210k.
- Bili 2.4, ALT 45, AST 52, Alk Phos 120, Cr 1.6. Hct 45%. BC neg. UA: normal

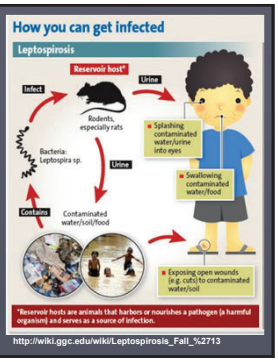
Question #3

Most likely diagnosis:

A. malaria
B. dengue
C. ehrlichiosis
D. leptospirosis
E. Zika

LEPTOSPIROSIS

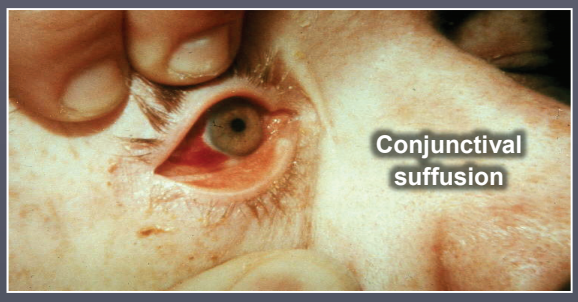
- Spirochetes excreted in urine of infected host & able to survive in wet environment
- Exposed intact skin to animal urine in water: veterinarians, farmers, loggers, triathletes, white water rafting, trapping
- Urine from cows, pigs, dogs, raccoons, rats, mice.
  - Summer & early Fall.



http://wiki.ggc.edu/wiki/Leptospirosis_Fall_%2713

LEPTOSPIROSIS

- Fever, myalgia, headache (aseptic meningitis late in course)
- **Conjunctival suffusion**, +/- rash
- In severe cases: jaundice, azotemia, pulm. hemorrhage
- Lab: serology by agglutination test, culture urine in Fletcher's medium
  - PCR & sequencing emerging
- Rx: **doxycycline** for outpatients, IV penicillin for inpatients
  - Jarisch-Herxheimer in first 2 hr.



Ingestion of animal products

Question #4

A 41 year old car salesman from Baltimore was admitted for a febile illness & found to have *Brucella melitensis* in his blood culture. He had attended a dinner a month prior where some family members from Greece had brought food from home. About two weeks prior to onset of fever, he had bought some lamb & beef at a farmer's market outside Baltimore.

Question #4

The most likely source of his brucellosis was which of the following:

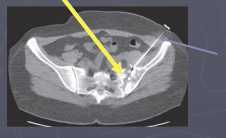
A. Home made sausage from Greece
B. Home made goat cheese from Greece
C. Cole slaw from a Baltimore delicatessen
D. Beef tartar, meat from the farmer's market
E. Lamb kabobs, meat from the farmer's market

BRUCELLOSIS

- Exposure to non-USA dairy or meat, **unpasteurized** cheese, uncooked meat,
- Slaughterhouse worker, meat packer, veterinarian
- Acute or indolent onset fever, aches
- Nodes, liver, spleen may be enlarged

BRUCELLOSIS

Later onset lesions in bone, liver
Epidymo-orchitis, endocarditis
sacroiliitis, tenosynovitis, meningitis



BRUCELLOSIS (con't)

- WBC normal or low, anemia, plt can be low
- DX: Blood culture, serology
- RX: Doxy plus rifampin or strep/gent
  - TMP-SMX in pregnant or young children

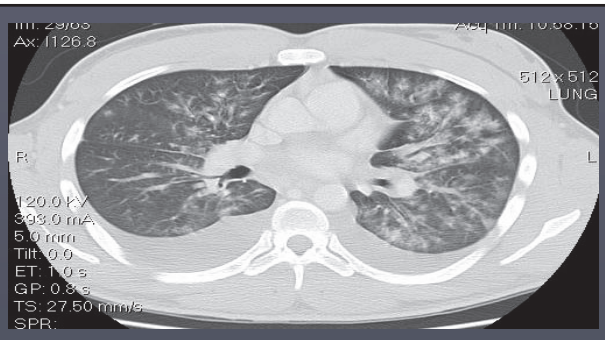
Inhalation of animal products

Case

- A 22 year old previously healthy male contractor returned from Afghanistan one week prior to presentation. He had a three day history of fever, myalgia, arthralgia, mild headache & cough. He had vomited once & had mild midepigastric, nonradiating pain.
- The facility he was hired to guard was adjacent to the path that the local sheep & goat herders used on their way to market & he had purchased a wool rug from one of the locals. He remembers shaking it hard to get rid of the dust.
- He reported that some members of his guard unit also had flu-like illness from which they recovered without treatment.

Case

- Examination was normal except for a variable temperature up to 102°F
- WBC **3.3**K, platelets **121**K, creatinine 1.2, AST **144**, ALT **154**, alk phos 88, total bilirubin 0.6
- Admission chest Xray was normal
- Ceftriaxone was begun but the patient remained febrile & had the chest CT shown on the next slide



Question #5

Which of the following is the most likely diagnosis?

A. brucellosis
B. anthrax
C. leptospirosis
D. Q fever
E. Visceral leishmaniasis

Q FEVER

- *Coxiella burnetii*: tiny cocco baccilus
  - Infects cows, sheep, goats, cats, etc.
- Spores survive in straw, manure, meat, *parturient tissue* for months.
  - Aerosol, ingest raw milk
- Acute pneumonia (in half cases), fever, headache, hepatosplenomegaly
- **Chronic endocarditis** on native or prosthetic valves
- **Granulomatous hepatitis**
  - **Doughnut granulomas**
- DX: serology, valve PCR or immunocytochemistry
- RX: acute: Doxycycline or levofloxacin or azithromycin
- Chronic: doxycycline plus hydroxychloroquine

A 54-year-old man with a history of multiple myeloma presented with intermittent fevers, chills, fatigue, & weight loss for 1 month. +splenomegaly, ↑LFTs, ↓plt

Rat Bite Fever

- Rat-bite fever (RBF): infection caused by 2 different bacteria:
  - *Streptobacillus moniliformis*, the only reported bacteria that causes RBF in North America (streptobacillary RBF): fever, chills, myalgia, headache, & vomiting; rash
    - Gram negative; can culture
  - *Spirillum minus*, common in Asia: fever, ulceration at the bite site, lymphangitis, lymphadenopathy, distinct rash of purple or red plaques
    - Darkfield needed to diagnose; culture negative
- Most infected after contact with rodents carrying the bacteria
  - Consumption of food or water contaminated with the urine & droppings of rodents carrying the bacteria.
- Penicillin treatment

https://www.cdc.gov/rat-bite-fever/index.html

QUICK SUMMARIES

Summary of Key Exposures

- Flea bites from rodents or outdoor cats in contact with wild rodents:
  - *Yersina pestis* PLAGUE (New Mexico, Colorado, Arizona)
- Wild game or their ticks: handling, cleaning muskrats, beavers, rabbits, squirrels
  - TULAREMIA

Summary of Key Exposures

- Eating unpasteurized cheese from overseas, including goat cheese:
  - BRUCELLOSIS
  - Unpasteurized queso *could suggest* ***Listeria***
    - Stem likely to include pregnant woman

Summary of Key Exposures

- Animal **urine** on intact skin: hiker, farmer, forestry, veterinarian, swimming, falling in water or rafting in contaminated water
  - **Leptospirosis**
- Handling overseas animal **hair**, **hides**
  - **Anthrax**
- Slaughterhouses, veterinarians, parturient cats, sheep handlers, living downwind of sheep/cattle farms
  - **Q Fever**

Key Clinical Syndromes

Culture negative endocarditis
- Homeless: *Bartonella quintana*
- Animal exposure: *Coxiella burnetii*

Kaposi-like skin lesions: *Bartonella henselae*

Tender lymph node: bartonellosis, tularemia, plague

Fever + jaundice: leptospirosis

Sacroiliitis: brucellosis

Rat bite in US: *Streptobacillus moniliformis*

Rat bite in Asia: *Spirillum minus*

Other Zoonoses

- There are many zoonoses
- Be sure to review them before the boards

Chikeka & Dumler *Clin Microbiol Infect* 2015; 21: 404–415

The End

Thank you!

D.aronoff@vanderbilt.edu
@DMAronoff

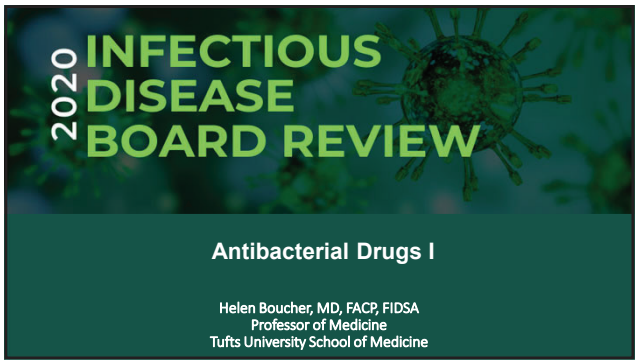
55

Antibacterial Drugs I

Dr. Helen Boucher

55 – Antibacterial Drugs

Speaker: Helen Boucher, MD



CASE

- 64 year old woman with diabetes mellitus, hypertension, coronary artery disease, osteoarthritis, depression, and recently diagnosed MRSA skin infection on her leg presents with 24 hours of fever, chills and shakes
  - Presented with abscess that was drained; linezolid prescribed 5 days earlier
  - 24 hours ago: chills, malaise and tremors
  - No diarrhea, abdominal pain, skin rash
- Current medications: lantus insulin, linezolid, hydrochlorothiazide, aspirin, metoprolol, sertraline, tramadol. No allergies.

3

Exam

- T 101.6F, BP 146/88, HR 100, RR 20, Sat 97%RA
- HEENT, chest clear, CV, abdomen normal
- Leg with 5 cm wound with pink granulation tissue, scant purulent drainage on dressing; no tenderness, surrounding erythema, warmth or edema
- Neuro: alert and oriented to person, place and time; CN II-XII intact, motor and sensory intact; 3+ bilateral patellar reflexes, resting tremor worse in legs, + clonus
- Labs wbc 7.5, 72%p, 20%l, 5 mono, 2 eo, 1 baso, hct 39, plt 160, Na 145, K 3.9, Cl 96, CO2 20, BUN/Cr 30/1.4 (baseline)

Progress: Neurology consult pending

4

ARS

In addition to blood cultures, chest x-ray, urine analysis and culture, you recommend

A. STAT blood glucose
B. Discontinuation of linezolid
C. MRI of the leg
D. Brain imaging and lumbar puncture

5

Serotonin Syndrome Related to Linezolid

- Linezolid is a MAO inhibitor, interacts with SSRIs, tramadol and other rx to cause serotonin syndrome
  - Lawrence et al. CID 2006; 42: 1578

Other answers:

- Addition of parenteral dalbavancin –reasonable if failure of therapy of the ABSSSI was considered
- MRI of the leg - failure of source control might be considered
- Brain imaging and lumbar puncture – reasonable for concern of brain infection

6

Case

- 74 year-old man admitted for elective surgery for metastatic cancer of unknown primary
- Presented 6 months earlier with persistent cough. Chest x-ray showed a solitary lung lesion and chest CT confirmed a lung nodule. Lung wedge resection was nondiagnostic. MRI showed two brain lesions in the cerebellum and left temporal lobe. Lung needle biopsy was non-diagnostic. He was referred to Neurosurgery to discuss treatment options for brain metastasis
- Exam notable for unsteady gait. MRI: increase in size of the temporal lesion, new ring-enhancing lesions in cerebellum with surrounding edema
- Dexamethasone started and he was admitted for brain biopsy

7

Case

- Past medical history: hypertension, CAD
- No smoking, alcohol, drug use. No pets. Travel to California, Arizona, Europe
- Family history – father + colon cancer
- Medication: dexamethasone; NKDA
- T 37C, BP137/84, HR94, RR16, O2 SAT 100%.
- Neuro - unsteady gait, muscle strength 5/5 throughout, normal DTR
- Wbc 13.2, 95%polys, hct 31.7, platelets 495, BUN 13/Creat 0.62

8

ARS#

Which of the following is the best initial therapy?

A. meropenem and TMP/SMX
B. pyrimethamine and sulfadiazine
C. chemotherapy and radiation
D. vancomycin and cefepime

9

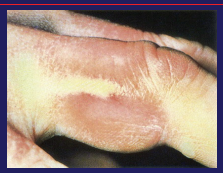
Nocardiosis

- Gram-positive bacterial infection caused by aerobic actinomycetes in the genus *Nocardia*
- Epidemiology: 2/3 immunocompromised, 1/3 immunocompetent
- Pneumonia, brain abscess, lymphadenitis
- Can disseminate to virtually any organ, particularly the central nervous system
- Tends to relapse or progress despite appropriate therapy
- Different *Nocardia* species/strains have different susceptibility patterns
  - Send for species ID and susceptibility testing
- Treat with 2-3 drugs pending susceptibility
  - TMP-SMX
  - Carbapenem (imi/meropenem)
- Also linezolid, amikacin, third-generation cephalosporins, minocycline, extended spectrum fluoroquinolones (eg, moxifloxacin), tigecycline, and dapsone

10

Case

A 38 year old male lobsterman presents with a 4 day history of worsening erythema, warmth and pain in his middle finger. A biopsy of the site reveals small, slightly curved, gram-positive, catalase negative bacillary organisms



11

ARS

Which of the following is the most likely organism causing this infection?

- *Vibrio vulnificus*
- *S. pyogenes*
- *S. anginosus* group
- *Erysipelothrix rhusiopathiae*

12

Erysipeloid "Whale Finger"

Erysipelothrix rhusiopathiae

- α-hemolytic, gram positive (though loses staining readily – may look gram neg), catalase negative
- Confused with listeria, arcanobacterium (but they are β-hemolytic)
- Found in environment – soil, grow readily in slime layers on fish
- Swine = major reservoir
- Occupational exposure highest risk

Treatment:

- Susceptible to b-lactams, quinolones, clindamycin
- Resistant to vancomycin, TMP-SMX, aminoglycosides

13

Case

- 22 year old man with substance use disorder presents to OPAT clinic on day 24 of parenteral oxacillin for MSSA bloodstream infection. He feels well but notes decreased appetite over the last few days. No nausea, vomiting, diarrhea, rash, fever, chills or sweats. No problem with the PICC line or difficulty infusing
- Exam unremarkable; PICC site without erythema, drainage, warmth, redness or palpable cord
  - White blood cell count 8, normal differential
  - normal electrolytes, BUN/Cr 18/0.6, urine analysis normal
  - ALT 250, AST 142, Alk phos 117, T Bili 1.3
  - Hepatitis B surface antigen negative
  - Hepatitis C RNA not detected, HIV negative

14

ARS#

- Which of the following agents is best to replace oxacillin:

1. Ceftaroline
2. Daptomycin
3. Linezolid
4. Cefazolin
5. Vancomycin

15

Outcomes in MSSA Bacteremia B-Lactam Versus Vancomycin

	B-Lactam N = 44	Vancomycin N = 28	P - value
Infection-related Mortality	5 (11%)	11 (39%)	0.005

Risk Factors for Failure (multivariate anal)		
Vancomycin Tx	6.5 (1.4-29.4)	

- Higher mortality in ceftriaxone-treated B-lactam patients
- No difference in mortality between patients who received initial vanco and those who had vanco switched to B-lactam (33% vs. 41%, p 0.7)

Lodise et al. AAC 2007; 51(10): 3731-33

16

Outcomes in MSSA Bacteremia Cefazolin Versus Vancomycin

	Cefazolin N = 46	Vancomycin N = 77	P - value
12 Week Failure	13%	31%	0.02

Risk Factors for Failure (multivariate anal)		
Vancomycin Tx	3.53 (1.15-13.45)	0.04
Reten HD cath	4.99 (1.89-13.76)	0.001

- Cefazolin patients older and had more metastatic infections at baseline
- Only 9% of vancomycin patients had allergies to PCN/cephalos

Stryjewski et al. CID 2007; 44: 190-6

17

For MSSA, use a β-lactam

MAJOR ARTICLE

Comparative Effectiveness of Beta-Lactams Versus Vancomycin for Treatment of Methicillin-Susceptible *Staphylococcus aureus* Bloodstream Infections Among 122 Hospitals

Jennifer S. McDaniel,[1,2,3] Eli N. Perencevich,[1,2,3] Daniel J. Diekema,[2,4,5] Loreen A. Herwaldt,[2,4,5] Tara C. Smith,[1,4] Elizabeth A. Chrischilles,[1] Jeffrey D. Dawson,[6] Lan Jiang,[6] Michihiko Goto,[2,3] and Marin L. Schweizer[2,3,7]

- β-lactams associated with 35% lower mortality
- Vancomycin is clearly inferior for MSSA bacteremia

McDaniel et al, Clin Inf Dis 2015;61:361-67

18

Case

- 45 year old woman admitted for cholecystitis has MSSA bloodstream infection related to thrombophlebitis at IV site
- TTE showed normal valves
- Started on parenteral cefazolin with plan to treat for 4 weeks
- At 2nd week OPAT visit (cefazolin day 14)
  - Exam unchanged
  - White blood cell count 8.4, hemoglobin 6.7
  - normal electrolytes, BUN/Cr 32/1.0
  - AST 23, ALT 16, Alk phos 55, T Bili 1.8, LDH 459, haptoglobin < 8

19

ARS Question # 1

After discontinuing cefazoin, you recommend:

A. Piperacillin-tazobactam
B. Ampicillin-sulbactam
C. Meropenem
D. Moxifloxacin

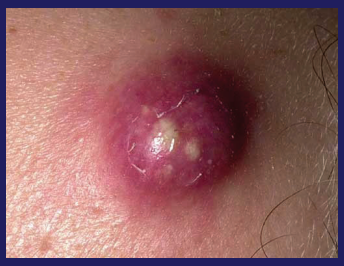
20

Cephalosporin Toxicity

- Hypersensitivity reactions , rash
- GI disturbances
  - Nausea, vomiting, diarrhea (+/- C. difficile)
  - GB sludge or pseudocholecystitis with ceftriaxone
- Hematologic toxicity (class effect)
  - Eosinophilia
  - Hemolytic anemia, positive Coomb's test
- Hepatotoxicity
- Nephrotoxicity (interstitial nephritis)
- Neurotoxicity – tremor, confusion, seizure, encephalopathy
  - Worse with renal failure

21

45 year old man from Miami
Painful lesion not responsive to cephalexin



Diameter: 3cm

22

ARS Question

In addition to incision and drainage, which of the following is the best oral therapy?

A. Doxycycline
B. Delafloxacin
C. Tedizolid
D. TMP/SMX

23

TMP-SMX for *S. aureus* ABSSI

- For skin/skin structure infections:
  - Resistance among CA-MRSA: 0-17%
  - ?Poor coverage of Group A Strep
  - Clinical data for use in skin infections
    - TMP/SMX superior to placebo with I&D
    - Success common with outpatient Rx

1. d'Oliveira RE, et al. *Microb Drug Resist.* 2003;9:87-91
2. Iyer S, Jones DH. *J Am Acad Derm.* 2004;50:854-858.
3. Miller LG, et al. *Clin Infect Dis.* 2007;44:483–492.
4. Ruhe JJ, et al. *Clin Infect Dis.* 2007; 44:777-784.
5. Duong M, et al. *Ann Emerg Med.* 2010;55:401-407
6. Schmitz GR, et al. *Ann Emerg Med.* 2010; 56:283-287.
7. Frei CR, et al. *J Am Board Fam Med.* 2010;23:714-719.
8. Fridkin SF, et al. *New Engl J Med.* 2005;352:1436-1444.
9. Frazee BW, et al. *Ann Emerg Med.* 2005;45:311-320.
10. Miller LG, et al. *Clin Infect Dis.* 2007; 44:471–82
11. Talan et al *N Engl J Med* 2016; 374:823-832

24

Antibiotic Therapy for Small MRSA Abscesses

- 1220 patients with abscess 2-5 cm diameter, 45% MRSA, all had I&D
  - TMP-SMX (320 mg/1600 mg 2x/d) better than placebo
- > 780 patients with abscess ≤5 cm (45 % ≤2 cm), 49% MRSA, all had I&D
  - TMP-SMX or clindamycin better than placebo
- Systematic review/meta-analysis > 2400 patients with drained abscess
  - Lower failure in patients who received antibiotics vs placebo (7% versus 16%); odds ratio for cure 2.3 (95% CI 1.7-3.1)
  - Antimicrobial therapy may also decrease the risk of recurrent skin abscess

Talan et al. N Engl J Med. 2016;374(9):823. Daum et al. N Engl J Med. 2017;376(26):2545. Gottlieb et al. Ann Emerg Med. 2019;73(1):8. Epub 2018 Mar 9

25

Unresponsive Female with a Red Arm

- 61 year old female admitted to an outside hospital with unresponsiveness
- Blood glucose >1000 mg/dl and hypotensive on admission
- Noted to have desquamating L hand with L arm erythema, swelling, and bullae
- Placed on pressors and transferred for further care

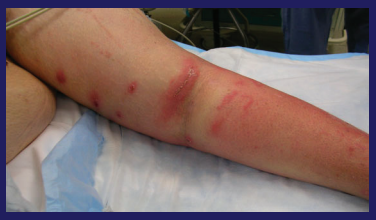
26

Unresponsive Female with a Red Arm

- Past Medical History
  - Diabetes mellitus, HTN
- Vitals: BP109/48 on levophed, HR 71 RR 31 Temp 37.9F, 98% on 40% Fio_2
- Exam: intubated/sedated
  - Erythematous furuncles on abdomen, bilateral lower extremities, L arm
    - Patchy erythema, tense edema
    - Hand with erythema, bullae
- Pertinent labs: BUN/creat 17/0.8, wbc 37k

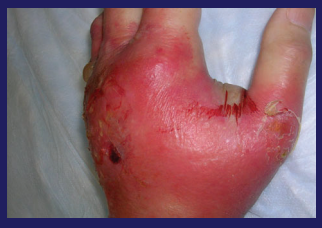
27

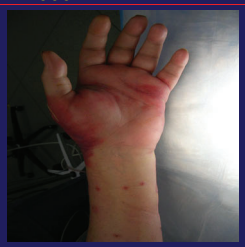
Unresponsive Female With DM Presented With Shock, Glucose > 1000



28

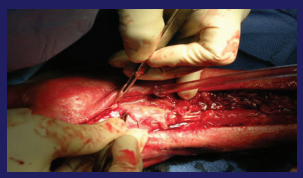
Unresponsive Female With DM, Presented With Shock, Glucose > 1000

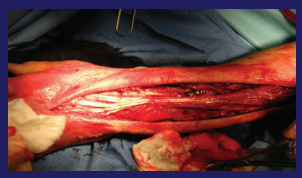




29

Intra-operative





30

Hospital Course

Operative findings
- Muscles and tendons intact
  - No bulging noted
- Return to the OR the next day
  - Incision extended to the digits
  - Gross purulence
- Blood cultures negative
- Tissue and wound cultures grew *S. aureus*
  - Susceptible to vanco, clindamycin, gent, rifampin, Tetracycline, TMP/SMX, linezolid
  - Resistant to penicillin, oxacillin, erythro
    - CA-MRSA

31

Hospital Course - Progress

- Repeated surgical debridement
- Extubated HD #10

- Additional history
  - Animal/insect contact: dog at home with fleas
    - Pt bathed dog and developed small itchy bites

32

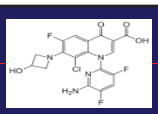
ARS Question #3

The best therapy includes

A. Delafloxacin
B. Vancomycin
C. Linezolid
D. TMP/SMX

33

Delafloxacin



- Broad spectrum anionic fluoroquinolone
- FDA approved ABSSI
- Potential advantages:
  - First FQ with MRSA activity (not effective vs GC)
  - Oral bioavailability
  - Accumulates in acid pH (intracellular)
  - Efficacy in obese patients
- Safety – > 2100 subjects studied prior to pivotal ABSSSI trials
  - MILD GI effects most common
  - No QTc Prolongation observed
  - Phototoxicity not observed
  - No effect on LFTs or glucose
  - No tendon rupture cases to date

Saravolatz LD and Stein GE. Clin Infect Dis. 2018

34

Antibiotic Challenges Case

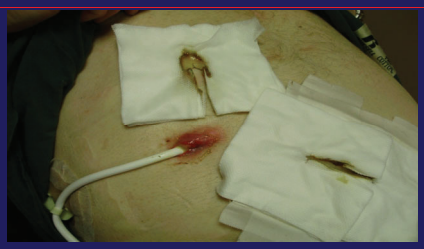
57 year old man with endstage non-ischemic cardiomyopathy, valvular heart disease, hypothyroidism, diabetes
- Cardiogenic shock
- Left Ventricular Assist Device (LVAD)
- Listed for transplant

35

Case (continued)

Two months later…
- Pain and drainage from driveline exit site
- History of trauma 3 days prior
- Exam 10cm surrounding cellulitis, purulent drainage
- Gram stain 4+ polys, many gram-positive cocci in clusters
- VAD wound culture + MRSA
- Vancomycin initiated

36



37

Case (continued)

- Imaging with CT + enlarging collection surrounding the aortic limb of the VAD with ? sternal osteomyelitis; new, progressive subcutaneous fat stranding and skin thickening along abdominal wall at DL exit site with internal mesenteric fat stranding
  - Cellulitis vs mesenteritis
- Blood cultures + MRSA
- Progress
  - Difficulty administering and obtaining vancomycin levels in ambulatory patient with VAD
  - Fluctuating vancomycin levels and renal function

38

ARS Question
Which of the following is the best therapy for this ambulatory patient?

A. Oral Linezolid
B. IV Daptomycin
C. Oral TMP/SMX
D. IV Dalbavancin
E. IV Ceftaroline

39

Linezolid and Tedizolid

	Linezolid	Tedizolid
FDA approval	ABSSSI, PNA, VRE; NOT BSI (Black Box Warning)	ABSSSI
Dosing	600mg twice daily IV/oral x 10 days	200mg once daily IV/oral x 6 days
Activity	Similar spectrum to include MRSA, VRE, *Nocardia* spp, Mycobacteria	
MRSA Pneumonia	Superior to vancomycin?	Study vs linezolid complete
Safety	Bone marrow (platelets)	? More safe than linezolid
	Serotonin syndrome, lactic acidosis, peripheral/optic neuritis	Not studied in neutropenic patients

40

Daptomycin for *S. aureus* Bacteremia and Right IE

SAB/IE Study Issues
- Design - dapto alone vs. combo/init low dose gent
- Vanco MIC_{90} 0.5µg/ml – higher in many centers in 2008

Daptomycin 6mg/kg iv daily - ? Higher doses
- Follow CPK – espec CrCl < 30 ml/min or high dose
  - Not for pneumonia
    - Inactivated by pulmonary surfactant → failed pneumonia studies
    - Seems to be OK for septic pulmonary emboli
  - Resistance on therapy
  - Use with caution with retained foreign body/undrained abscess

Benvenuto et al. *Antimicrob Agents Chemother.* 2006;50:3245
Cunha BA et al. *Heart Lung.* 2006;35:207-11; Boucher and Sakoulas CID 2007

41

TMP/SMX for MRSA BSI/Endocarditis

Conflicting data vs. vancomycin
- Old study showed longer duration of SAB, potentially worse outcomes with TMP/SMX for MSSA SAB
- More recent retrospective matched cohort study of patients with MRSA BSI treated with TMP/SMX or vancomycin
  - Similar duration MRSA SAB
  - Numerically fewer relapsed MRSA SAB
  - Similar mortality, renal toxicity

Option for salvage MRSA therapy

Markowitz N et al. *Ann Intern Med.* 1992;117:390-398
Goldberg E et al. J Antimicrob Chemother. 2010;65:1779

42

31 year old homeless woman with substance use disorder and history of recurrent MRSA skin infections presents with a 12cm diameter thigh abscess. She reports active IV drug use this AM

No medications, no known allergies

- T 102, BP 96/58, P 110, RR 18, Sat 96% room air
- Nontoxic appearing. o/p with dry mucosa, no thrush, chest clear, CT tachy + S1, S2, abdomen – normal bowel sounds, soft, nontender; extremities, left leg with 12cm diameter fluctuant area on anterior thigh; 22 cm diameter overlying erythema, with warmth and induration; exquisitely tender to palpation; visible track marks over arms and legs. Neuro + fine tremor

43

Laboratory data:

- wbc 14k, 88%P, 8L, 4mono
- Na 134, K 3.4, Cl, Hco2, BUN/Cr 29/1.2
- AST 34, ALT 48, Alk P 122, T bili 1.2
- Rapid HIV negative
- X-ray of leg – no fracture, no gas
- Blood cultures obtained
- Patient declines hospital admission, will allow incision and drainage

44

ARS#

Which of the following is most appropriate for this patient?

1. Vancomycin
2. Ceftaroline
3. Dalbavancin
4. Daptomycin

45

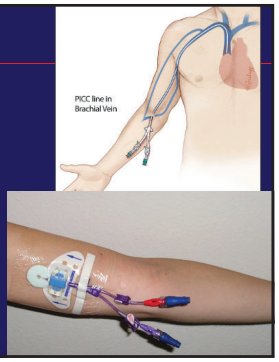
Long-acting Lipoglycopeptides

	Dalbavancin	Oritavancin
FDA approval	ABSSSI vs vanco then linezolid	ABSSSI vs vanco
Dosing	1000 mg followed by 500 mg one week later or 1500 mg once (30 minute infusion) Dose adjustment if CrCL < 30 mcg/mL	1200 mg once (3 hour infusion) No dose adjustment (minimal renal excretion)
Activity	Some hVISA/VISA strains *VanB* VRE only	Some hVISA/VISA strains *VanA* and *VanB* VRE
BSI/osteo	Case series	Few cases
Susceptibility	Inferred from vancomycin	Inferred from vancomycin
Safety	? Liver dysfxn	? Liver dysfxn osteo
Coag interference	No	Falsely elevated aPTT first 24-48 hrs Increased warfarin exposure

46

Why consider oral antibiotics?

- Less intravenous access complications
- Reduced frequency of hospital follow-up appointments
- Fewer restrictions in activities of daily living and return to work



POET *S. aureus* Patients

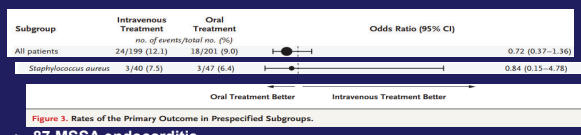


Figure 3. Rates of the Primary Outcome in Prespecified Subgroups.

- 87 MSSA endocarditis
- Most common oral regimens:
  - Dicloxacillin + rifampin (N=15)
  - Amoxicillin + rifampin (N=13)
- Take-home for SAB oral step-down therapy: apply to MSSA only, no extracardiac complications

Iversen et al, NEJM 2018, doi:10.1056/NEJMoa1808312

48

Case

- 30 year old healthy teacher presents with 1cm abscess on the left thigh, no systemic illness
- PMHx menorrhagia
- Meds: oral contraceptive, ferrous sulfate
- Afebrile, exam otherwise normal
- ER MD performs incision & drainage, advises abstaining from shaving
- Tetanus booster administered
- You are asked to recommend further therapy

49

ARS Question

You prescribe doxycycline for acute bacterial skin infection. You advise

A. Taking doxycycline with food
B. Avoiding sun exposure
C. Taking doxycycline with morning medications
D. Discontinuing oral contraceptive

50

Tetracycline Absorption/Adverse Effects

- Absorption in the proximal small intestine and the stomach
  - Doxycycline is 95% bioavailable with or without food, whereas
  - Tetracycline bioavailability reduced x 50 percent if taken with food
- Absorption of tetracyclines decreased with administration of chelating multivalent cations (ie, aluminum, calcium, iron, magnesium)
- Adverse effects:
  - Gastrointestinal (N/V), hepatotoxicity rare but fatal
  - Photosensitivity
  - Tooth discoloration
  - Teratogenic
  - Vertigo - minocycline
  - Death - tigecycline black box warning
  - Heme (rare), minocycline associated lupus

51

Case

- 42 year old healthy man presents in February with cough, T38C, wheezing
- Rapid flu test positive; SARS CoV-2 PCR negative
- Discharged home
- 5 days later returns to ER with T 39C, dyspnea, oxygen sat 90% RA
- CXRay + dense RLL infiltrate
- Sputum gram stain 4+ polys, 4+ G+ cocci in clusters
- WBC 21,000, 96% polys, creat 1.2, Lactate 2.4
- Sputum /blood cultures sent

52

ARS Question

In addition to supportive care, the best therapy includes:

A. Linezolid
B. Ceftriaxone
C. Azithromycin
D. Daptomycin

53

Treatment of Community-Acquired Bacterial Pneumonia (CABP)

<u>Outpatient</u>

Healthy – macrolide or doxycycline

(+) comorbidity or risk factor for drug-resistant S. pneumoniae (DRSP):

Respiratory quinolone

β-lactam + macrolide

<u>Inpatient, non-ICU</u>

Respiratory quinolone

β-lactam + (macrolide or quinolone)

54

Empirical CABP Coverage in ICU

No Pseudomonas	Beta-lactam + macrolide/quinolone
	PCN allergy: quinolone + aztreoman
Pseudomonas?	anti-Pseudomonal beta-lactam + quinolone
	anti-Pseudomonal beta-lactam + AG + azithro/levo
	PCN allergy: aztreonam + AG + levo
MRSA?	add vancomycin or linezolid to above

IDSA Guidelines 2007 (revision pending):
https://academic.oup.com/cid/article/44/Supplement_2/S27/372079

55

Risk factors for MRSA in CABP

- Gram-positive cocci in clusters on sputum Gram stain
- Known colonization with MRSA
- Risk factors for colonization with MRSA (eg, end-stage renal disease, contact sport participants, injection drug users, those living in crowded conditions, men who have sex with men, prisoners)
- Recent influenza-like illness
- Antimicrobial therapy (particularly with a fluoroquinolone) in the prior three months
- Necrotizing or cavitary pneumonia
- Empyema

56

Risk Factors for DRSP in CABP

- Age >65 years
- Beta-lactam, macrolide, or fluoroquinolone therapy within the past three to six months
- Alcoholism
- Medical comorbidities
- Immunosuppressive illness or therapy
- Exposure to a child in a daycare center
- Healthcare exposure (LTC)
- Recent tx/repeated course of therapy with beta-lactams, macrolides, or FQ = risk for pneumococcal resistance to the same class of antibiotic - use an agent from an alternative class

57

Abx Options for MRSA Pneumonia

- Vancomycin
- Linezolid/Tedizolid
- Clindamycin (D test negative)
- Ceftaroline
- Omadacycline
- Lefamulin
- Delafloxacin

58

FOCUS
Ceftaroline CABP FDA Analysis/Early Endpt

	Ceftaroline	Ceftriaxone	Tx Diff (95% CI)
Day 4 response	69.5%	59.4%	10.1 (-0.6, 20.6)
S. pneumo	54/74 (73.0%)	42/75 (56.0%)	16.9 (1.4, 31.6)
S. aureus	14/24 (58.3%)	17/31 (54.8%)	0.7 (-24.7, 26.2)

*MITT included pts who received study drug, had baseline pathogen isolated. Success required BOTH clinical stability and symptom improvement.

File et al. CID 2011, File et al. CID 2012, www.fda.gov

59

Ceftaroline
Safety and Monitoring

- Rash, GI disturbances – like other cephalosporins
- Hematologic toxicity (class effect)
  - Eosinophilia
  - Positive Coomb's test
- Hepatotoxicity – LFT abnormalities 1-7%
- Neurotoxicity – tremor, confusion, seizure, encephalopathy
  - Worse with renal failure

60

New Tetracyclines

	Omadacycline	Eravacycline
FDA approval	ABSSSI, CABP	cIAI, not cUTI (failed studies)
Dosing	200 mg loading dose over 60 min day 1, 100mg IV over 30 min or 300mg orally once daily No dose adjustment for renal/hepatic impairment	1mg/kg IV q 12h (over 60 minutes) Dose adjustment with hepatic impairment
Activity	Broad spectrum: Gram-pos including MRSA, VRE; Gram-neg including ESBL, CRE (not all); anaerobes	
Issues	Limited activity vs carbapenem-resistant *K. pneumoniae*	High MIC *Pseudomonas*, *Burkholderia* spp.
Safety	GI, rash, ?heart rate	GI, rash

61

Lefamulin CABP
FDA Analysis/Early Endpt (ITT)

	Lefamulin N = 276	Moxifloxacin+/- LZD N = 275	Tx Diff (95% CI)
Day 4 response	87.3%	90.2%	-2.9 (-8.5, 2.8)
S. Pneumo	82/93 (88.2%)	91/97 (93.8%)	ND
S. aureus	10/10	4/4	ND

File et al. CID 2019

62

Case

- 73 year old man with prostate cancer, presented after rapid deterioration at home (<24hrs): feeling unwell, nausea and coffee-ground vomiting, followed by lethargy/difficulty speaking; intubated
- Never smoker, rarely drinks alcohol
- Never used IV drugs
- Lives with his wife at home
- Retired engineer

63

Case

- BP 102/73 (on levophed), HR 72, Tm 100.1 Tc 98.7, RR 16 Sat 95% on FiO2 40%
- General: Intubated, unresponsive
- HEENT: Anisocoria, left pupil fixed and dilated, right responds to light, no conjunctival hemorrhage, minimal stiffness in the neck
- Chest clear
- Heart : S1 S2 RRR, no murmur
- Abd: normal bowel sounds, soft NT ND
- Ext: no joint swelling, no stigmata of endocarditis

64

Case (continued)

- WBC 13.7, Hb 10 Plt 150
- BUN 20, Cr 0.8, LFTs normal
- Lactate 1.2
- CXR RLL infiltrate
- Brain MRI Early subacute, nonhemorrhagic, cerebral as well as cerebellar hemispheric microembolic infarcts most probably ascribable to a central embolic source
- CSF WBC 975 (neutrophils 85%), RBC 192, Glucose <5, Protein 540
- Blood Cx + *S. pneumoniae*, penicillin MIC 2 mcg/ml, ceftriaxone MIC < 0.5 mcg/ml

65

ARS Question
You recommend which of the following:

A. Penicillin
B. Ceftriaxone
C. Vancomycin
D. Moxifloxacin

66

S. pneumoniae Penicillin Breakpoints

	Minimum Inhibitory Concentration (MIC) (mcg/mL)		
	Susceptible (S)	Intermediate (I)	Resistant (R)
Updated	≤2	4	≥8
Previous	≤0.06	0.12-1.0	≥2

The susceptible breakpoint for meningitis caused by *S. pneumoniae* remains unchanged (≤ 0.06 mcg/mL)

Weinstein et al. CID 2009

67

Case (continued)

You recommend therapy with ceftriaxone 2g IV every 12 hours

- He improves clinically
- On day 9 of therapy, you are called back as the patient has developed profuse watery diarrhea with abdominal cramping
- BP is normal, abdomen + normal bowel sounds, soft
- Wbc 30,000 with left shift
- BUN/Cr 65/1.8
- Lactate normal
- Stool positive for *C. difficile* toxin

68

ARS Question
The best therapy includes

A. Oral metronidazole
B. Oral vancomycin
C. Oral fidaxomicin
D. Fecal microbiota transplant
E. Intravenous Bezlotoxumab

69

Antibiotics Associated with *C. difficile*

Frequently associated
- Fluoroquinolones
- Clindamycin
- Cephalosporins (broad spectrum)
- Penicillins (broad spectrum)

Occasionally associated
- Macrolides
- Trimethoprim-sulfamethoxazole

Rarely associated
- Aminoglycosides
- Tetracyclines
- Metronidazole
- Vancomycin

70

Thank You!

- Henry Masur
- Sue Cammarata
- G. Ralph Corey
- Sara Cosgrove
- Mike Dudley
- Mike Dunne
- David Gilbert
- Susan Hadley
- Kenneth Lawrence
- Evan Loh
- Paul McGovern
- Federico Perez
- Debra Poutsiaka
- George H. Talbot
- Our patients and their families

71

56

Helicobacter and Clostridioides Difficile

Dr. David Aronoff

56 – Helicobacter and Clostridium Difficile

Speaker: David Aronoff, MD

2020 INFECTIOUS DISEASE BOARD REVIEW

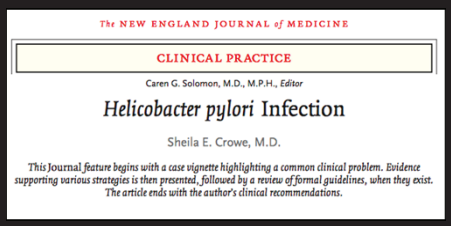
Helicobacter pylori and Clostridioides Difficile

David M. Aronoff, MD, FIDSA, FAAM
Professor of Medicine
Addison B. Scoville Jr. Chair in Medicine
Director, Division of Infectious Diseases
Vanderbilt University Medical Center

Disclosures of Financial Relationships with Relevant Commercial Interests

- None

HELICOBACTER PYLORI



The NEW ENGLAND JOURNAL of MEDICINE

CLINICAL PRACTICE

Caren G. Solomon, M.D., M.P.H., Editor

Helicobacter pylori Infection

Sheila E. Crowe, M.D.

This Journal feature begins with a case vignette highlighting a common clinical problem. Evidence supporting various strategies is then presented, followed by a review of formal guidelines, when they exist. The article ends with the author's clinical recommendations.

Recent review *N Engl J Med* 2019;380:1158-65.

Microbiology: *Helicobacter pylori*

Gastric Mucosa

- Spiral-shaped
- Flagellated
- Non-invasive

First isolated in 1983

Nobel Prize (Marshall & Warren, 2005)

NEJM 362: 1597, 2010

Agar

- Slow-growing (3-7 days)
- Gram negative rod
- Microaerophilic (5% O_2)
  - Catalase +
  - Oxidase +
  - **Urease +** → **Survival, Colonization, Diagnostic testing**

Urea → CO_2 + NH_3 → ↑pH

Question #1

A young woman undergoes upper endoscopy for unexplained nausea and vomiting. The stomach appears normal. Surveillance biopsies are taken and the gastric biopsy urease test is positive. The biopsies are most likely to show:

A. Hp organisms, but no gastric or esophageal inflammation.
B. Hp organisms plus gastric inflammation (gastritis).
C. Hp organisms plus esophagitis.
D. Neither Hp organisms, nor inflammation because the urease test is often false positive with a normal endoscopy.

Question #2

What is the most likely source for humans to acquire *H. pylori* infection?

A. Perinatally from mother
B. Ingestion of raw vegetables
C. Ingestion of undercooked meat
D. Ingested tap water from a municipal source
E. Contact with infected secretions from another human

Helicobacter pylori: Key Points

- Humans are the only natural Hp host
- Infects > 50% of the world's population
  - US ~20-40%*
- A leading chronic infection in humans
  - Similar to dental caries
- Majority are asymptomatic but all have chronic active gastritis
- Severity of gastritis varies depending on the Hp strain & the host

*At greater risk, African Americans, Hispanics, Native Americans

NEJM 380:1158-65, 2019
NEJM 362:1597, 2010
Gut 66:6, 2017

Transmission of *H. pylori*

- Exact route of transmission is not known
- Likely **fecal-oral or oral-oral**
- Intrafamilial spread – (person-to-person, esp. mother-to-child)
- Low socioeconomic status, poor sanitation, crowding associated with ↑transmission

JAMA 282:2240, 1999 & Crowe SE, UpToDate (2018)

Disease Paths for *Helicobacter pylori* Infection

Asymptomatic gastritis	85-90%
Peptic ulcer (DU, GU)	1-10%
Gastric cancer	0.1-3%
MALT lymphoma	<0.01%

DU, duodenal ulcer
GU, gastric ulcer
MALT, mucosal-associated lymphoid tissue

NEJM 347: 1175, 2002
Gut 66:6, 2017

H. pylori: Disease Associations

- #1 cause of chronic gastritis
- PUD: 90% DU, 80% GU
- MALT lymphomas (72 – 98%)
- Gastric Cancer (60 – 90%)*

Hp causal

- Iron deficiency anemia, B12 deficiency, ITP
- Eradication Hp neither causes nor exacerbates GERD
- Hp poss. **reduces** risk for Barrett's esophagus/esophageal CA

HP is classified by WHO as a Class 1 carcinogen.
MALT = mucosal-associated lymphoid tissue

Maastricht V. Gut 66:6, 2017
Kasahun GG, Infect Drug Resist 13:1567-1573, 2020

Question #3

A 25-year-old African American woman complains of 6 weeks of symptoms consistent with dyspepsia unrelieved by current use of antacids & an OTC PPI.

The best approach to the diagnosis of *H. pylori* infection in this patient is:

A. Immediate Hp serology
B. Immediate Hp stool antigen EIA
C. Endoscopy with rapid urease test (RUT)
D. Immediate ^{13}C Urea Breath Test
E. D/C PPI for 2 weeks then Hp stool antigen EIA

Diagnosis of *H. pylori* Infection

Noninvasive (global)	Sensitivity	Specificity	
Urea Breath Test (^{13}C)	> 90 – 95%	> 90 – 95%	Live Hp
Stool Antigen (monoclonal)	> 90 – 95%	> 90 – 95%	Live & dead Hp
Serology	85%	79%	Detects exposure

Biopsy-based (sampling error)	Sensitivity	Specificity	
Rapid urease test	90%	95%	2-5 bx recommended
Histology	90 – 95%	95 – 98%	
Culture	73%	100%	Difficult

UBT considered 'best test'. Antigen test is usually less expensive.
Use only monoclonal stool Ag tests.
Histology requires 10^4 organisms to visualize

BMJ 344:44, 2012

Testing Limitations for Hp

PPI
Antibiotics
Bismuth
Bleeding
} Interfere with all Hp tests

False negatives due to decreased Hp burden.
Recommend delay diagnostic testing until:

- PPI stopped for 2-4 weeks **(OTC antacids & H2RA do not affect UBT/SA testing)**
- Antibiotics, bismuth stopped for 4 weeks
- Bleeding stopped for 4-8 weeks

Crowe SE, UpToDate (2018)
Crowe SE, NEJM 380:1158-65 (2019)

Initial Diagnosis of *H. pylori* with Dyspepsia

- Stool antigen test (SAT)
- Urea Breath Test (UBT)
  - 'Test and Treat' in younger population (< 60 yo)
- Endoscopy mandatory if ≥60 years old or 'alarm symptoms or signs':
  - Unexplained iron-def anemia
  - GI bleeding
  - Unintentional weight Loss
  - Palpable mass
  - Severe abdominal pain
  - Persistent vomiting
  - Progressive dysphagia / odynophagia

Crowe SE, UpToDate (2018)
Crowe SE, NEJM 380:1158-65 (2019)

Question #4

- Which of the following is the most appropriate next step for evaluating a 29 year old previously healthy but overweight male patient with typical retrosternal heartburn symptoms?
  - A. Stool antigen test for *H. pylori*
  - B. Urea breath test for *H. pylori*
  - C. No testing for *H. pylori*
  - D. Serological testing for *H. pylori*
  - E. Empiric therapy for *H. pylori* regardless of testing

Explanation for Q#4

- *H. pylori* is not implicated as an etiological factor in gastroesophageal reflux disease
- Treatment for (eradication of *H. pylori*) can increase the risk for Barrett's esophagus and esophageal adenocarcinoma
- Serology is not a recommended test for *H. pylori* anymore

Reference: Siddique O, *et al. AJM* 2018

Question #5

A 23 yo Eastern European woman presents with persistent epigastric discomfort diagnosed as Hp+ gastritis by endoscopy. Fecal Hp antigen is also positive. As a child, she was treated repeatedly with PCN/amoxicillin for recurrent tonsillitis.

What do you recommend for therapy?

A. Clarithromycin + amoxicillin + PPI
B. Metronidazole + erythromycin + PPI
C. Bismuth subsalicylate + TCN + metronidazole + PPI
D. Metronidazole + amoxicillin + PPI
E. PPI therapy alone given her age

Question #6

After treatment of this patient for Hp gastritis, the *H. pylori* stool antigen test should be repeated:

A. On the final day of *H. pylori* therapy
B. Two weeks after completion of *H. pylori* therapy
C. Eight weeks after completion of *H. pylori* therapy
D. The test should not be repeated to assess cure

Questions #5 & 6: Explanation

- Clarithromycin resistance in Hp is really common in Eastern Europe
- Repeated exposure to amoxicillin could increase risk for resistant Hp
- Note, tetracycline is better than doxycycline
- Test of cure should be done at least 4 weeks after therapy is completed

Crowe SE, NEJM 380:1158-65 (2019)

Who should be treated for *H. pylori* infection?

Houston Consensus Conference on Testing for *Helicobacter pylori* Infection in the United States

Hashem B. El-Serag,[*,‡] John Y. Kao,[§] Fasiha Kanwal,[*,†,‖] Mark Gilger,[¶,#] Frank LoVecchio,[**] Steven F. Moss,[††] Sheila Crowe,[§§] Adam Elfant,[‖‖] Thomas Haas,[¶¶] Ronald J. Hapke,[##] and David Y. Graham[*,‡]

- "We recommend that all patients with active *H pylori* infection be treated"
- "Infection causes chronic progressive damage to the gastric mucosa that in 20%–25% of individuals will result in life-threatening clinical outcomes such as peptic ulcer or gastric cancer"

El-Sarag HB, *et al. Clin Gastroenterol Hepatol 2018;16:992–1002*

Who should be **tested & treated** for *H. pylori* infection?

Established Indications

- PUD (active/prior hx)
- MALT lymphoma
- Atrophic gastritis
- After gastric CA resection
- 1st degree relative w/ gastric Ca

Consider

- Non-ulcer dyspepsia*
- Use of NSAIDs/ASA
- Long-term PPI use
- Fe deficiency anemia (unexplained)
- ITP (low evidence base)
- Live in high gastric Ca region
- Asymptomatic infection**

*estimate ~10% respond
Goal: eradicate **prior to atrophy or metaplasia. Treatment reverses atrophy but not metaplasia.

Crowe SE, NEJM 380:1158-65 (2019)
Chey W, Am J Gastroenterol;114:1829–1832 (2019)

Principles of Hp Therapy

Goal: To use a regimen with >90% therapeutic success.

1. Ask about abx exposure hx (clarithromycin/metronidazole/fluoroquinolones)
2. Discuss adherence
3. Use high dose PPI (BID dose; increase gastric pH>4-5)
4. Longer (**14 days**) rather than shorter treatment courses
5. Combination drug therapy
6. Consider abx resistance patterns & testing*

Outcome is determined by Hp antibiotic sensitivity, drug dosing, treatment duration & treatment compliance. Smoking inhibits therapeutic responses.

*clarithromycin, metronidazole, levofloxacin

Fallone CA, *et al. Gastroenterology.* 2016 Jul;151(1):51-69.e14

Table 2. Evidence-based Treatment Regimens for *H. pylori* Infection in North America, Listed in Recommended Order.*

Treatment Type	Components	Duration	Comments†
		days	
Clarithromycin-based triple therapy‡	PPI, clarithromycin, and amoxicillin (twice daily for all antibiotics)	14	Recommended unless patient has documented allergy to ampicillin or high level of clarithromycin resistance
Bismuth-based quadruple therapy (Pylera‡)	PPI, bismuth, tetracycline, and nitroimidazole (four times daily for all antibiotics)	10–14	Recommended if patient has high level of clarithromycin resistance or history of macrolide use
Concomitant therapy	PPI, clarithromycin, amoxicillin, and nitroimidazole (twice daily for all antibiotics)	10–14	Not appropriate in patient with high level of clarithromycin resistance or documented allergy to ampicillin
Sequential therapy	PPI and amoxicillin; then PPI, clarithromycin, and nitroimidazole (twice daily for all antibiotics)	7, then 7	Not appropriate in patient with high level of clarithromycin resistance or documented allergy to ampicillin
Hybrid therapy	PPI and amoxicillin; then PPI, amoxicillin, clarithromycin, and nitroimidazole (twice daily for all antibiotics)	7, then 7	Not appropriate in patient with high level of clarithromycin resistance or documented allergy to ampicillin
Levofloxacin-based triple therapy	PPI, levofloxacin (once daily), and amoxicillin (twice daily)	10–14	Not appropriate in patient with documented allergy to ampicillin
Fluoroquinolone-based sequential therapy	PPI and amoxicillin; then PPI, levofloxacin, and nitroimidazole (twice daily for all antibiotics)	5–7, then 5–7	Complicated with regard to treatment adherence; not appropriate in patient with documented allergy to ampicillin

Evidence-based Treatment Regimens for *H. pylori* Infection in North America Listed in Recommended Order

Crowe SE, NEJM 380:1158-65 (2019)
Chey W, Am J Gastroenterol;114:1829–1832 (2019)

H. pylori & Antimicrobial Resistance

Amoxicillin	Low (<5-10%)
Tetracycline	Low (<5-10%)
Clarithromycin	High (10-50%)
Metronidazole	High (10-80%)*
Levofloxacin	High? (5-30%)

Ask about history: clarithromycin, quinolones & metronidazole
Rates of resistance show substantial geographic differences.
Prior, even distant, Abx hx can inform likelihood of Hp Abx resistance.
*Nitroimidazole resistance may be overcome by increased dosing (≥1500 mg/day).
NOTE: Rx with amoxicillin & tetracycline yields low response rates.

Aliment Pharmacol Ther 43:514, 2016
Maastricht V. Gut 66:6, 2017
Kasahun GG, Infect Drug Resist 13:1567-1573, 2020

Management Issue:
Test of cure for *H. pylori* Infection

- Stool antigen test Perform ≥ 4 weeks post-rx*
- Urea Breath Test Perform ≥ 4 weeks post-rx.

Some recommend testing 6-8 wks post-rx.

Endoscopy required if gastric ulcer, for example.

*FDA-approved

Maastricht V. Gut 66:6, 2017

KEY TAKE AWAYS

DIAGNOSIS:

- In most: Stool Hp antigen test, UBT
- If ≥60 years old or alarm symptoms / signs then endoscopy is mandatory

KEY TAKE AWAYS

TREATMENT:

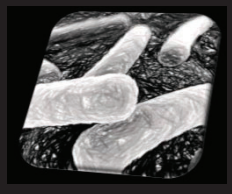
- Triple or Quadruple therapy
- Increasing emphasis on antibiotic resistance testing
  - Fecal or biopsy genotypic testing for clarithromycin
  - MIC testing for clarithromycin, nitroimidazole, FQ resistance

KEY TAKE AWAYS

FOLLOW UP:

- TOC mandatory (stool Hp antigen test, UBT)
- At least 4 weeks after completion of therapy

CLOSTRIDIOIDES DIFFICILE

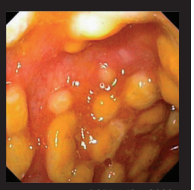


C. DIFFICILE INFECTION (CDI)

Most common health care-associated infection, USA
Leading cause of gastroenteritis death, USA

Ooijevaar RE, *et al. Clin Micro Infect.* 2018; 24(5):452-462

McDonald C, *et al. Clin Infect Dis.* 2018;66(7):987-994



Lancet 371:1486, 2008

56 – Helicobacter and Clostridium Difficile

Speaker: David Aronoff, MD

Antibiotic-associated Diarrhea (AAD)

- Common
  - In 5-25% of antibiotic treatment courses especially with > 3 days of Abx but one dose is sufficient
- 10-40% of AAD is associated with *C. difficile* infection (CDI) but nearly all AA **colitis** is CDI
- Disruption of colon microbiome & bile acid physiology are key mechanisms

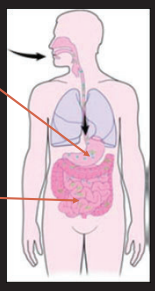
Pathogenesis of CDI

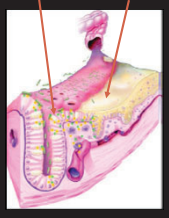
1. **CDI spores** survive in the environment for long periods of time. Following ingestion, they traverse the acidic environment of the stomach.

2. Spores germinate within the intestine.

3. Altered lower intestine flora (due to antimicrobial use) allows proliferation of *C. difficile* in colon.

4. Toxin A & B Production leads to colon damage +/- pseudomembrane.

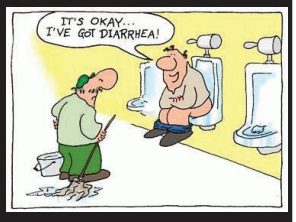




Slide adapted from CDC.gov. Sunenshine & McDonald Cleve Clin J Med 2006; 73(2):187-197.

Common Clinical Manifestations

- Watery & mucusy diarrhea up to 10 - 15 times daily
- Lower abdominal pain & cramping
- Low grade fever (15%+)
- Leukocytosis (around 15,000 cells/μl)
- Nausea
- Anorexia
- Malaise

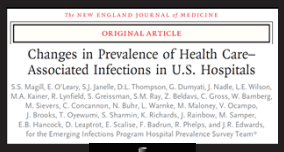


Complications of CDI

- Sepsis ± multiple organ dysfunction
- Megacolon: need for surgical intervention
  - Colectomy
  - Loop ileostomy
- Bowel Perforation
- Lack of treatment response
- Recurrent infection (20%+)
  - Relapse
  - Reinfection

Epidemiology of CDI

2015



Top Causative Pathogens	% of HAI	Rank
C. difficile	15	1
S. aureus	11	2
E. coli	10	3
Candida spp.	6	4
Enterococcus spp	5	5
Enterobacter spp.	5	6
P. aeruginosa	5	7
K. pneumo/oxytoca	5	8
Streptococcus	5	9

Magill S, *et al. NEJM* 2018;379:1732-44.
Photo from http://www.mckeeassociates.com/blog/2015/07/healthcare-associated-infections-plague-12-

Major Risk Factors for Acquisition of CDI

1. **Antibiotic use**
   - Disruption of microbiome
2. **Recent hospitalization or LTCF**
   - Increased exposure
   - Co-morbidities reduce immunity or alter microbiome
3. **Age > 65 years**
   - Reduced gastric acidity
   - Impaired immunity
   - Altered microbiome

REMEMBER:
Even healthy people in the community without antibiotic exposure can get CDI

Dubberke E, *et al. Infect Control Hosp Epidemiol* 2011;32(4):360-366
Pacheco & Johnson. *Curr Opin Gastroenterol* 2013, 29:42-48
Loo V, *et al. NEJM.* 365;18

Minor Risk Factors for Acquisition of CDI

4. Gastric acid suppression (**proton pump inhibitor**)
   - Reduced biochemical defense
   - Altered microbiome
5. Abdominal surgeries
   - Altered microbiome
6. Immunocompromised host
   - Impaired mucosal immunity
   - Altered microbiome

McFarland LV. *Curr Opin Gastroenterol.* 2009 Jan;25(1):24-35
Dubberke E, *et al. Infect Control Hosp Epidemiol* 2011;32(4):360-366
Pacheco & Johnson. *Curr Opin Gastroenterol* 2013, 29:42-48

CDI Severity

- **Leukocytosis**
- **AKI**
- **Sepsis/shock**
- **Megacolon**

Stool frequency is not part of severity assessment

Clinical Definition	Supportive Clinical Data
Nonsevere	Leukocytosis with a WBC count of ≤15,000 cells/mL and a serum creatinine level <1.5 mg/dL
Severe	Leukocytosis with a WBC count of ≥15,000 cells/mL or a serum creatinine level >1.5 mg/dL
Fulminant	Hypotension or shock, ileus, megacolon

Table from Wilcox M. *IDSE* (2018)
McDonald LC, *et al. Clin Infect Dis.* 2018 Mar 19;66(7):987-994

C. difficile Diagnostic Testing

Whom to test?

Appropriate epidemiology/ill with diarrhea/endoscopic findings

No laxatives within last 48 hrs

Test diarrheal stools (unless ileus). *One stool.*

>3 liquid stools over 24h

Only test specimens if patient > 1 year old

McDonald LC, *et al. Clin Infect Dis.* 2018 Mar 19;66(7):987-994

C. difficile Diagnostic Testing

Simplified approach:

Diarrhea* + **Toxigenic *C. difficile* &/or toxin in stool** → **TREAT**

***No laxatives or other obvious causes**

C. difficile Diagnostic Testing

Nucleic acid amplification test (NAAT; PCR):

Detects the gene for toxin B

Advantages
- **High sensitivity**
- **Rapid**
- **Relatively inexpensive**

Disadvantages
- **Does not detect actual toxin**
- **Cannot differentiate colonization from infection**

Patient selection is critical

C. difficile Diagnostic Testing

Glutamate dehydrogenase (GDH) antigen EIA:

Detects *C. difficile* bacteria by secreted antigen

Advantages
- **High sensitivity**
- **Rapid**
- **Relatively inexpensive**

Disadvantages
- **Does not detect toxin**
- **Detects NON-toxigenic strains**
- **Cannot differentiate colonization from infection**

Must be combined to test for toxin (NAAT or EIA)

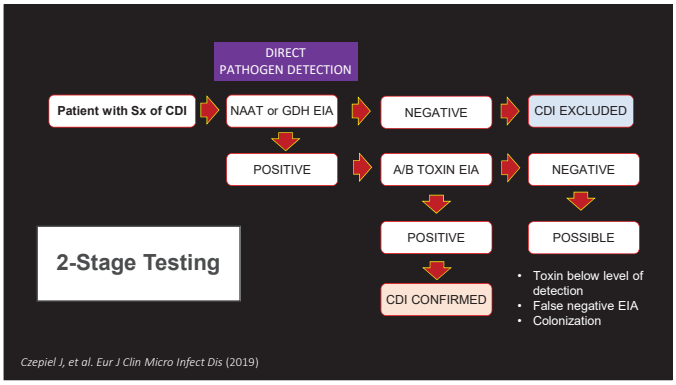
C. difficile Diagnostic Testing

Toxin A/B detection by EIA:

Detects *C. difficile* toxin(s) directly

Advantages	Disadvantages
• Good specificity • Rapid • Relatively inexpensive	• Poor sensitivity • False positives possible

Usually used in a 2-step protocol with NAAT or GDH



Czepiel J, et al. Eur J Clin Micro Infect Dis (2019)

CDI TAKE AWAYS

Careful selection of patients for testing, especially with NAATs, is extremely important

Only patients with diarrhea (≥3 stools in ≤24 hrs)

NO formed or soft stools (unless ileus)

NO 'Test of Cure'

Question #7

- 67 year old woman develops diarrhea while hospitalized for community acquired pneumonia. She is afebrile, her WBC count is 12,000/μl, creatinine is 1.2 mg/dl (baseline 1.0 mg/dl) and she is experiencing 12 small loose stools daily with abdominal cramping. Stool PCR is positive for *C. difficile* toxin B. Which of the following therapies is recommended?
  - Metronidazole 500 mg po TID x 10 days
  - Vancomycin 500 mg PO qid x 10 days
  - Vancomycin 125 mg PO qid x 10 days
  - Bezlotoxumab + vancomycin x 10 days
  - Fidaxomicin 200 mg PO BID + metronidazole 500 mg PO TID x 10 days

Therapy of CDI

- D/C antibiotics/change to 'lower risk abx'
- No antiperistaltics
- This is a time of transition for treatment guidelines
- Recurrent CDI occurs in **≥1 in 5** patients

McDonald LC, *et al. Clin Infect Dis.* 2018 Mar 19;66(7):987-994

Therapy of CDI

Table 1. Recommendations for the Treatment of *Clostridium difficile* Infection in Adults

Clinical Definition	Supportive Clinical Data	
Initial episode, non-severe	Leukocytosis with a white blood cell count of ≤15 000 cells/mL and a serum creatinine level <1.5 mg/dL	
Initial episode, severe[b]	Leukocytosis with a white blood cell count of ≥15 000 cells/mL or a serum creatinine level >1.5 mg/dL	
Initial episode, fulminant	Hypotension or shock, ileus, megacolon	• VAN, 500 mg 4 times per day by mouth or by nasogastric tube. If ileus, consider adding rectal instillation of VAN. Intravenously administered metronidazole (500 mg every 8 hours) should be administered together with oral or rectal VAN, particularly if ileus is present.

VANCOMYCIN 125 mg po QID x 10 d
FIDAXOMICIN 200 mg po BID x 10 d

No more metronidazole

McDonald LC, *et al. Clin Infect Dis.* 2018 Mar 19;66(7):987-994

Recurrent CDI

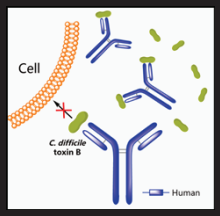
Table 1. Recommendations for the Treatment of *Clostridium difficile* Infection in Adults

Clinical Definition	Supportive Clinical Data	Recommended Treatment[a]
First recurrence	…	• VAN 125 mg given 4 times daily for 10 days if metronidazole was used for the initial episode, OR • Use a prolonged tapered and pulsed VAN regimen if a standard regimen was used for the initial episode (eg, 125 mg 4 times per day for 10–14 days, 2 times per day for a week, once per day for a week, and then every 2 or 3 days for 2–8 weeks), OR • FDX 200 mg given twice daily for 10 days if VAN was used for the initial episode
Second or subsequent recurrence	…	• VAN in a tapered and pulsed regimen, OR • VAN, 125 mg 4 times per day by mouth for 10 days followed by rifaximin 400 mg 3 times daily for 20 days, OR • FDX 200 mg given twice daily for 10 days, OR • Fecal microbiota transplantation[c]

McDonald LC, *et al. Clin Infect Dis.* 2018 Mar 19;66(7):987-994

Recurrent CDI

- Bezlotoxumab, a monoclonal antibody directed against toxin B produced by C. difficile, has been approved as adjunctive therapy for patients who are receiving antibiotic treatment for CDI & who are at high risk for recurrence



McDonald LC, *et al. Clin Infect Dis.* 2018 Mar 19;66(7):987-994
Figure from http://en.pharmacodia.com/web/drug/1_9806.html

Prevention of C. *difficile* Disease (HCW & visitors)

Contact precautions for patient care.
Gloves, gowns while diarrhea persists.
Single rooms
Handwashing with SOAP & WATER
Alcohol gel rubs do not kill *Cd* spores
Sporocidal solutions for hospital cleaning.
(eg. hypochlorite solutions)
Antibiotic restriction policies
(Antimicrobial stewardship programs).

Lancet ID 17:194, 2017 Scotland
Lancet ID 17:411, 2017 England

CDI **TAKE AWAYS**

Epidemiology
- Most CDI is health-care associated

Diagnosis
- Need to demonstrate toxin B in stool with NAATs, EIA
- Send only unformed stools when diarrhea meets CDC definition

Treatment: Primary or Recurrent CDI
- Vancomycin & fidaxomicin > Metronidazole
- Bezlotoxumab & fidaxomicin associated with lower risk for recurrent CDI
- Consider FMT for second or more recurrence

Prevention
- Hand wash as alcohol gels ineffective
- Bleach
- Antimicrobial Stewardship Programs

Thank you
D.aronoff@vanderbilt.edu
@DMAronoff

57

Fungal Disease in Normal and Abnormal Hosts

Dr. John Bennett

57 - Fungal Disease in Normal and Immunosuppressed Hosts

Speaker: John Bennett, MD

2020 INFECTIOUS DISEASE BOARD REVIEW

Fungal Disease in Normal and Immunosuppressed Hosts

John E. Bennett, MD
Bethesda, MD

Disclosures of Financial Relationships with Relevant Commercial Interests

- None

Plan for the talk

- Endemic mycoses (dimorphic)
- Molds (hyphae): aspergillosis, mucormycosis, fusariosis
- Yeasts (round budding cells:
  - malassezia, cryptococcosis, candidiasis
- Questions

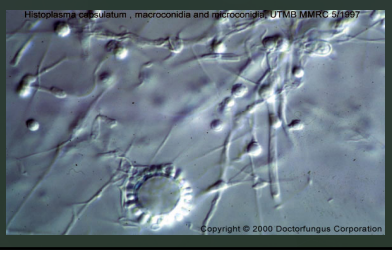
What is an endemic fungus

- Grows in certain environments as a mould and infects humans who inhale spores
- USA
  - Histoplasmosis
  - Coccidioidomycosis
  - Blastomycosis
- Overseas
  - Talaromycosis marneffei (Penicilliosis marneffei)
  - Paracoccidioidomycosis (South American blastomycosis)

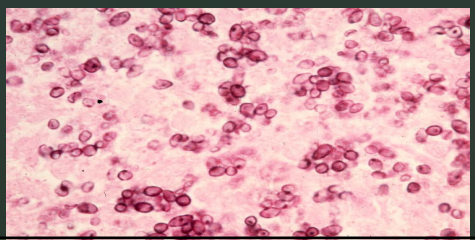
All the endemic mycoses are caused by dimorphic fungi

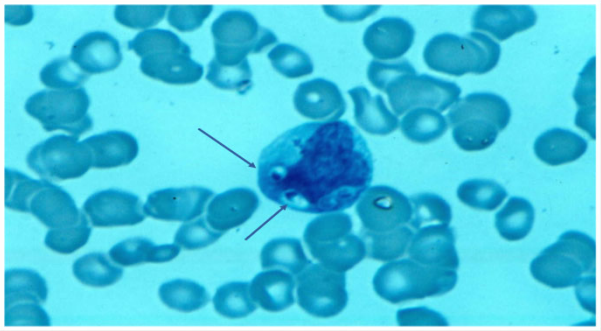
- What's a dimorphic fungus?
- Mould in nature and in room temp culture
- Rounded form in infected tissue

Histoplasma capsulatum room temperature

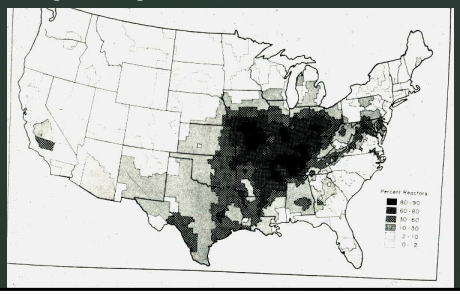


HISTOPLASMA CAPSULATUM
in tissue, GMS (silver) stain



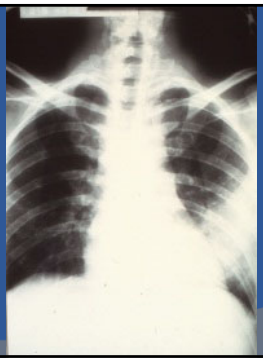


Histoplasma capsulatum endemic area in USA



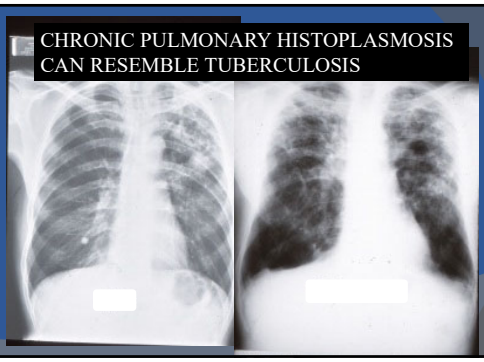
Pulmonary Histoplasmosis

- **Acute pneumonia** 2 wks after exposure to dust from rich earth (digging, raking) or bat guano (caving). Antibody or antigen test. Self-resolving.
- Difficult to culture from sputum.
- Lung nodule may persist



ACUTE PULMONARY HISTOPLASMOSIS RESEMBLES COMMUNITY ACQUIRED PNEUMONIA

CHRONIC PULMONARY HISTOPLASMOSIS CAN RESEMBLE TUBERCULOSIS



57 - Fungal Disease in Normal and Immunosuppressed Hosts

Speaker: John Bennett, MD

Disseminated histoplasmosis

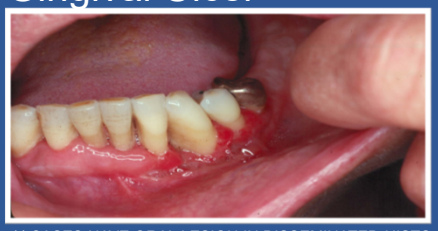
- Immunosuppression, including TNF blockers, AIDS, solid organ transplant
  - subacute fever, pancytopenia, hypoadrenalism, miliary lung lesions, mucosal lesions
  - yeast-like cells in tissue, mold on culture
  - urine antigen test usually positive

Uncommon manifestations

-endocarditis, chronic meningitis

Rx: ampho B followed by itraconazole

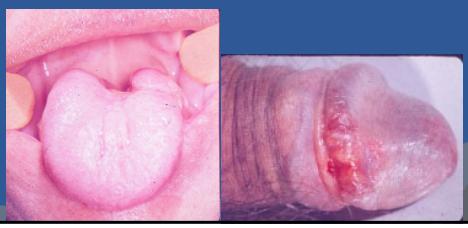
Gingival Ulcer



¼ CASES HAVE ORAL LESION IN DISSEMINATED HISTO

TONGUE AND PENILE LESIONS

MUCOSAL LESIONS CAN RESEMBLE SQUAMOUS CARCINOMA

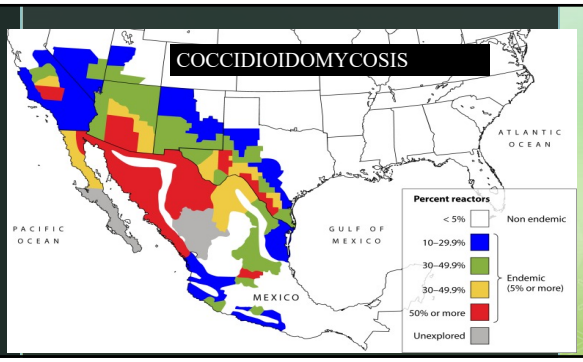


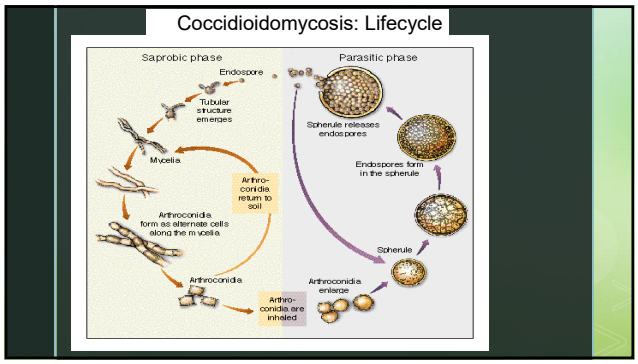
HISTOPLASMOSIS ENDOCARDITIS OF EXCISED AORTIC VALVE LEAFLETS. CULTURE "NEGATIVE" ENDOCARDITIS

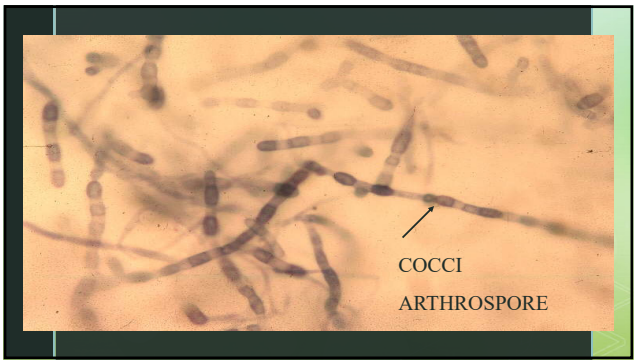
Coccidioidomycosis=Valley Fever

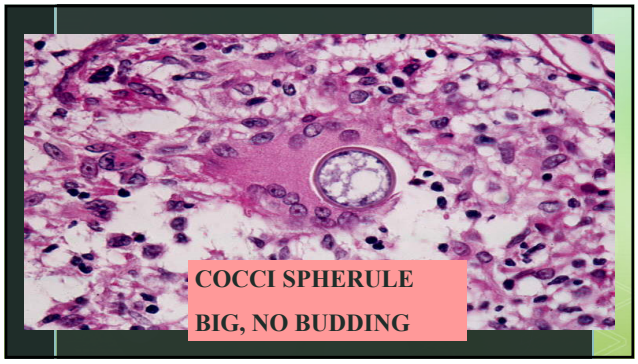
- Two species, one disease:
  - C. immitis and C. posadasii. Both serious lab hazards
- . Acute pneumonia 2 wks after inhalation: arthralgias or erythema nodosum may accompany. Resolves.
- Residual nodule or thin walled cavity may persist
- Dissemination: bone, skin, chronic meningitis
- Serum and CSF serology useful. Eosinophilia in CSF.
- Rx: fluconazole. Nonmeningeal: itraconazole

COCCIDIOIDOMYCOSIS



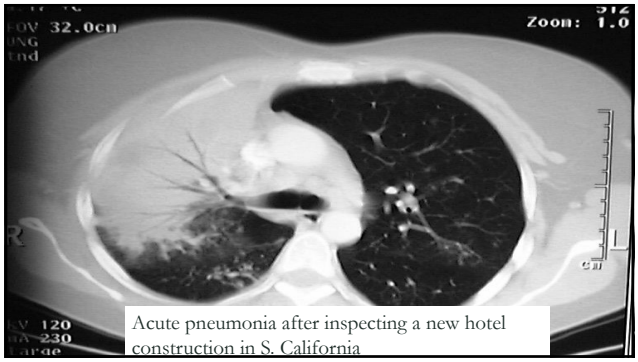


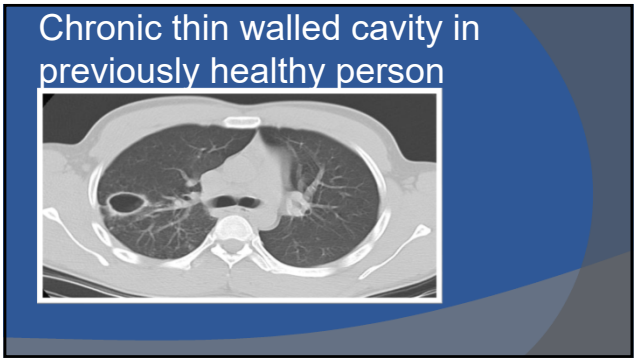




Ethnic differences. Kern county 1937 disseminated coccidioidomycosis

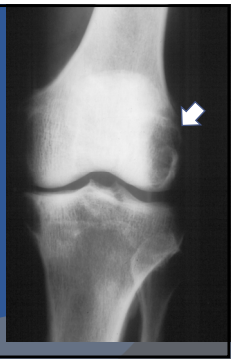
Race	cases/100,000	case ratio
Caucasian	82	1.0
Mexican	284	5.4
African American	1,122	13.7
Filipino	14,550	17.5





COCCIDIOIDES DISSEMINATES TO BONE, CNS, SKIN

NOTABLE FEATURES:
-CHRONICITY
-PUS
-EOSINOPHILIA (low grade)
-SLOW RESPONSE TO FLUCONAZOLE OR ITRACONAZOLE-



BLASTOMYCOSIS

BLASTOMYCES DERMATITIDIS, B. GILCHRISTII
MOLD IN NATURE, BROAD-BASED BUDDING IN TISSUE

MOIST EARTH NEAR RIVER, BEAVER DAMS.

NORMAL HOST

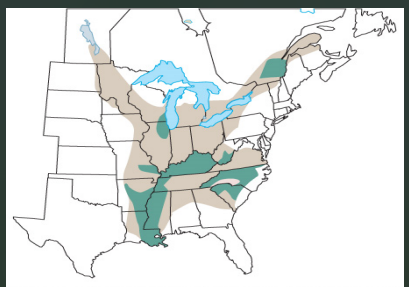
ACUTE PNEUMONIA MAY SELF HEAL

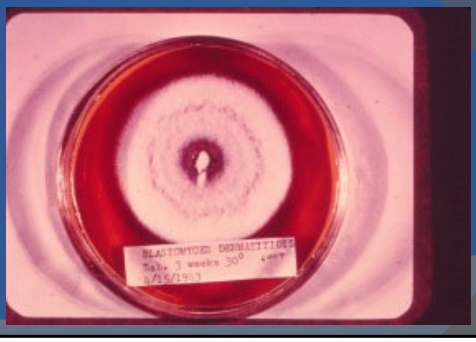
INDOLENT, PROGRESSIVE PNEUMONIA
DISSEMINATES TO SKIN, BONE, MALE GU TRACT

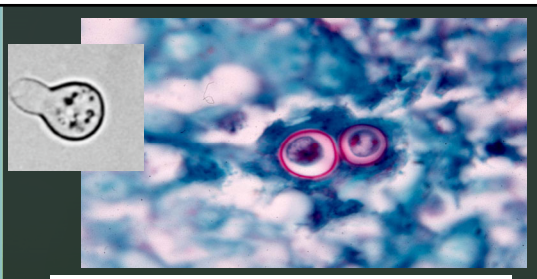
DX. CULTURE OR SKIN BIOPSY

RX: ITRACONAZOLE

Blastomycosis endemic area in USA

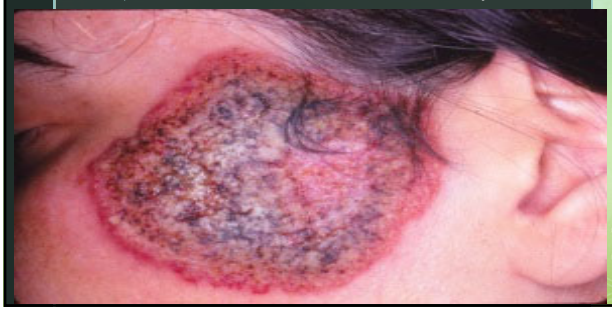


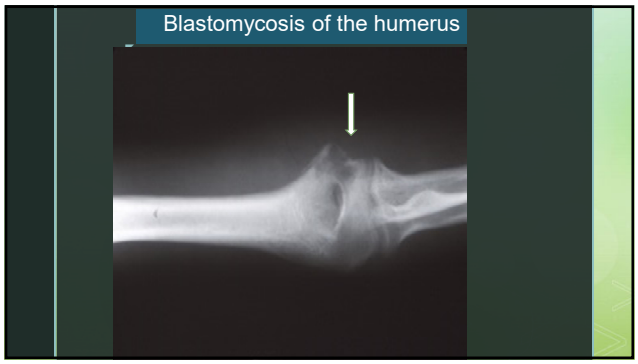


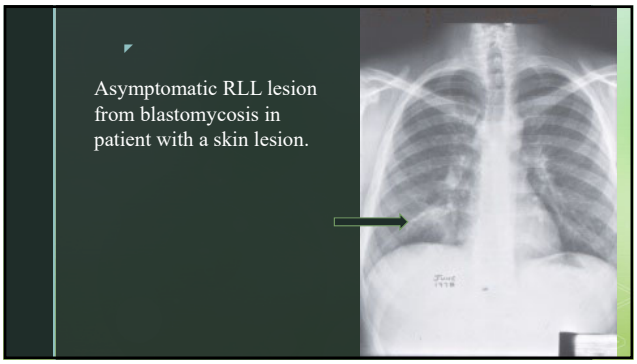


THICK WALLED BUDDING CELLS OF *BLASTOMYCES DERMATITIDIS*

Well demarcated skin lesion with crust: blastomycosis







Treatment of blastomycosis

- Amphotericin if severe
- Itraconazole 200 mg bid 6-12 months
- Fluconazole less effective
- Posaconazole: perhaps?

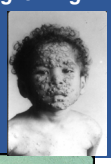
Paracoccidioides brasiliensis

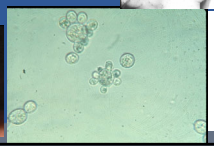
Multiply budding yeast, slow growing mold.

-Acute or subacute infection in children with fever, wt loss, lymphadenopathy, hepatosplenomegaly and often lesions in skin and mucosal membranes

-Indolent infection, largely men over 30 yrs old working on farms in Latin America, presenting as lesions of the mucous membranes and skin. Asymptomatic infiltrates on chest xray. Can be latent for decades in adults

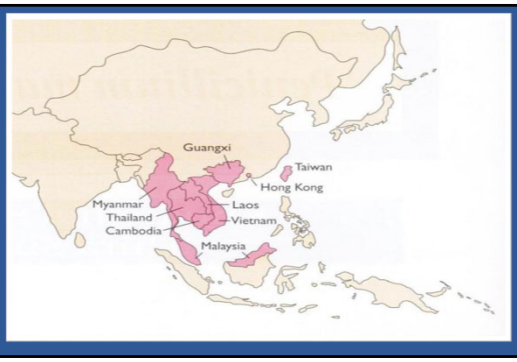
-Serodiagnosis in endemic areas. Biopsy.

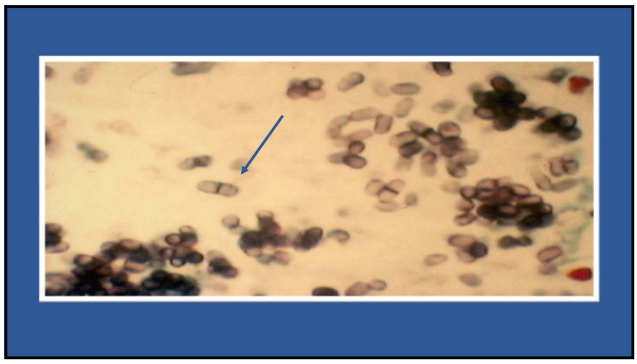


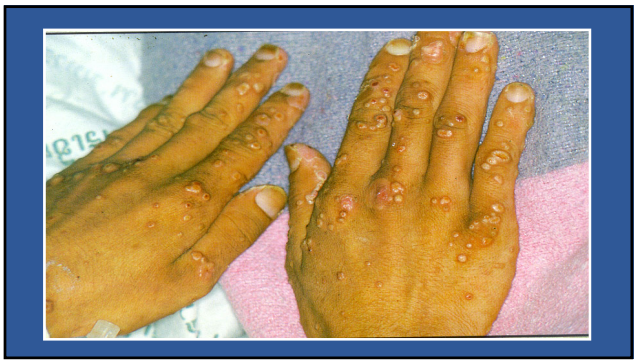



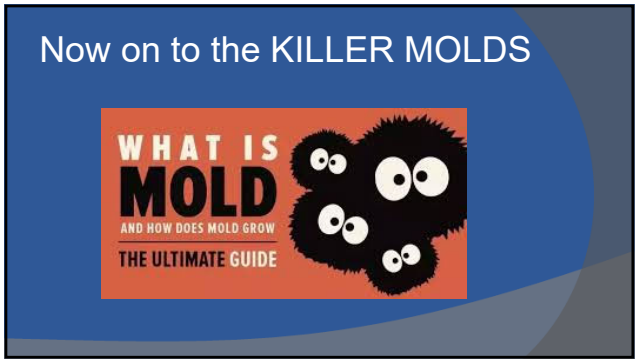

TALAROMYCOSIS

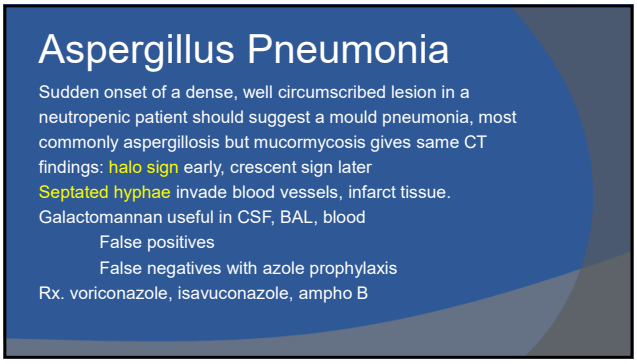
- Talaromyces marneffei
  - yeast in tissue, mold in culture
  - divides by binary fission, no budding
- Thailand, South China
- Bamboo rats
- AIDS, normal children
- Skin lesions, lymph nodes, liver, spleen, bone
- Diagnosis: Methenamine silver stain of skin or other tissue. Blood culture
- Treatment: ampho B then itraconazole.

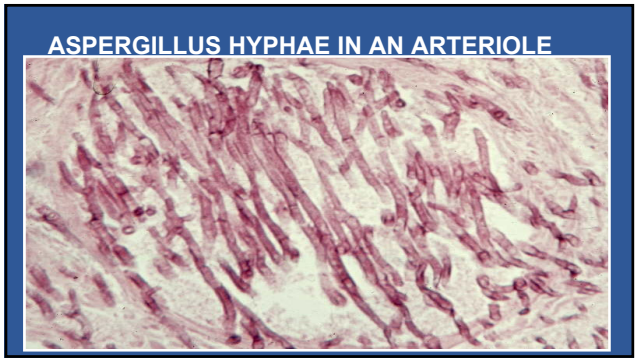


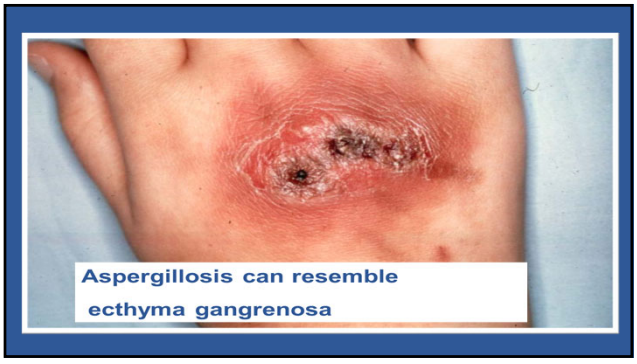


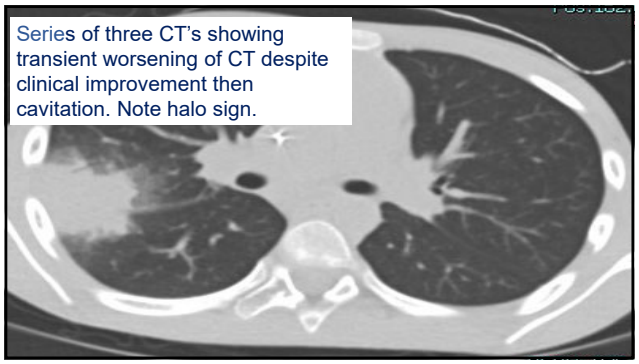


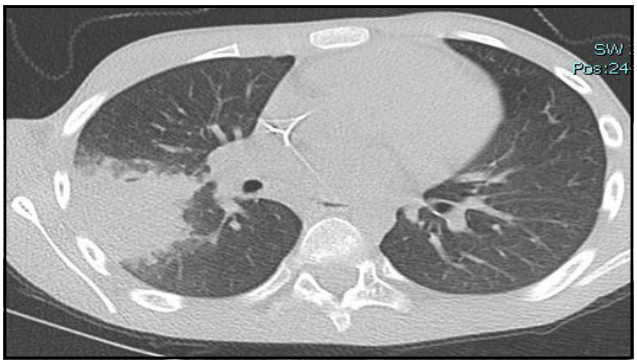


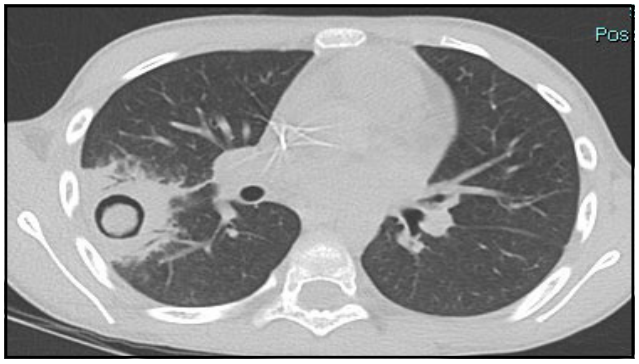






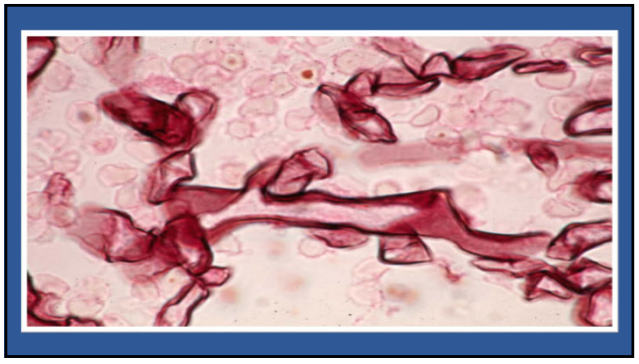






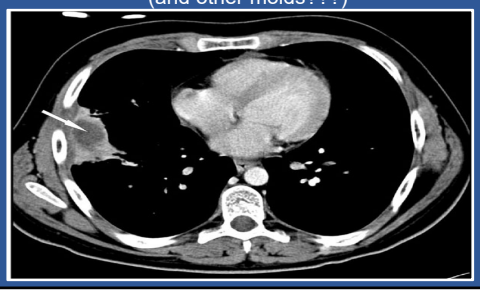
MUCORMYCOSIS

- Infection acquired by inhaling spores into lung or paranasal sinus
- Rhizopus, Rhizomucor, Mucor, Cunninghamella, Apophysomyces, Saksenaea
- Broad, flexible nonseptate hyphae, right angle branching
- Prolonged neutropenia, desferoxamine, steroids,
- Poorly controlled diabetes mellitus
- Hyphae invade blood vessels, causes infarction and necrosis. May form cavity if PMN's return.
- Rx. Ampho B. Posaconazole f/u. Isavuconazole???



Mucormycosis mimics cavernous sinus thrombosis following sinusitis

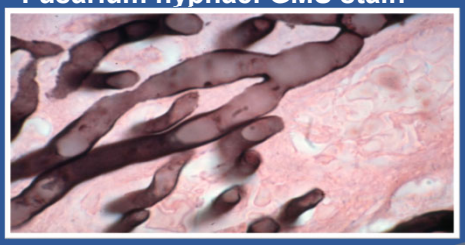
Reverse halo (Hypodense sign) in mucormycosis (and other molds???)

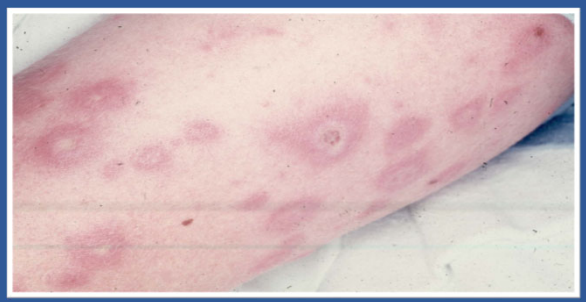


Fusariosis

Severely immunocompromised patients
Mold, looks like Aspergillus in tissue
Red, tender skin nodules
Blood culture grows mold in a third to half the patients
RX: response poor in severe neutropenia
PMN transfusions?
Fusarium solani: ampho?
Other Fusarium species : Voriconazole?

Fusarium hyphae. GMS stain





Scedosporiosis

- *Sc. apiospermum (Pseudallescheria)*: hyphae and clinical disease resemble Aspergillus. Immunosuppression. Near drowning. Ampho resistant. Voriconazole.
- *Lomentosporium prolificans (Scedosporium prolificans)*. Similar infection but resistant to all antifungals

Candidiasis: testable points

- Candidemia (IDSA guidelines):
  - remove IV catheter if possible
  - dilated fundoscopic exam in first week
  - Intravitreal drug if vitritis or macular lesion
  - Candida auris: hospital transmission. Azole resistant.

Cryptococcus neoformans or Cryptococcus *gattii*

- *C. gattii* more likely to be lung, non HIV patient, S.California, Vancouver Island, overseas
- Start ARV after 2-10 wks of antifungal Rx in HIV naïve patients.
- Daily lumbar punctures for pts with opening pressure of
- at least 25cm and symptoms
- Antigen in serum, CSF : specific. Sensitivity variable.
- Screening for antigenemia in HIV: Africa. Fluconazole if CSF neg.

IRIS in Cryptococcosis

- Weeks or months after ARV and antifungal Rx for meningitis:
- Fever, headache, high opening pressure, seizures, cranial nerve palsies, new MRI lesions
- Key: all cultures negative.
- Dry cough, substernal pain
- Swollen nodes in mediastinum, hilum
- Rx: NSAIDS or prednisone

Beta-D glucan test

- Blood test positive in many mycoses (usually not cryptococcosis or mucormycosis)
- Many sources of false positivity
- *Pneumocystis jirovecii* also positive
- BAL beta-D glucan: sensitive for PCP but very variable

BUT FIRST 10 questions to test your knowledge

Case 1

42 yr WF with Crohn's disease taking adalimumab is admitted to a Chicago hospital because of 6 weeks of low grade fever, pancytopenia and a 10 pound weight loss. Hydrocortisone 200 mg daily was begun for low serum cortisol not responding to Cortrosyn stimulation. Micafungin was given for yeasts seen in peripheral blood smear that were not growing on routine culture.

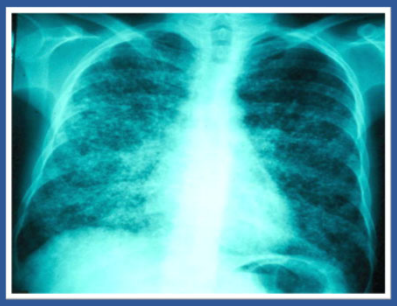
Question #1

The most helpful diagnostic test would be which of the following:

A. Fungal blood culture
B. CT of abdomen
C. PPD
D. Bone marrow aspirate
E. Urine for Histoplasma antigen

Case 2

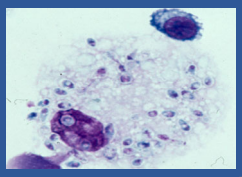
- 30 yo male business man from India presented with fever and dypnea while visiting Washington, DC
- Found to be HIV positive, with CD4 of 50.
- Diffuse infiltrate on chest xray, O2 sat of 65%, given trimethoprim-sulfa and prednisone. Failed to improve and went for BAL.



Question #2: BAL smear

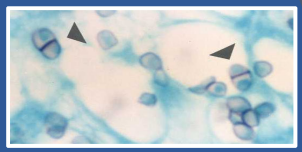
This organism usually resides in which of the following:

A. Sandflies
B. Desert dust
C. Rich, moist soil
D. Cat feces
E. Kissing bugs



Case #3

A 45 yr old Vietnamese business man came to the US to seek medical attention for an illness of 4 weeks duration, with low grade fever, weight loss, anorexia and the recent appearance of painless skin lesions. Biopsy of the skin lesions show is shown to the right.



Question #3

Which of the following is most likely:

A. Talaromyces marneffei
B. Histoplasma duboisii
C. Fusarium oxysporum
D. Cryptococcus gattii
E. Paracoccidioides brasiliensis

Case 4

35 yr male 68 days post allogeneic bone marrow transplantation for myelodysplastic syndrome, receiving methylprednisolone 500 mg for Grade III GVHD of the gastrointestinal tract developed fever, several painful, red skin nodules and a blood culture growing a mold.

Question #4

The most likely fungus is which of the following:

A. Scedosporium apiospermum (Pseudallescheria boydii)
B. Scedosporium (Lomentospora) prolificans
C. Apophysomyces elegans
D. Fusarium multiforme
E. Alternaria alternata

Question #5

44 yr previously healthy male accountant in Washington DC presented with the acute onset of confusion that was preceded by three months of headache. Cranial MRI was normal. Lumbar CSf had an opening pressure of 350mm CSF, WBC 250/cu mm, glucose 22 mg /dl, protein 125 mg/dl and cryptococcal antigen titer 1:512. Liposomal amphotericin B was begun at 5.0 mg/kg IV daily. On the third day of treatment he complained that the room was too dark and was found to have visual acuity of hand motion only in both eyes.

Question #5

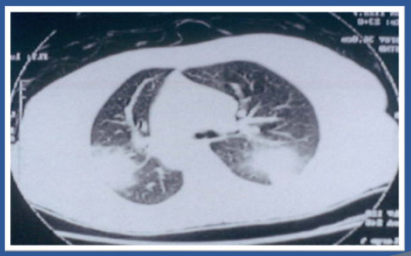
The most important next step in this patient is which of the following:

A. start flucytosine
B. start fluconazole
C. Start acetazolamide (Diamox)
D. Begin daily lumbar punctures
E. Start dexamethasone

Case 6

39 yr old man with severe aplastic anemia and absolute neutrophil count of 25/cu mm developed the sudden onset of fever and pulmonary infiltrates not responding to five days of ceftazidime. The CT is shown in the next slide.

Case # 6 Continued



Question #6

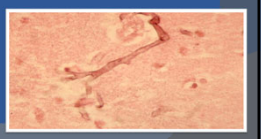
The most likely cause of his fever is which of following:

A. Mulch in his garden
B. Spray from the air conditioner water tower
C. Pigeon droppings near the air conditioner inlet
D. Visitor with a cough
E. Reactivation of a prior infection

Question #7

The fungus shown is best treated with a drug that has which of the following mechanisms of action

A. binds to membrane sterols
B. Inhibits sterol 14-alpha demethylase
C. Inhibits glucan synthesis
D. Blocks DNA synthesis
E. Inhibits squalene epoxidase



Case #8

- 47 WM executive referred from Baltimore because of severe headaches, diplopia, high fever of 1 wk's duration
- 4 wks PTA: Maui resort one week
- 3 wks PTA: ranch outside Tucson 1 wk
- 2 wks PTA: back at work in Baltimore
- 1 wk: PTA: Headache began
- Exam: Temp 38.5 C. Looks ill. Photophobia, nuchal rigidity, right CN6 palsy
- CBC, Chem 7 normal. CSF : Glucose 55, Protein 58, WBC 330 (20% eos). Negative cryptococcal antigen on CSF, serum Lyme serology and RPR. MRI with contrast normal. Worsens during 2 wks ceftriaxone. CSF cultures for bacteria, fungi, tbc neg to date.

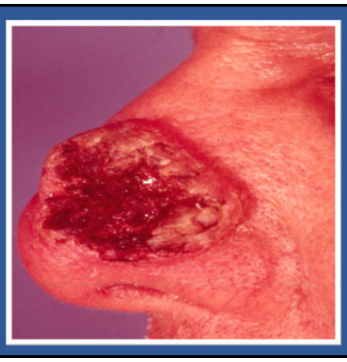
Question #8

The most helpful diagnostic test would be:

A. CSF cytology
B. Stool O&P
C. Dietary history
D. Fungal serology
E. Leptospirosis serology

Case #9

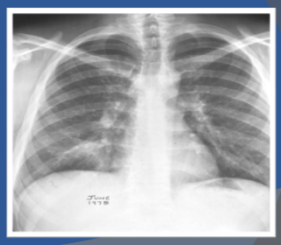
- 55 year construction engineer living in Raleigh, North Carolina, was sent to Iraq for one month of consultation. On return, he had the slow development of a painless, crusted lesion on his nose.
- He was not aware of any preceding lesion there but had numerous insect bites over exposed areas of his body while in Iraq.
- He was otherwise in good health and was an avid rose gardner.
- Routine lab work was normal but chest xray showed an asymptomatic infiltrate.



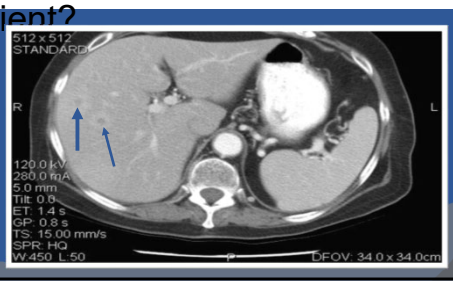
Question #9

The most likely source for the skin lesion and lung lesion is:

A. Camel's hair rug he bought in Iraq
B. Insect bite in Iraq
C. Inhalation of soil organism from North Carolina
D. Scratch from thorn in his garden
E. Insect bite in USA



Case 10: What are these lesions in a recently neutropenic patient?



Question #10

Which is the most likely

A. Bartonella henselae
B. Candida tropicalis
C. Fusarium oxysporum
D. Aspergillus flavus
E. Streptococcus anginosus

Take Home Points

- Histo: TNFα blockers. Miliary infiltrates. Addison's
- Talaromyces marneffei: SE Asia. Skin lesions. Septum in dividing cells
- Fusarium: skin nodules. Blood culture with mould
- Ecthyma gangrenosa: aspergillosis, mucor, bacteria

More take Home Points

- Aspergillosis: halo sign, crescent sign
- Mucormycosis : Can mimic cavernous sinus thrombosis. Aseptate. Ampho.
- Crypto: LP for high OP. IRIS.
- Cocci: solitary lung cavity. Eosinophilic meningitis
- Blasto: indolent skin+lung lesion
- Candida: liver, spleen lesions in neutropenics

The end.
Thanks

email
john_bennett@comcast.net

58

Tuberculosis in Immunocompetent and Immunosuppressed Hosts

Dr. Susan Dorman

58 - Tuberculosis in Normal and Compromised Hosts

Speaker: Susan Dorman, MD

2020 INFECTIOUS DISEASE BOARD REVIEW

Tuberculosis in Normal and Compromised Hosts

Susan E. Dorman, MD
Professor of Medicine
Medical University of South Carolina

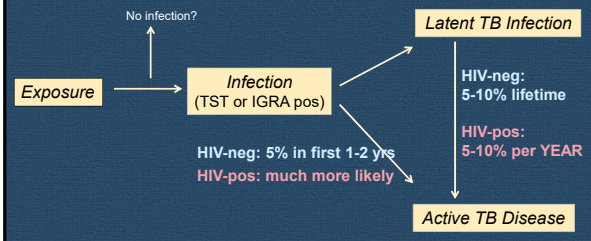
Disclosures of Financial Relationships with Relevant Commercial Interests

- Contracted Research – Sanofi-Aventis

Outline

- **Active TB disease**
  - Clinical presentations
  - Diagnosis
  - Treatment
  - Special considerations w/respect to HIV, other immunocompromising conditions
- **Drug-resistant TB**
- **Latent TB infection**
  - Diagnosis
  - Treatment
- **BCG**
  - Vaccination
  - Immunotherapy for bladder cancer and BCG-osis

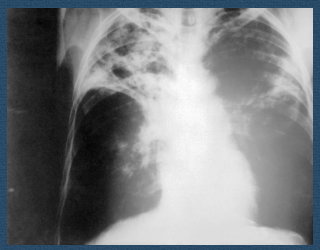
Overview of TB Epidemiology



Risk factors for TB INFECTION	Risk factors for PROGRESSION TO TB DISEASE	
Exposure to TB case	**Recent TB infection**	CXR fibrotic lesions c/w prior TB
From TB endemic area	**HIV infection**	Intestinal bypass/gastrectomy/chronic malabsorption
Homelessness	**TNF-alpha inhibitors**	CA head or neck, Hodgkins, leukemia
Incarceration	Immunosuppression	
Works in healthcare or corrections	End stage renal dz	
Injection drug use	Diabetes	
	Silicosis	

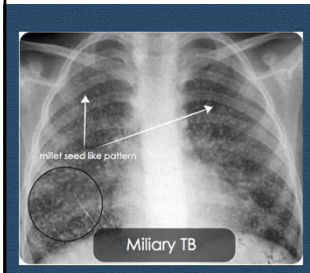
Active TB disease: clinical presentations

- Fever, sweats, wt loss
- Cough if pulmonary
- Usually subacute to chronic (wks to months)
  - Can be acute in immunocompromised
- Upper lobe/apical cavity is 'typical'
  - With surrounding infiltrate
  - + / - adenopathy

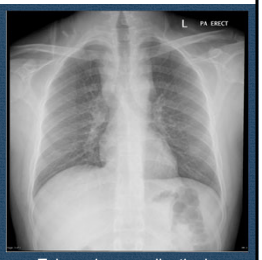


58 - Tuberculosis in Normal and Compromised Hosts

Speaker: Susan Dorman, MD



https://s-media-cache-ak0.pinimg.com/564x/6d/fc/0a/6dfc0a3780da9c42c52fd



Tuberculous mediastinal lymphadenopathy

http://images.radiopaedia.org/images/5440907/ba7efaf8df7333e5eef8f4a964dd8e_jumbo.jpg

Active TB disease: clinical presentations

Extrapulmonary

- CNS (meningitis, focal tuberculomas)
- Lymphadenitis (cervical, thoracic, abdominal)
- Bone and joint
  - Vertebral (thoracic, lumbar, anterior wedging, +/- psoas abscess)
  - Consider TB in DDx of chronic osteomyelitis, arthritis
- Pleural
- Abdominal/pelvic
  - GU ('sterile' pyuria; obtain multiple cultures; can be associated with infertility)
  - GI (can mimic inflammatory bowel disease; obtain cultures, histopathology)

Obtain specimens from affected sites:
AFB smear
Mycobacterial culture
NAAT/PCR
Histopathology

Disseminated

- Advanced HIV, significant iatrogenic immunosuppression
- Can present as sepsis
- Mycobacterial blood cultures, obtain respiratory specimens

Active TB disease: diagnosis

FIRST – CONSIDER TB IN THE DDx

Smear microscopy	current nucleic acid amplification tests	culture
		
LOD: 10,000 cfu/ml	100 cfu/ml	1-10 cfu/ml
Sensitivity: LOW	MEDIUM	HIGH

ADJUNCTIVE:
IGRA, TST: do not distinguish latent from active; NEG test does not rule out active TB
Chest X-ray, other radiology: can be suggestive of active TB; not specific
Histopathology: can be suggestive of active TB; not specific

Active TB disease: diagnosis

Smear microscopy for acid fast bacilli

- * ***TAKE HOME POINT: a negative smear does <u>not</u> exclude dx of active TB*** *
- Low sensitivity: takes a lot of bacilli (10,000 cfu/ml) to make a smear positive
- Overall around 50-60% sensitive for pulmonary TB
- Much less sensitive in advanced HIV (30-50%)
- In pulmonary TB, the yield of smear microscopy increases if multiple specimens are obtained
- Not specific for M.tb (most mycobacteria look alike)
- Good PPV in TB endemic settings

Active TB disease: diagnosis

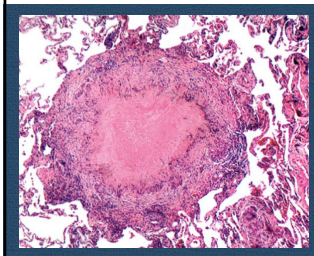
Nucleic Acid Amplification Tests

- E.g. 'Xpert MTB/RIF'
- Sensitivity of currently available NAATs 'in between' that of smear and culture
- A negative test does not rule out TB
- High specificity for *M. tuberculosis* (by design)
- Xpert MTB/RIF detects *M. tuberculosis* and also rifampin resistance (NO info about INH)
- Procedures designed for, validated for sputum
  - Can use for other specimens but test can be falsely negative due to inhibitors of amplification rxn

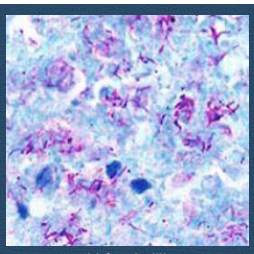
Active TB disease: diagnosis

Mycobacterial Culture

- **The most sensitive method**
- SLOW (3-6 weeks)
- Once growth observed, the lab performs additional tests to identify species (e.g. *M. tuberculosis*)
- Considered the gold standard, but not 100% sensitive
  - Pulmonary TB around 90-95% sensitive
  - Extrapulmonary TB much less sensitive



Caseating granuloma



acid-fast bailli on
Ziehl Neelsen smear micrscopy

http://pathhsw5m54.ucsf.edu/overview/tb.html

Question 1

38 y/o M physician, previously healthy, with periodic travel to South Africa for medical research work. Reports a positive TST six years ago, and admits poor adherence with a course of isoniazid preventive therapy at that time. Now with 5 weeks of fever, chills, night sweats, 10-lb wt loss, productive cough. CXR shows RUL cavitary lesion. Sputum GeneXpert MTB/RIF test result is "MTB detected" and "Rifampin resistance not detected" (culture results pending), HIV test is negative, liver chemistries are normal. What is the best course of action?

A. Prescribe 9 months of isoniazid for presumed latent TB infection
B. Do nothing pending culture results
C. Start TB treatment with rifampin, isoniazid, PZA, ethambutol
D. Start TB treatment with rifampin, isoniazid, PZA
E. Start TB treatment with a regimen for multidrug-resistant TB

Active TB disease: treatment

1st line tx = RIPE

- **Rifampin, Isoniazid, PZA, Ethambutol x 2 months then**
- **rifampin plus isoniazid x 4 more months (continuation phase)**
- Use pyridoxine (vitamin B6) to prevent neuro toxicity of INH

Always start with daily treatment

- Daily more efficacious than intermittent
- In HIV-pos, intermittent tx associated with emergence of RIF resistance

Active TB disease: treatment

Extend continuation phase therapy for

- Pulmonary dz if cavitation and cx pos at end of tx month 2 (9 months total)
- CNS TB (usually 9-12 months total duration)
- Bone and joint TB (6-9 months total duration)

Corticosteroids indicated for TB meningitis

- Pericardial TB: previously universally recommended BUT recent placebo controlled randomized trial showed no difference in outcomes overall

Active TB disease: treatment durations

months	1	2	3	4	5	6	7	8	9	10	11	12
Pulmonary (including pleural)	Rifampin INH PZA EMB		Rifampin + INH									
Pulmonary that is cavitary plus cultures still pos at completion of 2 months of tx			Rifampin + INH									
Bone and Joint (6 to 9 months)			Rifampin + INH			Consider extending to 9 mos						
CNS (9 to 12)			Rifampin + INH							Consider extending to 12 months		

Question 2

The 38 y/o M physician is started on rifampin, isoniazid, PZA, ethambutol (plus pyridoxine) for presumed pulmonary TB. About 3 weeks later the culture grows *M. tuberculosis*, susceptible to those drugs. About 4 weeks into TB treatment the patient reports several days of progressive nausea, anorexia, abdominal discomfort. Liver function testing shows ALT 380, AST 270. He reports no alcohol consumption or acetominophen.

Which drug is **least** likely to be associated with liver toxicity?

A. Rifampin
B. Isoniazid
C. PZA
D. Ethambutol

Active TB disease: treatment

Drug adverse effects

- **Hepatotoxicity: isoniazid, PZA, rifampin**
- **Peripheral neuropathy: isoniazid (use pyridoxine)**
- **Retrobulbar neuritis: ethambutol (color vision 1st affected)**
- Arthralgias: PZA
- Vestibular/ototoxicity: streptomycin > amikacin, kanamycin
- Nephrotoxicity: amikacin, kanamycin > streptomycin

Active TB disease: treatment

Drug-drug interactions: RIFAMPIN

- Potent inducer of hepatic cytochromes and uridine diphosphate gluconyltransferase; this results in increased metabolism (and decreased serum levels, potential decreased efficacy, potential need for increased doses) of other drugs metabolized by those enzymes
- Warfarin, hormonal contraceptives, methadone, corticosteroids, fluconazole, HIV PIs, HIV NNRTIs, HIV INSTIs, HIV CCR5 inhibitors, TAF*

**intracellular TFV-DP levels higher with TAF+RIF c/w TDF alone, but clinical outcomes not well-studied – if TAF+RIF used then monitor HIV VL*

Drug-resistant TB

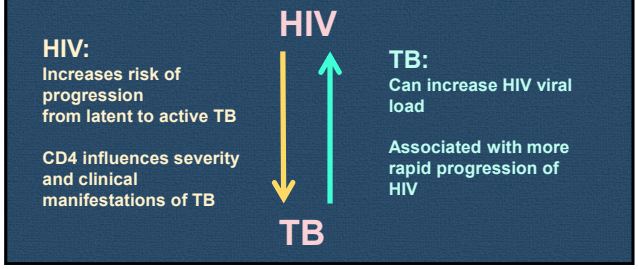
- Risk factors for:
  - Contact with drug-resistant TB case
  - From (or prolonged travel to) eastern Europe, former Soviet Union
  - Prior h/o TB treatment, esp if non-adherent with tx
- **MDR=resistance to isoniazid plus rifampin**
- **XDR=MDR plus resistance to fluoroquinolones plus at least one of the injectable 2nd line drugs (amikacin, kanamycin, capreomycin)**
- Treat with multiple agents against which the isolate is susceptible
- Never add a single drug to a failing regimen
- Bedaquiline (Sirturo™): novel drug, novel target (Mtb ATP synthase), FDA-approved for pulm drug-R TB when effective tx cannot otherwise be provided; QT prolongation; half-life 4 months; restricted access

Question 3

24 y/o M from Zambia, in U.S. for community college, recently tested HIV-positive with CD4 400, not yet on ART. He has a prominent anterior cervical lymph node but is otherwise well-appearing with normal BMI, normal liver and renal chemistries, and mild anemia. Lymph node biopsy grows *M. tuberculosis* in culture. What is the best course of action with respect to the timing of TB therapy and HIV therapy?

A. Start ART immediately, defer TB tx
B. Start TB tx immediately, defer ART until after completion of 6 months of TB tx
C. Start TB tx immediately, and start ART within about 8 weeks
D. Start both TB tx AND ART immediately

Active TB disease: Special considerations w/ respect to HIV



Active TB disease: Special considerations w/ respect to HIV

Clinical Presentation

- Lung cavitation may be absent in advanced immunosuppression
- Negative CXR does not exclude TB
- With advancing immunosuppression, risk for
  - 'Smear-negative' pulmonary TB
  - Extrapulm TB (with or WITHOUT pulm dz)
  - CNS TB
  - Widely disseminated TB/mycobacteremia

Active TB disease: Special considerations w/ respect to HIV

Drug-drug interactions

A rifamycin-based TB regimen is recommended despite drug-drug interactions

- **RIFAMPIN**
  - Accelerates clearance of PIs, NNRTIs, INSTIs, CCR5 inhibitors
    - INSTIs: rifampin + (DTG 50 mg **BID** or RAL **800** BID) OK for selected patients
    - TAF: intracellular TFV-DP levels higher with TAF+RIF than with TDF alone but clinical outcomes not well-studied. If TAF+RIF used then monitor HIV VL.
    - Good virologic, immunologic, clinical outcomes with rifampin + standard dose EFV regimens
    - Do not use rifampin with PI-based regimens
- **RIFABUTIN**
  - Weaker enzyme inducer than rifampin
  - A CYP450 substrate (rifabutin metabolism affected by NNRTIs and PIs)
  - PI-based ART: decrease rifabutin to 150 mg daily, or 300 mg every other day

Active TB disease: Special considerations w/ respect to HIV

When to start ART

- **CD4 < 50: within 2 weeks of starting TB tx**
- **CD4 ≥ 50: within 8 weeks of starting TB tx**
- HIV-infected pregnant women with active TB should be started on ART as soon as feasible (for maternal health and PMTCT)
- TB meningitis: be cautious (high rates of AEs and death in RCT); guidelines recommend NOT starting ART within first 8 weeks

Question 4

30y/o F with HIV, CD4=25, viral load 480,000 copies/mL, with microbiologically confirmed pulmonary TB. She was not on ART at the time of TB diagnosis. At the time of TB dx, treatment with rifampin/INH/PZA/ethambutol (plus pyridoxine) was started immediately. She tolerated TB treatment well, and efavirenz-based ART was started 12 days later. Four weeks after ART was started she reports new headaches, as well as R-sided weakness that is confirmed on physical exam. Which is most appropriate:

A. Stop TB tx immediately since this is likely a side effect of a TB drug
B. Obtain a brain MRI immediately
C. Perform a lumbar puncture immediately
D. Change TB treatment to cover drug-resistant TB
E. Stop ART immediately

Active TB disease: Special considerations w/ respect to HIV

Immune reconstitution inflammatory syndromes (IRIS)

- Paradoxical worsening of TB when ART started after TB tx; unmasking TB when ART started in setting of not-yet-recognized TB
- Typically 2 weeks to 3 months after starting ART
- Risk factors: CD4<50, high pre-ART VL, severe TB, short interval between initiation of TB tx and ART
- Protean manifestations
  - Fever, new lesions, extension of prior lesions

Active TB disease: Special considerations w/ respect to HIV

Immune reconstitution inflammatory syndromes (IRIS)

- General clinical approach
  - Deal promptly with any 'limited space' issues (CNS inflammation, obstructing adenopathy, etc): corticosteroids; surgery if indicated
  - Consider in DDx: malignancy, other OI, wrong original dx of TB, drug-resistant TB; clinical eval is patient-specific
  - NSAIDs if mild; corticosteroids if more severe/refractory signs/sx (prednisone 1.5 mg/kg/d x 2 wks then 0.75 mg/kg/d x 2 wks - Meintjes et al AIDS 2010;24:2381)
  - **Continue TB treatment plus ART**

Active TB disease: Special considerations: transplant recipients

- **Transplantation-associated immunosuppression increases the risk of active TB disease if the person is infected**
- 'atypical' presentations leading to delayed dx
  - 1/3 to 1/2 is disseminated or extrapulmonary
  - 4% of cases thought to be donor derived
- High mortality
- DDI between **rifampin** and calcineurin inhibitors (e.g. cyclosporine, tacrolimus), mammalian target of rapamycin inhibitors (e.g. sirolimus/everolimus), corticosteroids…….at risk for graft rejection
  - Monitor drug levels of calcineurin inhibitors, mTORs
  - Use rifabutin instead of rifampin

Active TB disease: Special considerations: TNF-alpha inhibitors

- ***TNF-alpha inhibitors markedly increase the risk of active TB if infected***
  - Can present with atypical TB (e.g. non-cavitary pulm dz, extrapulmonary, disseminated)
  - Increased TB morbidity, mortality
  - Full monoclonal IgG1 mabs most potent (ie infliximab, adalimumab, golimumab)
- ***Test for latent TB infection (TST or IGRA) prior to starting anti-TNF agents***
  - If LTBI, then initiate LTBI tx prior to starting anti-TNF
  - Limited data on optimal duration of delay between initiating LTBI treatment and initiating anti-TNF treatment (some say 2-8 weeks)

Question 5

24 y/o U.S. born M whose wife (with whom he lives) was recently diagnosed with smear-positive pulmonary TB. During a contact investigation, the 24 y/o M had a strongly positive IGRA assay, and is referred to you. He has no other known TB contact, and reports a negative TST years ago. What is the most appropriate next course of action?

A. Start preventive therapy immediately using daily isoniazid
B. Start preventive therapy immediately using weekly isoniazid plus rifapentine
C. Repeat the IGRA assay
D. Start INH/RIF/PZA/EMB immediately for active TB
E. Obtain medical history, perform TB symptom review and CXR

Latent TB infection (LTBI): diagnosis

Tuberculin skin test

- A mix of antigens; can have 'false-pos' test due to prior BCG vaccination, NTM
- Intradermal inoc, measure induration at 48-72 hours (pos rxn lasts a few days)
- Cut-offs based on likelihood of true exposure, risk of progression to active TB if infected (5 mm; 10 mm; 15 mm)
- Adjunctive in diagnostic eval for active TB
- Booster effect:
  - Some people infected with Mtb may have neg rxn to a TST if many years have passed since Mtb infection. However, the TST PPD stimulates immune response to Mtb antigens, and a subsequent TST can be positive.
  - "Booster effect" can be mistaken for TST conversion
  - Use 2-step TST for individuals who may be tested periodically (e.g. HCW)

Latent TB infection (LTBI): classification of tuberculin skin test results

≥ 5 mm is POS	≥ 10 mm is POS	≥ 15 mm is POS
HIV-infected	Recent arrival (w/in 5 years) from TB high prevalence area	Persons with no known risk factors for TB
Recent TB contact	Injection drug use	
CXR with fibrotic changes	Residents & employees of high-risk settings (HWC, corrections, homeless shelters)	
Organ transplantation	Mycobacteriology lab staff	
Prednisone ≥ 15 mg/d x 1 month or more	Children < 5 years old	
TNF alpha antagonists	Medical conditions: diabetes, silicosis, end-stage renal dz, gastrectomy or small bowel bypass, solid organ transplant, CA head and neck	

Latent TB infection (LTBI): diagnosis

Interferon gamma release assays

- QuantiFERON-TB tests; T-SPOT.TB
- Blood-based; in vitro stimulation of WBC with protein antigens specific for *M. tuberculosis*
- **No cross-reactivity with BCG** (*M. kansasii* and *M. marinum* can cause false pos IGRA)
- Sensitivity is approx same as that of TST
- Can be negative in immunosuppressed
- As for TST, adjunctive in diagnostic eval for active TB
- Lots of 'issues' around performance in clinical care; not fodder for board Q's

Latent TB infection (LTBI): diagnosis

Excluding active TB is a key component of the diagnosis of latent TB infection

- **ROS** (fever, wt loss, cough, night sweats, focal signs/sx that could be assoc with extrapulmonary TB)
- **Chest X-ray** to exclude occult pulmonary TB

Latent TB infection (LTBI): treatment

Preferred

- Isoniazid plus rifapentine once weekly x 12 doses (3HP)
- Rifampin daily for 4 months (4R)
- Isoniazid plus rifampin daily for 3 months (3HR)

Alternative

- Isoniazid daily for 6 months (or 9 months)

Notes:
Rifampin + PZA NOT recommended (hepatotoxicity)
No age cut-off for LTBI treatment

Latent TB infection (LTBI): treatment

- Perform LFTs prior to tx in adults with risks for hepatotoxicity (etoh, risk for viral hepatitis, other hepatotoxic meds)
- Monthly ROS for adverse effects
  - Peripheral neuropathy (numbness/tingling extrems) if on INH (use Vitamin B6=pyridoxine)
  - Hepatotoxicity (N/V, abd discomfort, jaundice)
  - LFT monitoring as clinically indicated

Bacille Calmette-Guerin (BCG)

- Attenuated live vaccine (from *M. bovis*)
- ***Neonatal vaccination***
  - Decreases incidence of severe forms of childhood TB
  - No/very limited impact on adult TB
  - Regional lymphadenitis can occur after vaccination; typically no treatment needed
  - Disseminated infection can occur in immunocompromised (treatment indicated)

Bacille Calmette-Guerin (BCG)

Immunotherapy for bladder cancer

- Intravesicular administration
- Complications
  - granulomatous prostatitis or hepatitis, epididymo-orchitis, spondylitis, psoas abscess, miliary pulmonary, dissem/sepsis
  - Contemporaneous with BCG tx or up to years later
- Treatment
  - Inherent resistance to PZA
  - Treat with rifampin + INH + ethambutol

THANK YOU

Susan Dorman [DORMAN@MUSC.EDU]

TB Summary: *Active TB Disease*

- Standard tx for pulmonary TB
  - 2 months RIF/INH/PZA/EMB then 4 months INH/RIF
  - Always start with daily treatment
- Hepatotoxicity: PZA, INH, RIF
- Rifampin has drug-drug interactions that can reduce effectiveness of other drugs (warfarin, OCPs, methadone, steroids, fluconazole, PIs, NNRTIs, INSTIs)
- Rifabutin is an alternative to rifampin, esp in HIV
- A negative smear does not exclude TB
- TST and IGRAs do not distinguish active from latent TB

TB Summary: *TB in HIV*

- Cavitary dz with preserved CD4; o/w usually noncavitary pulmonary and/or extrapulmonary; disseminated with very low CD4
- Timing of ART start (for those not already on):
  - If CD4<50, start ART within 2 weeks; otherwise within 8 weeks
- IRIS (unmasking of TB or paradoxical worsening):
  - Look for other causes (other OI's, malignancy, unrecognized drug-resistant TB)
  - Continue TB tx and ART, relieve symptoms (NSAIDS, steroids if needed)
  - Can have emergencies (i.e. CNS inflammation, SVC syndrome, etc)
- Rifampin has drug-drug interactions with PI's, most NNRTIs, INSTIs

TB Summary: *Latent TB Infection*

- IGRAs have approx same sensitivity as TST
- BCG does NOT cause false-pos IGRA
- No age cut-off for treatment (targeted testing of those at risk for TB)
  - At risk for having been exposed
  - At risk for progression to active TB once exposed
- Preferred: 3HP, 3HR, 4R (6H or 9H as alternatives)
- Exclude active TB (ROS, CXR) prior to LTBI tx

Supplemental Question I

28 y/o F from Honduras with 4 weeks of fever, cough with scant sputum, mild dyspnea. She is HIV-positive, CD4 250, and not on ART. A PPD was positive at her last visit with you, but she did not return for f/u. Chest X-ray shows increased interstitial markings. O2 saturation is 95%. Sputum PCP is negative, and AFB smear negative x 2, with mycobacterial cultures incubating (results pending). What additional tests should you perform?

A. None, since the negative AFB smears rule out TB
B. Sputum GeneXpert MTB/RIF nucleic acid amplification test
D. Urine lipoarabinomannan (LAM) test
E. Sputum adenosine deaminase test

Supplemental Question II

In which individual would 6 mm induration in response to TST be considered positive?

A. 6 mm induration is never considered positive
B. 6 mm induration is always considered positive
C. A 30 y/o M with HIV-infection
D. A 30 y/o M who is healthy with no risk factors for TB exposure or progression
E. A 30 y/o M who is a healthy healthcare worker without known TB exposure

59

Management of HIV-Related Opportunistic Infections II

Dr. Henry Masur

59 - Management of AIDS-Related Opportunistic Infections II

Speaker: Henry Masur, MD

2020 INFECTIOUS DISEASE BOARD REVIEW

Management of AIDS-Related Opportunistic Infections II

Henry Masur, MD, FIDSA, MACP
Clinical Professor of Medicine
The George Washington University

Disclosures of Financial Relationships with Relevant Commercial Interests

- None

Question #1

A 50 year old male has HIV (CD4=40 cells/uL and HIV viral load =600,000 copies/uL) has central nervous system toxoplasmosis documented by a compatible CT of the head and a positive CSF PCR for toxoplasma.

The patient also has cryptosporidiosis with 4 stools per day plus considerable nausea and thus has limited food intake.

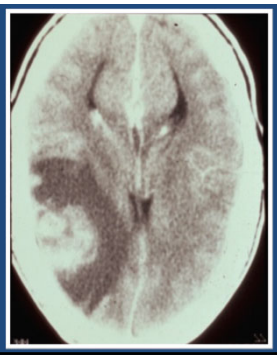
The pharmacy cannot obtain sulfadiazine or pyrimethamine.

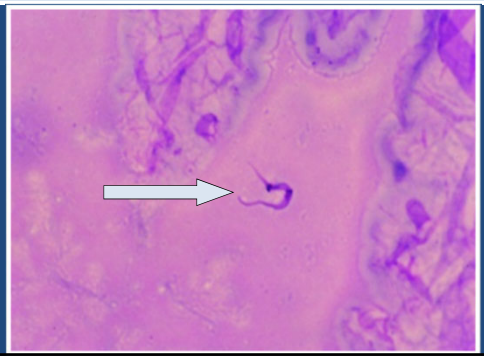
The best option for therapy of the toxoplasmosis would be:

A. Atovaquone
B. Clindamycin plus primaquine
C. Trimethoprim-Sulfamethoxazole
D. Azithromycin plus Doxycycline
E. Nitazoxanide

Question #2

- A 39 year old female from Brazil presents to an ER with a seizure.
  - Her CT scan is shown
  - Her HIV serology is positive
  - CD4 = 20/μL
  - VL = 100,000 copies/μL
- It is thought to be unsafe to perform an LP.
- She is started on sulfadiazine and pyrimethamine.
- ARVs are held until her acute problem is under control.
- After 10 days, she has not improved and a brain biopsy is performed (see image).



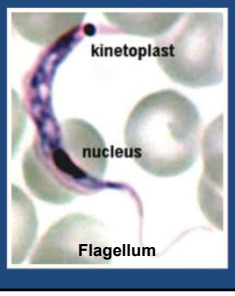


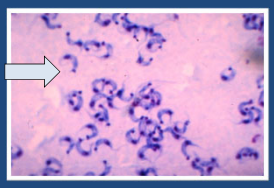
Question #2

What is the most likely diagnosis?

A. Toxoplasmosis
B. Cysticercosis
C. Leishmaniasis
D. Trypanosomiasis
E. Acanthamoeba

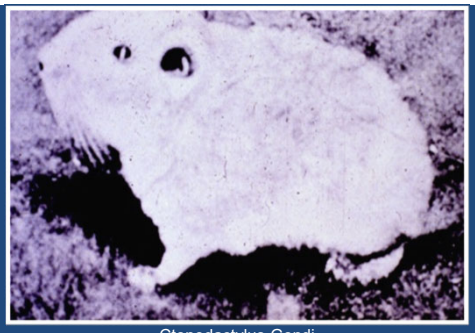
Trypanosoma cruzi
Blood Smear and CSF



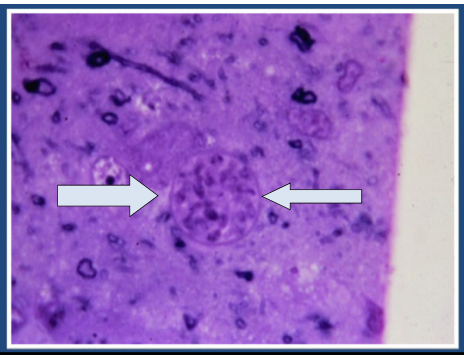


Badero et al, AIDS THERAPY, 4th Ed

Toxoplasmosis



Ctenodactylus Gondi



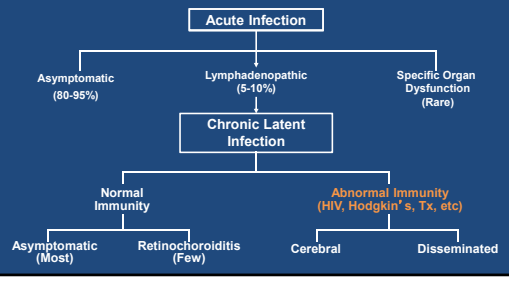
Incidence of Toxoplasmosis

- **Common (30%) before ART and chemoprophylaxis**
- **Seroprevalence in General Population**
  - US-20%
  - Some areas of Europe, Africa: 80%
- **Disease "never" occurs in seronegative patients except**
  - Acute infection
  - Insensitive assay
  - Loss of ability to make antibody

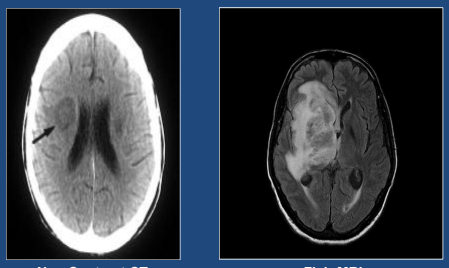
Transmission of Toxoplasma

- **Feline feces (cats, but also lions etc)**
  - Oocysts begin to be excreted 20 - 24 days post infection
  - Excretion persists 7 - 21 days
- **Rare Meat (Lamb>Beef>Pork)**
- **Unusual**
  - Raw shell fish, goat milk (reported 2009-2010)
  - Iatrogenic
    - Transfusion/Needle injury/transplant
- **Congenital**
  - Acute acquisition by mother during gestation
  - Chronic infection in immunosuppressed mother

Clinical Manifestations of Toxoplasmosis when Acquired Post-Partum



CNS Toxoplasmosis



Non Contrast CT | Flair MRI

Evaluation of CNS Mass Lesions in Patients with HIV/AIDS

- Toxoplasmosis
- Lymphoma
- Tuberculosis
- Fungus
- Nocardia
- Bacterial
- Syphilis
- Kaposi
- Chagoma
- Glioblastoma

Radiologic Results
Non-specific although certain features suggestive
Look for Extra CNS lesions for biopsy

Laboratory Studies to Perform
Serology: Toxo IgG, Toxo PCR
Serum Crypt Ag and Histo ag
Blood culture - AFB, fungus
CSF - Crypt Ag
PCR (EBV, CMV, Toxo)
Urine - Histo Ag

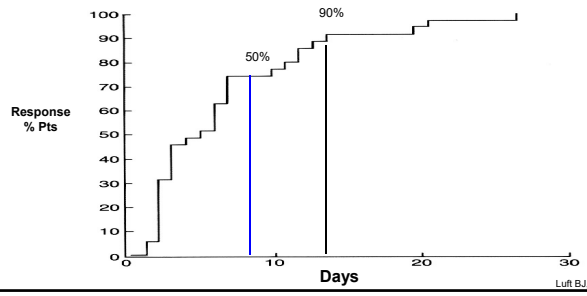
Response to Empiric Therapy

Empiric Diagnosis of CNS Toxo

- **Compatible CT or MR plus**
- **CD4 Count <100 cells/uL plus**
- **Toxo IgG antibody positive plus**
- **Not on TMP-SMX prophylaxis plus**
- **Response to therapy within 2 weeks**

Time to Neurologic Response

35 CNS Toxo Patients Treated with Clindamycin - Pyrimethamine



Luft BJ, NEJM 1993

Definitive Diagnosis of Cerebral Toxoplasmosis

- **Brain biopsy**
- **Serum PCR**
- **CSF PCR**

Therapy for Cerebral Toxoplasmosis

- **Preferred Regimen**
  - Sulfadiazine plus pyrimethamine plus leucovorin
- **Alternative Regimens**
  - Trimethoprim-sulfamethoxazole
  - Clindamycin plus pyrimethamine
  - Atovaquone +/- Pyrimethamine

Adjunctive Therapies for CNS Toxoplasmosis

- **Corticosteroids**
  - Not routine
  - Only if increased intracranial pressure/symptoms/signs
- **Anticonvulsants**
  - Not routine
  - Only after first seizure

Primary Prevention of Toxoplasmosis in Patients with HIV

- **Indication**
  - Positive IgG and CD4<100 cells/uL
- **Drugs**
  - First Choice
    - TMP-SMX (one ds qd)
  - Alternatives
    - Dapsone-Pyrimethamine
    - Atovaquone + Pyrimethamine

Primary Prevention of Toxoplasmosis in Patients with HIV

- **For patients with CD4<200 who are on TMP-SMX or atovaquone for PCP prophylaxis**
  - Protective against Toxo
- **For patient on Aerosol Pentamidine or Dapsone for PCP prophylaxis**
  - If on dapsone: add pyrimethamine
  - If on Aerosol pentamidine: not protected

Non Tuberculous Mycobacterial Infections in HIV Infected Patients

You Need Microbiologic or Epidemiologic Clue on Exam!

• **Avium complex**	**Dissemination**
• **Hemophilum**	**Cutaneous abscesses**
• **Bovis**	**Adenitis, Dissemination**
• **BCG (Bovis)**	**Dissemination**
• **Genovense**	**Dissemination**
• **Scrofulaceum**	**Adenitis, Dissemination**
• **Xenopi**	**Lung nodules or infiltrates**
• **Malmoense**	**Cavitary lung, CNS ring lesions**
• **Chelonei**	**Skin, Soft Tissue, Joint, Bone**

Question #3

An HIV-infected patient is admitted to the hospital with three weeks of cough, fever, 25 lb weight loss, and anorexia. He is found to be HIV infected and to have a CD4 count =10 cells/uL and VL =500k

- **His chest x-ray shows diffuse interstitial infiltrates**
- **BAL =PCP by immunofluorescence**

Two weeks later while the patient is still in the hospital due to disposition issues, the lab reports
- **Three blood cultures and the BAL are growing a mycobacterium**
- **Probe = Mycobacterium avium complex**

What type of isolation is appropriate?
A. None
B. Droplet
C. Respiratory
D. Contact
E. Contract and droplet

Answer #3

- No isolation

Atypical mycobacteria, including M. avium complex, are not transmitted from person to person. They are acquired from environmental sources including food, dust, dirt, animals, and enter the human by a GI or respiratory route.

M. Avium is almost never the cause of pulmonary disease in HIV infected patients. In this case the M. avium, like CMV, was likely present in the lavage because the organism can be shed in various locations in HIV infected patients with low CD4 counts. MAC causes bacteremia, adenitis, enteritis, hepatosplenomegaly, but not pneumonitis in this patient population

ART should be started within two weeks of documenting the initial PCP and MAC. The MAC should be treated with azithromycin plus ethambutol +/- rifabutin pending macrolide susceptibility testing.

Mycobacterium Avium Intracellulare Complex

- **Epidemiology**
  - Ubiquitous in dirt, animals etc
- **Transmission**
  - Respiratory via dust
  - GI via food, water
  - Person-to-person unlikely
  - Environmental isolates correlate poorly with human isolate

Mycobacterium Avium Intracellulare

- **Risk factors**
  - CD4 < 50 or High VL
  - Colonization: GI / respiratory
- **Incidence pre ART: 20-40% (North America)**
  - Now declining with ART and probably non-ART related factors
- **Acute Disease: Clinical manifestations**
  - Fever, wasting, nodes, liver, spleen
  - Rare as cause of lung disease
  - Lab: ↑Alk Phos, ↓Hg,↓ Albumen

Mycobacterium Avium Intracellulare Diagnosis

- **Source of Isolates**
  - **Blood**
    - **Bactec (7-14 days),**
  - **Sputum/Stool/Urine**
    - **Low predictive value**
- **Lab Identification**
  - **Specific DNA Probes for specimens/ cultures**
  - **MALDI-TOF**

MAC: Susceptibility Testing

Recommended for primary isolates

- **Clari and Azithro**
- **Other drug testing not validated for MAC**

Treatment for MAC

- **Antiretroviral Therapy**
  - Start within 2 weeks of anti mac therapy
- **Specific Therapy**
  - Clarithro (or Azithro) + Ethambutol
    - Rifabutin optional 3rd drug: use if severe disease
    - Beware drug interactions with clari or rifabutin

Treatment for MAC

- **Response:**
  - Fever should decline within 2-4 weeks
  - Blood cultures should be negative in 2-4w
  - Repeat blood cultures only if symptoms
- **Stop chronic suppression:**
  - CD4 > 100 x 6M, asx and therapy >12 m

Salvage Therapy for MAC Not For Boards

- **No evidence-based standard**
- **Logical to be guided by in vitro susceptibility testing**
  - **Not standardized for MAC other than macrolides**
  - **Options: Amikacin, Ciproflox, Moxiflox, Mefloquine, Linezolid, Bedaquiline**

~~MAC Prophylaxis 2020~~

- **Primary prophylaxis against disseminated MAC disease is not recommended if ART initiated immediately (AII).**
  - Primary MAC prophylaxis, if previously initiated, should be discontinued if person is on ART (AI).

What Is This?

Immune Reconstitution Inflammatory Syndrome

- **Definition**
  - **Worsening manifestations or abrupt /atypical presentation of infection or tumor when ART started**
    - **Paradoxical-manifestation of pre-existing infection or tumor**
    - **Unmasking-manifestation of previously occult infection/tumor**
- **Timing**
  - **Few days to 6 months**
  - **Viral load drop more relevant than CD4 rise**
    - **(better lymphocyte function>number)**

Immune Reconstitution Inflammatory Syndrome

- **Predictors**
  - **Pre therapy low CD4 or high VL**
  - **Prior OI or short therapy for OI**
  - **High pathogen load**
- **Outcome-Morbidity Can Be Severe**
  - **Obstructed bowel, biliary tract, ureter, bronchus**
  - **Myocarditis, meningeal inflammation/increased ICP, serositis (pleura, peritoneum, pericardium)**

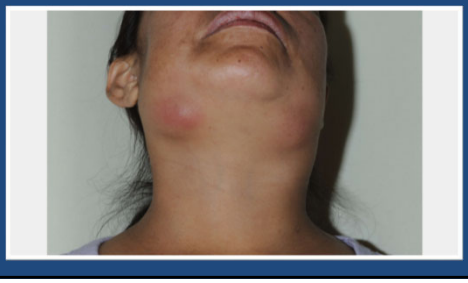
Pathogens Commonly Associated with IRIS

- **Mycobacterium avium complex**
- **Mycobacterium tuberculosis**
- **Cryptococcus neoformans**
- **Many others**
  - CMV retinitis, HBV
  - Mucocutaneous HSV and VZV
  - PCP, Histo
  - PML
  - KS

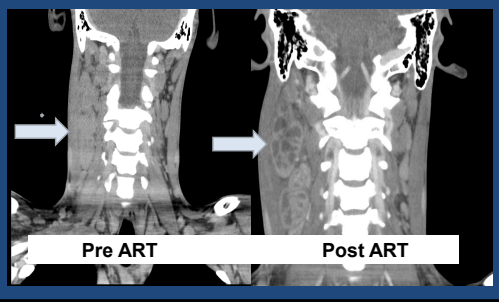
Management of IRIS

- **Reassess Diagnosis**
  - Evaluate for concurrent, additional OIs and tumors
  - IRIS-Diagnosis of exclusion
- **Treat IRIS**
  - Continue ART
  - Treat identified pathogen-usual practice without data
  - NSAIDS or Coritcosteroids
    - Prednisone 20-40mg qd x 4-8 weeks

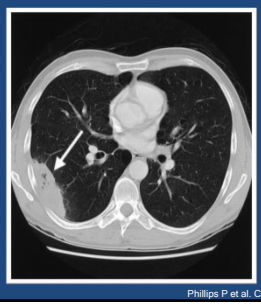
Immune Reconstitution Inflammatory Syndrome (Mycobacterium avium complex)



MAC IRIS in Patient with HIV



CT Scan: Pleural-Based MAC



Phillips P et al. Clin Infect Dis 2005;41:1483

Life Threatening IRIS –How Would They Test for These?

- **Unmasking**
  - Unrecognized lymphadenitis due to TB, MAC, Fungi
  - Unrecognized cryptococcal meningitis
  - Unrecognized CMV retinitis
  - Inflammation of Kaposi sarcoma skin lesion
  - Pulmonary infiltates due to PCP, fungi, TB
- **Exacerbation of Crypt Meningitis Increased intracranial pressure**
  - New focal findings
- **Transaminase Flair in Patient with Untreated HBsAg or HBcoreAb**
  - Transaminase flair due to HBV
- **Exacerbation of previously treated CMV retinitis, PCP, TB**

Question #4

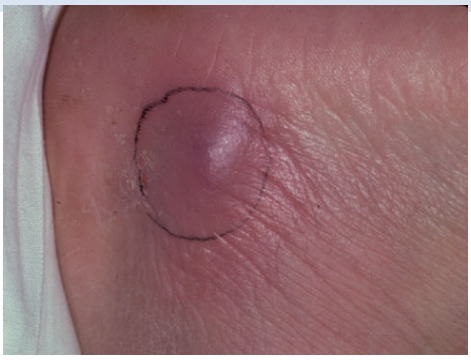
A 45 year old male with HIV (CD4<10 cells/cc3, VL> 100k) has been taking TMP-SMX and Efavirenz-Tenofovir-Emtricitabine only intermittently.

For the past 3 weeks he has had a low grade fever, mild weight loss, and a lesion which is shown on the next slide.

Aspiration of the lesion showed many AFB rods, non branching, but after 6 weeks nothing grew.

The lesion is to be aspirated again.

See next slide



Question #4

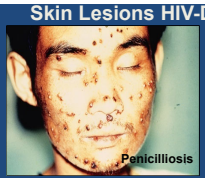
What advice do you give the lab and hospital epi?

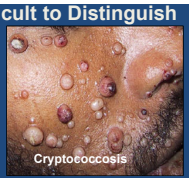
A. This should grow at 37°C
B. This should grow on conventional TB culture media
C. This most likely was acquired by acupuncture or some other manipulation.
D. This is treatable with trimethoprim-sulfamethoxazole
E. This can be cultured only at 32°C with iron enriched medium

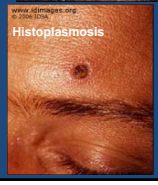
Fungal Diseases in HIV-Infected Persons

- **Candidiasis**
- **Cryptococcosis**
- **Histoplasmosis**
- **Coccidiomycosis**
- **Talaromyces**

Skin Lesions HIV-Difficult to Distinguish







HIV-Related Cryptococcal Meningitis

- **Clinical Presentation**
  - CNS manifestations typically develops over several weeks (median 2 weeks)
    - Crypt IRIS is typically more acute
  - Only 25% of those with positive CSF develop meningeal signs and symptoms
    - Most HIV related cases have extrameningeal involvement including fungemia
  - CD4 count < 100 cells/mm3
    - 90% cases

Diagnosis of Cryptococcal Disease

- **CSF**
  - Often minimal abnormalities with lymphocyte pleocytosis
    - But….can be negative with early disease when blood Cr Ag +
  - Opening pressure >20-25cm H20 60-80%
- **Blood Culture positive**
  - 60% of patients with clinical meningitis
  - Growth in < 7 days

Antigen Tests for Cryptococcal Disease

- **Blood, Serum, Plasma, CSF:**
  - **Antigen Latex Agglutination or**
  - **Enzyme Linked Immunoassay (EIA)**
    - False positive rarely occur
      - Trichosporon, Capnocytophaga, various chemicals
  - **Cryptococcal Lateral Flow Assay (IMMY LFA)**
    - **Dipstick test for blood and CSF**
    - Four fold higher titers than Latex Aggl or EIA
    - Good sensitivity and specificity

PCR Tests for Cryptococcal Disease C. neoformans and C. gatti

- **PCR for CSF**
  - Screening test available in multiplex assays
    - False negatives and false positive reported
    - Simultaneous antigen test should be performed if cryptococcal meningitis is suspected
  - May be useful for distinguishing
    - IRIS (PCR neg)
    - Relapse (PCR positive)

Therapy of Cryptococcal Meningitis

Liposomal Ampho B plus **Flucytosine***	**3-4 mg/kg qd** **25 mg/kg QID**	→ 2 weeks
Fluconazole 400 mg po qd		→ 8 weeks
Fluconazole 200 mg po qd		→ ≥ 52 weeks**

***5FC Associated with Earlier sterilization CSF, Fewer relapses**

- **** Stop after 12 m total therapy if-**
- **CD4 >100- 150 x >3m,**
- **Asymptomatic**
- **VL <50 copies**

Question #5

Patient presents with cryptococcal meningitis, severe headache, and opening pressure >25 cm H20 on day 1 of therapy

Which of the following would you initiate if the CNS symptoms persist on day 2

A. Dexamethasone
B. Acetazolamide
C. Mannitol
D. Lumbar puncture to remove fluid
E. Lumbar puncture for repeat diagnostic studies and MRI to assess for a second, concurrent infectious or neoplastic process

Elevated CSF Pressure

- **75% of patients have Opening Pressure >20 cm CSF**
  - Abnormal = >25 cm CSF
  - Left lateral decubitus, flat position
- **Symptoms**
  - Blurred vision, confusion, obtundation
- **Management: IF symptomatic and >25cm**
  - Remove volume to reduce pressure by half or <20cm H20
  - Continue Lps daily for symptomatic patients until stable for at least 2 days
  - Shunt if regular LPs required for "many" days
- **Not routinely recommended**
  - Corticosteroids, Mannitol, Acetazolamide

Monitoring Therapy for Cryptococcal Meningitis

- **During Therapy**
  - **Serial testing of blood or CSF Crypt Ag during therapy is not useful**
  - **Negative serum or CSF Ag is NOT required for termination of therapy**
- **Post Therapy CSF Culture**
  - **Advocated by some to determine likelihood of relapse**

Commonly Asked Questions

- **Liposomal Amphotericin B Induction for < 14 days**
  - No (not yet)
- **Fluconazole based regimens in US As Initial Rx**
  - No-not as effective as Ampho
  - Efficacy depends on dose of fluconazole

Asymptomatic Cryptococcal Antigenemia

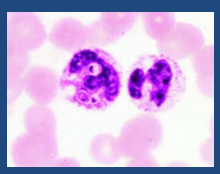
(Pre-emptive Therapy for Crypt Ag +/Low CD4)

- **Recommendation: Optional in US**
  - Screen patients with CD4<50-100
  - 2.9% of all patients positive, and 4.3% of patients with CD4< 50
  - Positive serum or CSF predicts development of active disease
- **If Positive: Perform LP and Blood Cultures**
  - If CSF positive
    - Treat like crypt meningitis/disseminated (Ampho/5FC)
  - If CSF negative
    - Treat with fluconazole x6 months

IDSA OI Guidelines for Crypt 2020

Histoplasmosis

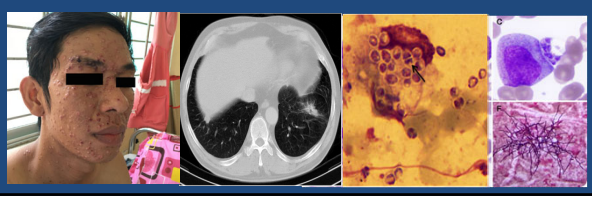
- **Clinical Presentation**
  - CD4>200 cells/uL
    - Focal disease like immunocompetent
  - CD4<200 cells/uL
    - Disseminated disease:
      - Fever, weigh loss, fatigue, hepatosplenomegaly
      - Meningitis, Septic Shock, GI manifestations also common



- **Diagnosis**
  - Antigen detection
  - BAL antigen also useful
  - Cultures useful but….takes several weeks to grow

Talaromyces – Formerly Penicilliosis marnefii

- **Rarely if Ever Seen in US**
- **Common in Asia transmitted by Bamboo Rat or Abiotically**
- **Serum antigen test (research) sensitive and specific**
- **Treat with Ampho or Itraconazole**



CMV

CMV Syndromes

- **Retinitis**
- **Colitis**
- **Ventriculitis**
- Radiculopathy, Myelitis, Mononeuritis Multiplex
- Esophagitis (uncommon)
- Adrenalitis (rare)
- Pneumonia (rare)

Diagnosis of HIV Related CMV Disease

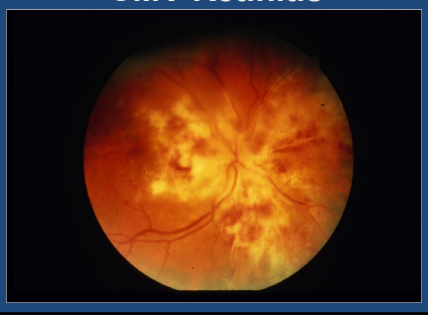
- **Serology**
  - Disease unlikely if IgG seronegative
  - Rarely done
- **Cytology**
  - Rarely useful
- **PCR**
  - Correlates with CD4 Count
  - *Low sensitivity and specificity* for clinical disease

Diagnosis of CMV Retinitis

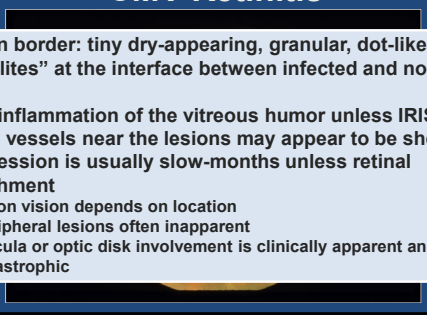
Funduscopic exam

- **PCR of blood not useful: 70% sensitive, very non specific**
- **Vitreal taps for diagnosis with PCR rarely necessary**
  - **Tap positive in 80% of cases**

CMV Retinitis



CMV Retinitis



- **Lesion border: tiny dry-appearing, granular, dot-like "satellites" at the interface between infected and normal retina**
- **Little inflammation of the vitreous humor unless IRIS**
- **Blood vessels near the lesions may appear to be sheathed**
- **Progression is usually slow-months unless retinal detachment**
- **Effect on vision depends on location**
  - **Peripheral lesions often inapparent**
  - **Macula or optic disk involvement is clinically apparent and can be catastrophic**

Therapy for CMV Retinitis
Ganciclovir intraocular implant no longer available!

- **Immediate sight-threatening lesions**
  - **ART**
  - **IV Ganciclovir or Valganciclovir 900 mg PO (bid x 14–21 days), then qd plus**
  - **Intravitreal ganciclovir x 4-7 doses over 1-2 weeks**
    - **Injections can be associated with infections or retinal detachment and hemorrhage**
- **Small peripheral lesions**
  - **ART**
  - **Oral valganciclovir**
  - **+/- intravitreal ganciclovir**

Failure of CMV Therapy

- **Early Failure-rarely due to CMV resistance**
  - Wait at least 10-14 days to see clinical or laboratory response
- **Late Failure**
  - UL97 (phosphotransferase gene) mutation
    - Low level: no cross resistance to Foscarnet, Cidofovir
    - Many respond to high dose GCV (10mg/kg q 12 h)
  - UL54 (polymerase gene) mutation
    - High level: cross resistant to cidofovir and some are cross resistant to Foscarnet depending on precise mutation

Salvage Therapy for CMV Retinitis

- **Systemic Options**
  - **Ganciclovir higher dose**
  - **Foscarnet IV**
  - **Foscarnet IV plus Ganciclovir IV**
  - **Cidofovir IV**
- **Intraocular**
  - **Ganciclovir or Foscarnet**

Thank You

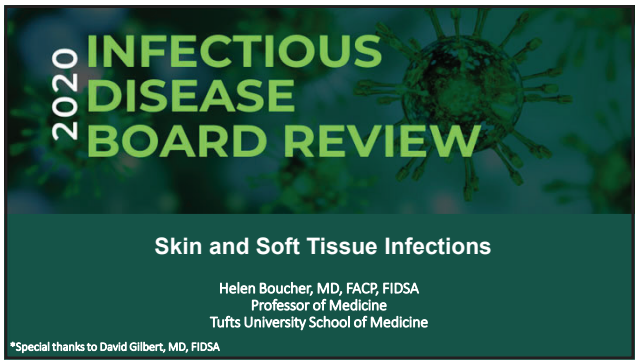
60

Skin and Soft Tissue Infections

Dr. Helen Boucher

60 – Skin and Soft Tissue Infections

Speaker: Helen Boucher, MD



Disclosures of Financial Relationships with Relevant Commercial Interests

- Editor
  - ID Clinics of North America
  - Antimicrobial Agents and Chemotherapy
- Treasurer, Infectious Diseases Society of America
- Member, ID Board, American Board of Internal Medicine
- Voting Member, Presidential Advisory Council on Combating Antibiotic Resistant Bacteria (PACCARB)

Question #1

A 25 year old female suffers a cat bite on the forearm.

She presents one hour later for care.

If no antibacterial is administered, the percentage of such patients that get infected is:

A. 0-10 %
B. 10-30 %
C. 30-70 %
D. 70-100 %

3

Management of Animal Bites

- Wound care: irrigate, debridement
- Image for Fracture or as baseline for osteo or to detect foreign body ?
- Wound closure: NO
- Anticipatory (prophylactic) antibiotics
- Vaccines (tetanus and rabies)

4

Cat Bites

- Most cat bites become infected with bacteria
- Wound types: puncture
- Microbiology: 63% polymicrobial
- Infection type:
  - nonpurulent wound with cellulitis, lymphangitis, or both (42%)
  - purulent wound without abscess (39%)
  - abscesses (19%)

Aerobic organisms	
Pasteurella	75
Streptococcus	46
Staphylococcus	35
Neisseria	35
Moraxella	35
Corynebacterium	28
Enterococcus	12
Bacillus	11
Anaerobic organisms	
Fusobacterium	33
Porphyromonas	30
Bacteroides	28

Abrahamian FM1, Goldstein EJ. Microbiology of animal bite wound infections. Clin Microbiol Rev. 2011 Apr;24(2):231-46. doi: 10.1128/CMR.00041-10; *NEJM 1999; 340: 85-92*

5

Pasteurella multocida

- In saliva of > 90% of cats and over 80% of wounds get infected
- Different species, *Pasturella canis*, in saliva of 50% of dogs and only 2-10% get infected
- Small aerobic Gram-Negative bacillus
- Hard to remember antibiotic susceptibility profile, but amoxicillin sensitive; alternatives can be tricky

6

Can you name 6 pathogens that can cause infection after cat bites?

1. ***Pasteurella species***
2. **Anaerobic bacteria: e.g., *Fusobacteria***
3. ***Bartonella henselae (Cat Scratch dis.)***
4. **Rabies virus**
5. ***S.aureus***
6. ***Streptococcal species***

7

Question #2

A 50 year old female alcoholic suffered a provoked dog bite. It was cleansed, tetanus toxoid given, and the dog placed under observation.

The patient is post-elective splenectomy for ITP. She received pneumococcal vaccine one year ago.

One day later, the patient is admitted to the ICU in septic shock with severe DIC and peripheral symmetric gangrene of the tips of her fingers/toes.

8

Question #2 Continued

Which one of the following is the most likely etiologic bacteria?

A. ***Pasteurella canis***
B. ***Capnocytophaga canimorsus***
C. ***Fusobacterium sp.***
D. ***Bartonella henselae***

9

Dog Bites and Splenectomy

- **Only 2-10 % get infected**
- **Potential pathogens from**
  - **Dog's mouth:**
    - ***Pasteurella canis, Capnocytophaga canimorsus***
  - **Human skin: *S. aureus, S. pyogenes***
- ***Capnocytophaga is an important* cause of overwhelming sepsis in splenectomized patients**
- ***Capnocytophaga***
  - ***Susceptible to: AM/CL, PIP/Tazo, Penicillin G, and clindamycin***
  - ***Resistant to: TMP/SMX and maybe vancomycin***

10

Question #3

A 45 year old USA homeless male presents with fever and severe polymyalgia. On physical exam, animal bite marks found around his left ankle. A faint rash is visible on his extremities. Within 24 hours, blood cultures are positive for pleomorphic gram-negative bacilli.

Which one of the following is the most likely diagnosis?

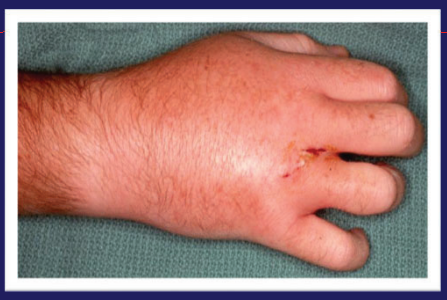
A. ***Pasteurella multocida?***
B. ***Haemophilus parainfluenza?***
C. ***Spirillum minus?***
D. ***Streptobacillus moniliformis?***

11

Rat bite fever

- **USA: *Streptobacillus moniliformis***
- **Asia: Spirillium minus**
- **Bites or contaminated food/water**
- ***S. moniliformis*:**
  - **Fever, extremity rash**
    - **Macular/papular, pustular, petechial, purpuric**
  - **Symmetrical polyarthralgia**
- **Treatment: Penicillin or doxycycline**

12



13

Question #4

A 35 year old male suffers a clenched fist injury in a barroom brawl. He presents 18 hours later with fever and a tender, red, warm fist wound. Gram stain of bloody exudate shows a small gram-negative rod with some coccobacillary forms. The aerobic culture is positive for viridans streptococci.

Which one of the following organisms is the likely etiologic agent?

A. *Viridans streptococci?*
B. *Eikenella corrodens?*
C. *Peptostreptococcus?*
D. *Fusobacterium species?*

14

Eikenella corrodens

- Anaerobic small gram-negative bacillus
- Susceptible to: penicillins, FQs, TMP/SMX, Doxy, and ESCs.
- Resistant to: Cephalexin, clinda, erythro, and metronidazole

15

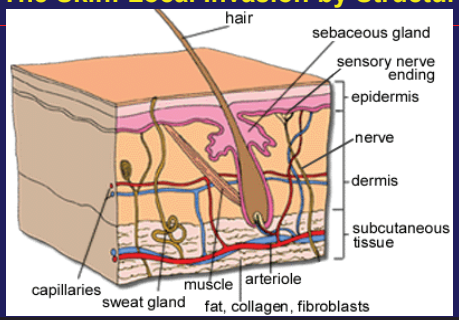
Question #5 (Extra Credit)

Medicinal leeches are applied to a non-healing leg ulcer. Which one of the following pathogens is found in the "mouth" of the leech ?

A. *Alcaligenes xylosoxidans*
B. *Aeromonas hydrophila*
C. *Acinetobacter baumannii*
D. *Arcanobacterium haemolyticum*

16

The Skin: Local Invasion by Structure

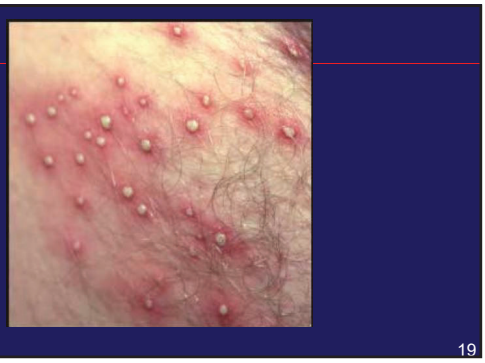


17

Skin Infections: Predisposing Factors

- Trauma to normal skin
- Immune deficiency
- Disrupted venous or lymphatic drainage
- Local inflammatory disorder
- Presence of foreign body
- Vascular insufficiency
- Obesity; poor hygiene

18

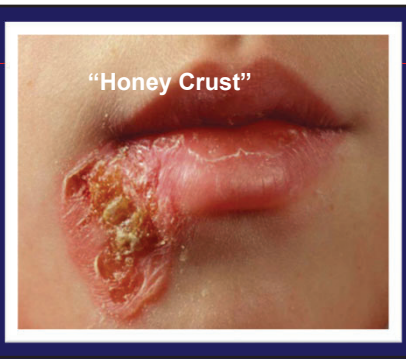

19

Purulence (sometimes mixed with blood) where hair follicles exit skin

- Diagnosis: Superficial Folliculitis
- Etiology:
  1. *S. aureus*
  2. *P. aeruginosa* (hot tub)
  3. *C. albicans (esp. in obese patient)*
  4. *Malassezia furfur - lipophilic yeast (former Pityrosporum sp)*
  5. Idiopathic eosinophilic pustular folliculitis in AIDS patients

20

21



22

Microbial etiology ?

Infection of outer layers of epidermis with production of "honey-crust" scales

Prevalent in warm, humid environments – esp. in children

Microbial etiology?

23

Streptococcal

Infection of outer layers of epidermis with production of "honey-crust" scales

Prevalent in warm, humid environments – esp. in children

Microbial etiology?

- Streptococci: Groups A, B, C, G

24

Name of clinical syndrome ?

Infection of outer layers of epidermis with production of "honey-crust" scales

Prevalent in warm, humid environments – esp. in children

Microbial etiology?

- Streptococci: Grps A, B, C, G

Name?

25

Streptococcal Infection of the Epidermis

Infection of outer layers of epidermis with production of "honey-crust" scales.

Prevalent in warm, humid environments – esp. in children.

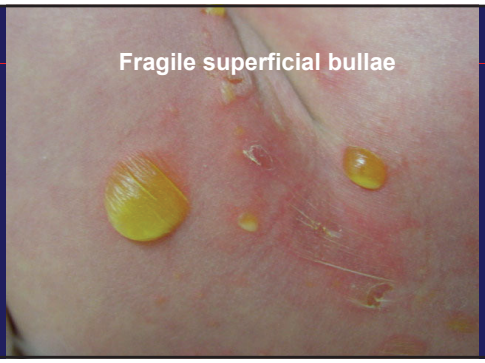
Microbial etiology?

- Streptococci: Grps A, B, C, G

Name?

- Streptococcal impetigo

26



27

Fragile Bullae in Epidermis

Diagnosis?

28

Fragile Bullae in Epidermis

Diagnosis?

- Bullous impetigo

29

Fragile Bullae in Epidermis

Diagnosis?

- Bullous impetigo

Etiology?

30

Fragile Bullae in Epidermis

Diagnosis?

- **Bullous impetigo**

Etiology?

- ***S. aureus***

31

Impetigo ("to attack")

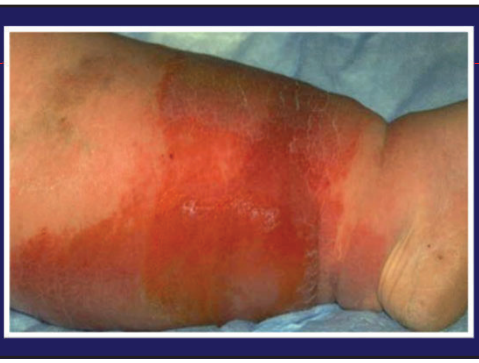
- **Bullous impetigo: *S. aureus***
- **Non-bullous impetigo: *S. pyogenes, group A***
- **So, empiric therapy aimed at *S. aureus* as could be MRSA**
- **Topical: topical antibiotic ointment (TAO), mupirocin, retapamulin**
- **Oral rarely needed**
  - **e.g, Clindamycin, doxycycline**

32

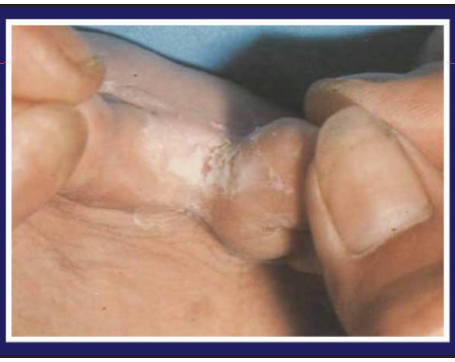
Complications of *S.pyogenes, S. dysgalactiae (Gps C&G)* impetigo

- **Post-streptococcal glomerulonephritis due to nephritogenic strains**
- **Rheumatic fever has "never" occurred after streptococcal impetigo**

33



34



35

Acute onset of painful, rapidly spreading red plaque of inflammation involving epidermis, dermis, and subcutaneous fat

NO PURULENCE

Diagnosis?

36

Acute onset of painful, rapidly spreading red plaque of inflammation involving epidermis, dermis, and subcutaneous fat

NO PURULENCE

Diagnosis?

- Erysipelas: Non-purulent cellulitis

37

Acute onset of painful, rapidly spreading red plaque of inflammation involving epidermis, dermis, and subcutaneous fat.

NO PURULENCE

Diagnosis?

- Erysipelas: Non-purulent cellulitis

Etiology?

38

Acute onset of painful, rapidly spreading red plaque of inflammation involving epidermis, dermis, and subcutaneous fat. NO PURULENCE

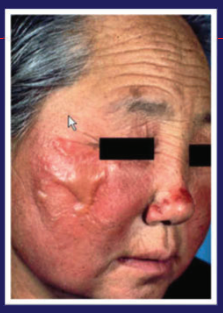
Diagnosis?

- Erysipelas: Non-purulent cellulitis

Etiology?

- Hemolytic Streptococci: Grp A now less common than groups C and G
- If on the face, could be *S. aureus*

39



40

Erysipelas ("Red Skin")

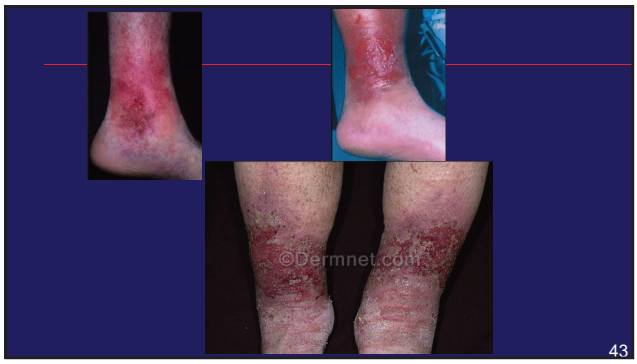
- Acute onset of painful skin, rapid progression +/- lymphangiitis
- Inflamed skin elevated, red, and demarcated
- Etiology: Streptococci--Gps. A,B,C, & G (*S.pyogenes, S. agalactiae, S.dysgalactiae subsp. equisimilis)*
- Predisposition:
  - Lymphatic disruption, venous stasis

41

Erysipelas and Cultures

- Usually no culture necessary
- Can isolate *S. pyogenes* from fungal-infected skin between toes
- Low density of organisms. Punch biopsy positive in only 20-30%
- Blood cultures positive in </= 5%
- Confused with stasis dermatitis

42



43

Stasis Dermatitis

- Looks like erysipelas; Patient often obese
- No fever
- Chronic, often bilateral, dependent edema
- Goes away with elevation
- Does not respond to antimicrobials
- Cadexomer iodine (IODOSORB) response rate 21% vs 5% for usual care

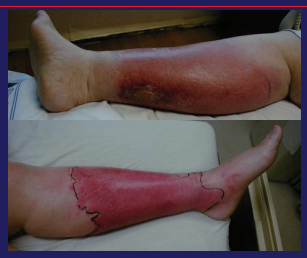
44

Treatment of Erysipelas (Non-purulent "cellulitis")

- Elevation
- Topical antifungals between toes if tinea pedis present
- Penicillin, cephalosporins, clindamycin
- Avoid macrolides and TMP/SMX due to frequency of resistance

45

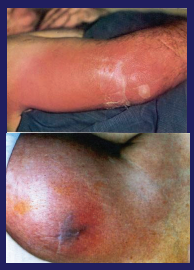
Cellulitis

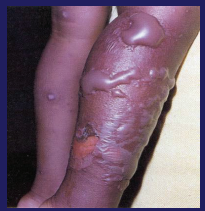


- Without localization or preceding macro or micro trauma: usually Beta strep. (usually GAS), extremities > face, elsewhere
- With localization (cut, pustule, etc) or preceding trauma: *S. aureus*

46

Severe Cellulitis





Microbiology: Streptococci (grp A>B,C,G); less often *S. aureus*; rarely GNR

47

Recurrent Cellulitis

- Frequently non-group A streptococci (esp. B,G)
- Relapse > recurrence
- Prophylaxis:
  - benzathine penicillin IM
  - oral penicillin; other systemic antibiotics
  - decolonization (nasal, elsewhere)

48

Risk factors for recurrent Cellulitis

- Lower Extremity
  - Post-bypass venectomy
  - Chronic lymphedema
  - Pelvic surgery
  - Lymphadenectomy
  - Pelvic irradiation
  - Chronic dermatophytosis
- Upper Extremity
  - Post-mastectomy/node dissection
- Breast
  - Post-breast conservation surgery, biopsy

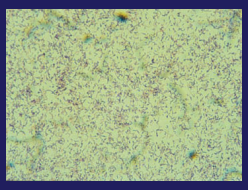
49

Erysipelothrix (Gram + rod)

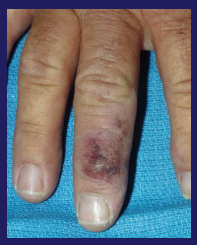
- On finger after cut/abrasion exposure to infected animal (swine) or fish
- Subacute erysipelas (erysipeloid)
- Severe throbbing pain
- Diagnosis: Culture of deep dermis (aspirate or biopsy)
- Treatment: Penicillin, cephalosporins, clindamycin, fluoroquinolone

50

Erysipelothrix rhusiopathiae Infection



Gram stain of the organism identified on culture



Resolving cellulitis caused by *Erysipelothrix rhusiopathiae*

51

Question #6

A 53 year old male construction worker has sudden onset of pain in his left calf. Within hours the skin and subcutaneous tissue of the calf are red, edematous and tender. Red "streaks" are seen spreading proximally

A short time later, patient is brought to the ER

Confused, vomiting, and hypotensive.

- Temp is 40C with diffuse erythema of the skin. Oxygen sat. 88% on room air
- WBC 3000 with 25% polys and 50% band forms. Platelet count is 60,000

(Continued)

52

Question #6 Continued

Which one of the following is the most likely complication of the erysipelas?

A. Bacteremic shock due *to S. pyogenes*?
B. Toxic shock due to *S. pyogenes*?
C. Bacteremic shock due to *S. aureus*?
D. Toxic shock due to *S. aureus*?

53

Toxic Shock Syn. (TSS): Staph vs Strep

Feature	Staphylococcal	Streptococcal
Predisposition	Tampon, surgery; colonization	Cuts, Burns, Varicella, erysipelas
Focal Pain	No	Yes
Tissue necrosis/inflammation	Rare	Common
N/V, renal failure/DIC	Yes	Yes
Erythroderma	Very common	Less Common
Bacteremia	Very rare	60%
Mortality	<3%	30-70%

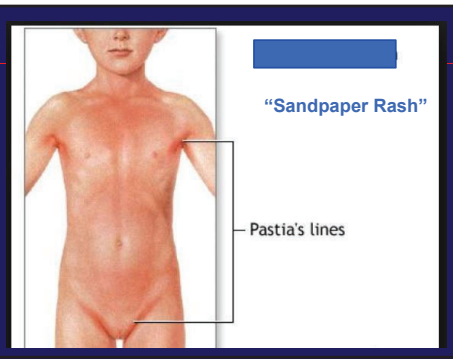
54

Sore throat and skin rash

- 20 year old man with 3 days of sore throat, fever, chills, and skin rash
- Rash is nonpruritic and involves abdomen, chest , back, arms ,and legs
- Exam: Exudative tonsillitis, strawberry tongue, rash, and tender cervical lymph nodes

55

56



57

The most likely diagnosis ?

- Infectious mononucleosis
- Coxsackie hand, foot and mouth disease
- Scarlet fever
- *Arcanobacterium hemolyticum*

58

Question 7:

- 18 year old male on anti- seizure meds for idiopathic epilepsy develops fluctuant tender furuncle on right arm
- He develops fever and generalized erythroderma; wherever he is touched, a bullous lesion develops
- Skin biopsy shows intra-epidermal split in the skin

59

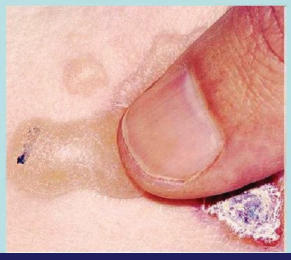
Question #7

Which one of the following is the likely etiology of the skin bullae?

A. *S. aureus* scalded skin syndrome?
B. Bullous pemphigus?
C. Drug-induced Toxic epidermal necrolysis (TEN)?
D. *S. pyogenes* necrotizing fasciitis?

60

Nikolsky sign

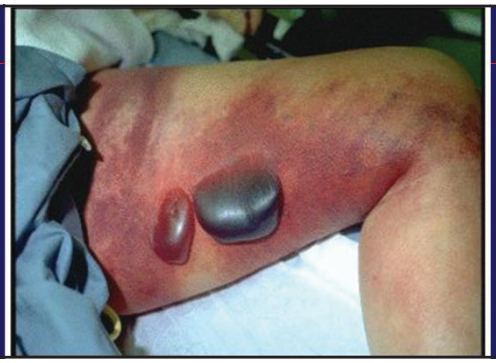


61

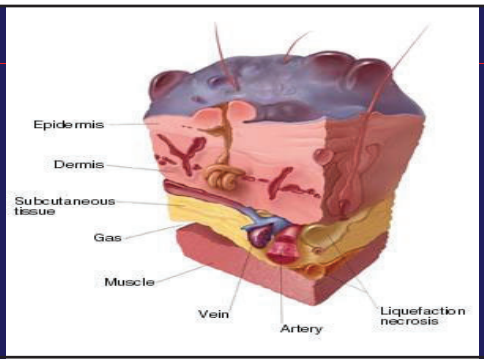
The Skin and Toxins of *S. aureus* and *S. pyogenes*

Organism	Toxin	Clinical Diagnosis
S.aureus colonization	TSST	TSS & Erythroderma
S. aureus colonization	Exfoliative toxin	Impetigo; scalded skin syndrome
Strept. pyogenes invasion	TSST	TSS; Erythroderma (not always)
Strept. pyogenes	Pyrogenic exotoxin	Pharyngitis; Scarlet Fever (sandpaper rash)

62



63



64

Erysipelas with loss of pain, hemorrhagic bullae, rapid progression..

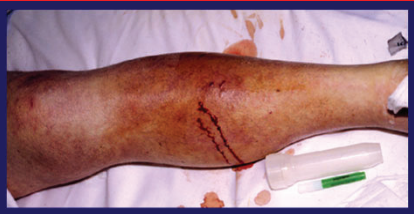
Necrotizing fasciitis due to which one ?

a. Streptococcal fasciitis
b. Staphylococcal fasciitis
c. Clostridial infection
d. Synergy between aerobe (*S.aureus, E.coli*) plus anaerobe (anaerobic strep, *Bacteroides sp*) equals Meleney's, Fournier's.

Lancet ID 2015;15:109

65

Necrotizing Fasciitis: at the bedside



Sudden onset excruciating pain & systemic toxicity
Note swelling of leg & 2 small purple bullae on anterior shin
Pressures in the anterior/lateral compartments (blood at needle entry) elevated; surgical exploration performed

66

Treatment of necrotizing fasciitis

- Think of it
- Surgical debridement: sometimes several times so as to achieve source control
- Appropriate antimicrobial therapy

67

Anatomy	Syndrome
Epidermis Skin Dermis	Erysipelas Impetigo Folliculitis Ecthyma Furunculosis Carbunculosis
	All of this is Cellulitis
Superficial fascia Subcutaneous tissue Subcutaneous fat, Nerves, arteries, veins Deep fascia	Necrotizing fasciitis
Muscle	Myonecrosis (clostridial and non-clostridial)

68

Question #8

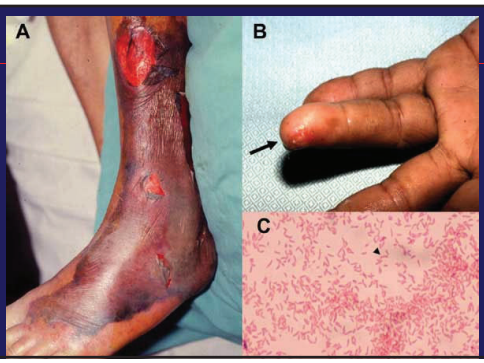
A 50-year-old male african american fisherman with known alcoholic cirrhosis suffers an abrasion of his leg while harvesting oysters.

Within hours, the skin is red, painful, and hemorrhagic bullae appear.

Which one of the following conditions predisposes to this infection?

A. G6PD Deficiency
B. Hemochromatosis
C. Sickle cell disease
D. Achlorhydria

69



70

Vibrio vulnificus

- Leading cause of shellfish(e.g., oysters)- associated deaths in USA
- Portal of entry: skin abasions or GI
- Liver disease, hemochromatosis, and exposure to estuaries are major risk factors
- Infected wounds manifest as bullae in 75%; primary bacteremia also occurs.
- Treatment (look up): doxy plus ceftriaxone (alternative is an FQ)

71

Organisms Whose Growth is Stimulated by Excess Iron

- *Vibrio vulnificus* **V**
- *Escherichia coli* **E**
- *Listeria monocytogenes* **L**
- *Aeromonas hydrophilia* **A**
- *Rhizopus species (Mucor)* **R**
- *Yersinia enterocolitica* **Y**

Definition: "The sails of a ship"

72

Thank You!

- David Gilbert

- Our patients and their families

73

Back up slides

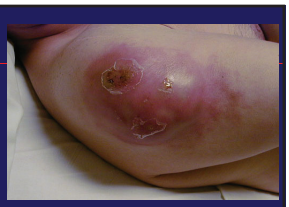
74

Common Masqueraders of Cellulitis

- Vascular Disorders
  - Superficial thrombophlebitis
  - Deep venuous thrombophlebitis
- Primary Dermatologic Disorders
  - Contact dermatitis
  - Insect stings or bites and other envenomations
  - Drug reactions
  - Eosinophilic cellulitis (Wells syndrome)
  - Sweet syndrome
- Rheumatic disorders
  - Gouty arthritis
- Immunologic-idiopathic disorders
  - Erythromelalgia
  - Relapsing polychondritis
- Malignant disorders
  - Carcinoma erysipelatoides
- Familial syndromes
  - Familial Mediterranean fever
  - Familial Hibernian fever
- Foreign-body reaction
  - Reaction to metallic implant
  - Mesh intolerance
  - Foreign-body granulomatous reactions

75

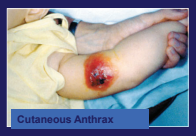
Skin Abscesses

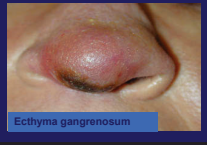


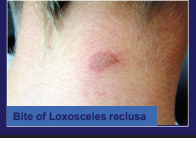
- Predisposing factors
  - *S. aureus* colonization
  - IV/SQ drug injection
  - Underlying diseases
    - DM, immunodeficiencies, etc
- Microbiology
  - *S. aureus: the vast majority*
  - Treatment: Drainage, antibiotics
  - Always cover *S. aureus.* Broad spectrum in special cases (septic IVDU)

76

CA-MRSA & CA-MRSA-Like Skin Lesions





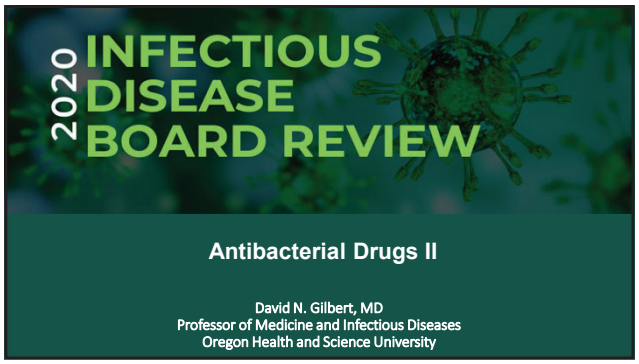


77

61

Antibacterial Drugs II

Dr. David Gilbert



Disclosures of Financial Relationships with Relevant Commercial Interests

- Consultant – Biomerieux, Biofire
- Research Grant – Biofire

Piperacillin-tazobactam

- Activity vs:
  - Enterobacteriaceae—Yes
    - Stable in presence of ESBLs—Variable
    - Stable in presence of Carbapenemases—No
  - *Ps.aeruginosa*—Yes, if…….
  - Anaerobic Gram Negative Bacilli—Yes

What is the ideal dose of Piperacillin-tazobactam ? It depends on:

- Targeted organism(s):
  - *Enterobacterales*—sensitive = MIC </= 8 ug/ml
  - *Ps. aerugi*nosa -----sensitive = MIC </= 16 ug/ml
- Volume of distribution: Increased if patient is septic, morbidly obese, on ECMO
- Target: Want protein-free time above MIC, fT> MIC, for at least 50% of the dosing interval
  - Probability of "target attainment" greatest with Continuous Infusion > Prolonged infusion> Intermittent Infusion

ProlongedDosing Piperacillin-tazobactam

- Vs. *Enterobacteriaceae*, normal renal function:
  - 3.375 gm IV over 30 minutes load, 4hrs later start 3.375 gm IV over 4 hrs and repeat q8h
- Vs. *Ps. aeruginosa*, normal renal function:
  - 4.5 gm IV load over 30 minutes, 4 hrs later start 4.5 gm IV over 4 hrs and repeat q8h
- Vs. Gram-negative bacilli and BMI > 30, normal renal function:
  - 4.5 gm IV load over 30 minutes, 4 hrs later start 6.75 to 9 gm IV over 4 hrs and repeat q8h

Piperacillin-tazobactam: AEs

- As for all beta-lactams:
  - Allergy, seizures, neutropenia, thrombocytopenia
  - Drug-drug interactions: Rare
- Pip-tazo:
  - Sodium overload--36-90 meq of sodium in a full daily dose ; can aggravate CHF management
  - Pseudo-enhancement of vancomycin-induced nephrotoxicity

Etiology of elevated Creatinine with Combination of P/T and Vancomycin

- RIFLE and KDIGO markers of AKI use serum creatinine as a surrogate for the GFR
- Creatinine is filtered by glomeruli and secreted by the renal tubules
- Known since 1980s that piperacillin competes with creatinine for tubular secretion
  - Shown in animals and humans
  - Increase in Creatinine does not reflect injured tubules
- Hence, elevation of the serum creatinine is expected
  - Similar to creatinine secretion blockade by trimethoprim, cimetidine, and selected antiretrovirals

* J. Clin Med 2019;8:781; J Antibiotics 1986; 39: 699; JAC 1994;34:555

Summary: Vanco:P/T as of 2020

- Vancomycin is potentially nephrotoxic
- Piperacillin-tazobactam alone has a very low potential to cause nephrotoxicity
- The reported increased ACUTE KIDNEY INJURY with V + P/T is at least partly due to the blockade of the renal tubular secretion of creatinine by piperacillin
- Current evidence would suggest that the combination of V+P/T is no more nephrotoxic than Vancomycin alone

Ampicillin-Sulbactam

- Activity vs.:
  - Enterobacterales—Yes, but decreasing
  - *Acinetobacter*—Sulbactam component yes (need high dose) and combination therapy
  - Anaerobic GNBs— Activity Equivalent to Pip/tazo
- Dose for sulbactam component for Acinetobacter* : 4 hr IV infusion of 9 gm of Amp-Sulb (6 gm Amp +3 gm Sulb) q8h

European J of Pharm. Sci. 2019; 136:104940

Cephalosporin "Generations"

Generation	Spectrum	Comment
First (Cefazolin)	*MSSA; E.coli, Kleb.sp.*	No activity versus enterococci
Second(Cefoxitin, Cefotetan)	Originally *Bacteroides fragilis*	*B.fragilis* resistance increasing
Third(Ceftriaxone[ctx])	Most of the aerobic GNBs: Enterobacterales	"Extended spectrum"
Fourth (Ceftazidime; Cefepime)	Antipseudomonal	Cefepime not porin dependent
Fifth (Ceftaroline)	Like CTX + MRSA	No act. enterococci
Sixth (Ceftolozane/Tazo)	ESBL producing GNBs	No activ. Vs. Bacteroides species
Seventh (Ceftaz/Avibactam)	(ESBL producing GNBs) & KPCs	Inconsistent activity vs Bacteroides

Cephalosporin "Generations"

Generation	Spectrum	Comment
Eighth: Cefiderocol	Metallo-Carbapenemase produced by Enterobacterales and Non-fermenters*	No activity vs Gram positives and anaerobic bacteria

* Non-fermenters: *Ps.aeruginosa, A. baumannii, Stenotrophomonas maltophila*

To survive bacteria are constantly mutating

- More than 2800 beta-lactamases reported
- Promiscuity among bacteria is rampant
- Not unusual to have additional mechanisms of resistance: e.g.,
  - Target change
  - Active efflux pumps
  - Decrease in permeability
  - Mechanisms of "R" not defined by phenotypic suscept. testing
- IF patient fails clinically and/or failure to eradicate pathogen, strongly consider whole genome sequencing
- NO surprise, hard to create "resistance " test questions

Ambler Molecular Classificaton of Beta-Lactamases*

Class	Subtypes	Inhibitor ??	Substrates
A	ESBLs KPCs;serine carbapenemases	Clavulanic Avibactam & Vaborbactam	ESCs Carbapenems
B (BAD!)	Metallo-carbapenemases	EDTA(lab testing only)	All beta-lactams except aztreonam & Cefiderocol
C	AmpC	None	Cephalosporins
D	Oxacillinase-48 Some ESBLs Serine carbapenemases (e.g., KPCs)	None Clavulanic Avibactam & Vaborbactam	Penicillins, Carbapenems, ESCs, & Aztreonam ESCs and Carbapenems

*Ambler: Based on nucleotide sequencing

Ceftriaxone "R" Enterobacterales

- 25% "R" of organisms in the order Enterobacterale worldwide; In Asia, 50% of *E.coli* are CTX resistant
- Most common mechanism of resistance:
  - Production of Extended spectrum beta-lactamases (ESBLs)
    - Phenothypic Dx: In vitro "R" to ceftriaxone and aztreonam; Lower MIC with clavulanic acid
  - If *Enterobacter species detected*: Production of Amp C cephalosporinases is the major concern
  - Carbapenems effective in presence of both ESBLs and AmpC enzymes
    - Are there any "carbapenem sparing" cephalosporins for ESBLs ?

MERINO Trial: P/T vs Mero for *E.coli*, *K.pneumoniae* ESBL Producers

- Design: PRDB.* 72 hrs from pos.culture to enroll; 30 minute infusions
- Endpoint: 30 day all cause mortality:
  - Piperacillin-tazobactam: 12.3 %
  - Meropenem: 3.7 %
- Issues:
  - Breakpoints/inoculum effect for P/T
  - Co-production of ESBL and oxacillinase
- Three confirmatory controlled trials in progress

* PRDB=Prospective Randomized Double-Blind

Collateral Damage from Carbapenem Therapy

- Selection of Carbapenem "R" strains of Enterobacterales, and/or Non-Fermenters (e.g., *Stenotrophomonas*)
- Selection of vanco "R" enterococci, MRSA, Candida species
- Nonetheless, based on the MERINO trial, Meropenem is Drug of Choice for treatement of ESBL producing *Enterobacterales*

Carbapenem Sparing Cephalosporins Active vs GNB producing ESBLs and/or AmpC

Cephalosporin active Vs:		
	AmpC producers	ESBL producers
Ceftazidime	Variable	Variable
Cefepime	If low MIC ; Big dose	If low MIC; Big dose
Ceftolozane-tazobactam	YES	YES
Ceftazidime-avibactam	YES (OK; $$$$$)	YES (OK; $$$$$)
Cefiderocol	YES (BIG OK; $$$$$)	Yes (BIG OK; $$$$$)

OK = OVERKILL

Reference: Curr Opin Infect Dis 2020;33: 78

Oral "Carbapenem-Sparing" Antibiotics for ESBL Producing Bacteria Causing UTI

- **F**osfomycin
- **A**moxicillin-clavulanate
- **N**itrofurantoin

Testable Cephalosporin AEs

- Allergy: Ceftazidime and Aztreonam have same side chain
- Ceftriaxone: Pseudo-cholelithiasis
- Cefepime: Non-convulsive status epilepticus
- No Drug-Drug interactions

Carbapenems: Spectrum

Active versus:	NOT ACTIVE versus
Enterobacterales +/- ESBLs	*MRSA*
*Pseudomonas aeruginosa**	*Stenotrophomonas maltophila*
Bacteroides fragilis	
Enterococcus faecalis	*Enterococcus faecium*
Listeria monocytogenes	*Acinetobacter (variable)*

*Resistance can emerge during therapy via porin closure and efflux pumps or acquisition of carbapenemase

Carbapenem Family

Carbapenem	Comment(s)
Imipenem-cilastatin	Avoid in meningitis patients: seizure potential
Meropenem	Less potential for inducing seizures
Ertapenem	Not active vs *Ps.aeruginosa*; Once daily therapy
Doripenem	↑mortality vs Imipenem in VAP trial
Meropenem-vaborbactam and Imipenem-cilastatin-relebactam	Active vs *Klebsiella* producing carbapenemases (KPCs); Not active vs metallo or Oxa 48 carbapenemases

FDA Approved Beta-Lactam Beta-Lactamase Inhibitor Combinations

Penicillins	Cephalosporins	Carbapenems
Amoxicillin-clavulanate	Ceftolozane-tazobactam	Meropenem-vaborbactam
Ampicillin –sulbactam	Ceftazidime-avibactam*	Imipenem-cilastatin-relebactam
Piperacillin-tazobactam		

Note: so far 6 Beta-lactam inhibitors and none inhibit class B metallo-carbapenemases

* Only avibactam inhibits chromosomally-mediated AmpC ESBLs

The Major Families of Carbapenemases

Non-Metallo (Serine at active site)	Metallo (Zinc at active site): VIN
KPC (Class A)	VIM (Class B)
OXA-48 et al (Class D)	IMP (Class B)
	New Dehli Metallo- Blasé (Class B)

KPC=Klebsiella-producing carbapenemases; OXA=oxacillinase; IMP=Imipenemase; VIM=Verona integron-encoded metallo Blamase; NDM= New Dehli metallo

Ambler Classification of Beta-Lactamases

Ambler Group	A	B	C	D
Binding Site	Serine	Metallo	Serine	Serine
Enzymes	ESBLs;KPCs	Carbapen-ase	Cephalo-ase	Oxacil—ase/Carba
TREATMENT:				
Ceftaz.-avi*	+	---	+	+(Oxa-48)
Mero-vabor*	+	---	+	---
Imi-relebact	+	---	+	---
Ceftaz-avi+AZ	+	+	+	+
Cefepime	---	---	---	+(Oxa)
Cefiderocol	+	+	+	+

*Active vs Ceftaz-avi resistant KPCs

ARQ #1

- 60 y.o. female smoker, admitted, intubated, and ventilated due to severe COPD with Acute Respiratory Failure.
- Chest X-Ray: New bibasilar infiltrates and Emphysema
- Empiric ceftriaxone and azithromycin
- Sputum positive for both rhinovirus and *Klebsiella pneumoniae* resistant to both ceftriaxone and azithromycin
- Also "R" to: all fluoroquinolones, aminoglycosides, pip/tazo, and all carbapenems

ARQ #1

- Which one of the following antibiotics would you select for this KPC infection ?
  - A. Tigecycline
  - B. Ceftazidime-avibactam
  - C. Aztreonam
  - D. Ceftolozane-tazobactam

Treatment of Carbapenem Resistant Enterobacteriaceae (CRE)

- *Klebsiella (or E. coli)* producing carbapenemase (KPC) most common
- Serine based as opposed to metallo-carbapenemase
- Serine Enyzme activity blocked by avibactam and vaborbactam; hence protects activity of : Ceftazidime-avibactam and Meropenem-vaborbactam
- Concomitant ESBLs inactivate aztreonam
- Tigecycline failures in pneumonia patients
- Ceftolozane-tazobactam is stable in presence of ESBLs but is hydrolyzed by KPCs

Beta-Lactam Treatment of Carbapenemase Producing GNBs

- Class A (KPCs-Klebsiella-Producing Carbapenemases):
  - Ceftazidime-avibactam
  - Meropenem-vaborbactam; Imipenem-cilastatin-relebactam
  - Cefiderocol
- Class B (Metallo-carbapenemases):
  - Ceftazidime-avibactam + Aztreonam
  - Cefiderocol
- Class C(cephalosporinases): Carbapenem
- Class D (OXA-type) carbapenemases (heterogeneous and low level enzymatic hydrolysis)
  - May be susceptible to ceftazidime and cefepime.
  - Ceftazidime –avibactam. Interest in combination therapy.
  - Not currently testable!

AZTREONAM (monobactam)

- Only beta-lactam with NO activity vs. Gram positive bacteria: e.g., *S. pneumoniae !!!!!!!!!*
- Safe with IgE mediated Pen/Ceph.allergy & aerobic GNB infection; cross allergenicity with ceftazidime
- In vitro resistance of GNB to aztreonam is a phenotypic marker for production of ESBLamases
- Stable in presence of metallo-carbapenemases; however, inactivated by concomitant ESBLs
- Use Ceftazidime-avibactam plus aztreonam to treat GNB co-producing ESBL and metallo-Carbapenemase

Aztreonam and Carbapenemases

Active versus:	NOT active versus:
Metallo-Carbapenemases (Gp B)	Klebsiella-producing Carbapenemases (KPCs)(Gps A & D)
Enterobacterales(if no ESBLs)	ESBL producers
Pseudomonas aeruginosa	*Acinetobacter; Stenotrophomonas*

Cefiderocol

- First cephalosporin stable in presence of GNB producing metallo-beta-lactamases
- "For complicated UTI due to susceptible GNB with no other treatment options"
- Spectrum of activity:
  - XDR Enterobacterales
  - XDR Non-fermenters (Steno, Pseudo, Acineto)
  - No activity vs gram + bacteria or anaerobic bacteria

Cefiderocol

- Clinical studies:
  - Microbial eradication: Imipenem 56% ; Cefiderocol 73%
  - Day 14 mortality: Best available therapy 12 %; Cefiderochol 25%
- Has catechol side chain that utilizes iron transport system (siderophore). "Trojan horse"
- No serious AE , so far: GI 2-4%, C.difficile, Seizures
- For salvage therapy when no other option available

Fluoroquinolones

Finally, beyond beta-lactams.

Fluoroquinolones (FQs)

- Family: Ciprofloxacin, Levofloxacin, Moxifloxacin, Delafloxacin
- The GOOD: Broad Spectrum of Activity, Large volume of distribution, High oral bioavailability
- The BAD: Increasing "R", Serious AEs(C.diff.) Many Drug-Drug interactions; 2016 FDA Safety Warning.
- Conclusions:
  - Uncomplicated infections(bronchitis)---AVOID
  - Severe infections---RISK vs Benefit

FQ Selected Activity(0-4+)

Bacteria	Ciprofloxacin: BID	Levofloxacin: Once daily	Moxifloxacin: Once daily	Delafloxacin: Once daily
Enterobacterale	4+	3+	3+	3+
Ps.aeruginosa	4+	2+	0	2+
Acineto; Steno	0	0	0	?
MRSA	0	0	0	4+(20% "R"
Anaerobes	0	0	4+	2+
Mycobacteria	0	4+	4+	0
Anthrax;*Sal.typhi*	4+	4+	4+	4+

Resistance ("R") to FQs

- Antibacterial due to blockade of DNA replication via binding to DNA Gyrase and Topoisomerase enzymes
- Multiple mech. Of "R":
  - Mutations of enzyme targets
  - Efflux pumps, altered cell wall permeation
  - Target protective proteins, drug acetylation
- Concomitant "R" of GNB to beta-lactams via:
  - Production of ESBLs
  - Production of Carbapenemases

FQ Pharmacology

- Parenteral:
  - Higher doses for *Ps.aeruginoa*
  - Excreted in urine
  - High concentrations in prostate
- Oral:
  - Bioavailability of 59-95%
  - Chelation by divalent cations decreasing bioavailibility:
    - Calcium
    - Iron
    - Zinc, Magnesium, Aluminum

FQ Adverse Events

- *Clostridioides difficle* (the leader) colitis
- Neurologic
  - Confusion, delirium, seizures (GABA blockade)
  - Peripheral neuropathy
  - Exacerbate myasthenia gravis
- Cardiovascular
  - Prolongation of QTc !!!
  - Aortic aneurysm and dissection
- Tendonopathy/Arthropathy
- Dysglycemic

QTc Prolongation: Potential Risk with all FQs except Delafloxacin

- >500 msec. or > 60 msec prolongation from baseline increases risk of torsades de pointes & ventricular fibrillation.
- Low serum K and/or Mg ; Concomitant drugs increase risk: e.g., mefloquine, haldol, fosphenytoin.
- None of FQs are high risk used alone; problem: concomitant drugs (cytochrome P-450 inhibition), electrolyte abnormalities.

Tetracyclines: The Family

- Doxycyline (Many indications)
- Minocycline(Many indications)
- Tigecycline (Don't use)
- Omadacycline(SSTIs, CABP)
- Eravacycline (cIAIs)

Tetracycline Activity Spectrum

Bacteria	Doxycycline	Minocycline	Omadacycline	Eravacycline
Aerobic GPCs	+	+	+	+
MRSA	+	+	+	+
Aerobic GNB	+	+	+	+
Rickettsial	+	+	+	+
Spirochetal*	+	+	+	+
Plasmodia	+	?	?	?
Ps.aeruginosa	0	0	0	0
Acineto/Steno.	0	Variable	+	+

*Borrelia, Treponema, Leptospira

Tetracyclines: Mechanism & "R"

- Antibacterial Mechanism:
  - Binds 30S ribosome, inhibits protein synthesis, Bacteriostatic
- Mechanisms of Resistance:
  - Reduced permeability and/or increased efflux
  - Blockade of ribosome binding site by protection proteins

Tetracycline Pharmacology

- Oral absorption impaired by multivalent cations
- Distribution largest with minocycline (greatest lipid solubility)
- Distribution and Tigecycline:
  - High intracellular levels; very low extracellular concentrations
  - FDA review found increased mortality
  - "Only use when no other option"
- Avoid in pregnancy and children < 8 y.o.

Tetracycline Pharmacology

- Oral absorption impaired by multivalent caions
- Distribution largest with minocycline (greatest lipid solubility)
- Distribution and Tigecycline:
  - High intracellular levels; very low extracellular concentrations
  - FDA review found increased mortality
  - "Only use when no other option"
- Avoid in pregnancy and children < 8 y.o.

Tetracycline Adverse Effects

- *Clostridioides difficile* colitis
- Photosensitivity
- Hepatotoxicity: minocycline; pregnancy
- Nephrogenic diabetes insipidus due to demeclocycline (for SIADH)
- Spirochetal infections and Jarisch-Herxheimer reactions
- Vertigo: Minocycline

Tetracyclines: In Vitro Activity versus MDR GNB

Bacteria	Minocycline	Omadacycline	Eravacycline
ESBL producers	0	+	+
KPCs	0	+	+
Metallo-Carbapen.	0	+	+
Acinetobacter	Variable	+	+
Stenotropho.	+	+	+

Aminoglycoside Family

- Amikacin
- Gentamicin
- Streptomycin
- Plazomicin
- Tobramycin

AG: Spectrum of Activity

- Active vs.:
  - Aerobic gram-negative bacteria
  - Typical and atypical mycobacteria
  - Variable: *Ps.aeruginosa, S. aureus* X 24 hrs
- No activity vs.:
  - Gram-positive cocci: e.g., *S.pneumoniae*
  - Anaerobic bacteria
  - Non-fermenters: *Acinetobacter sp., Stenotrophomonas maltophilia*
- Often part of combination therapy

AG: Mech. of Action & "R"

- Binds to 30s ribosome; Concentration-dependent Bactericidal activity
- Multiple mechanisms of resistance:
  - Most Frequent
    - Enzymatic alteration of drug: adenyl., acetyl., phosporyl.
      - Plazomicin not susceptible to enzymatic attack
    - Methylation of ribosomal binding site
  - Less Common
    - Efflux pump
    - Porin closure
- Bacteria "R" to beta-lactams often have concomitant "R" to AGs

AG: Pharmacology

- Basis of once daily dosing:
  - Concentration dependent cidal activity
  - Long post-antibiotic effect
- Result is improved antibacterial activity and less risk of toxicity
- EXCEPTION: Combination therapy of enterococcal endocarditis

AG: Shared Adverse Effects

- Nephrotoxicity: Acute tubular necrosis
- Ototoxicity:
  - Cochlear (genetic predisposition & non-reversible)
  - Vestibular (irreversible but host can compensate)
- Neuromuscular blockade (neomycin)

Polymyxin Family

- Polymyxin B
- Polymyxin E (Colistin)

Polymyxins: Mechanisms of "R"

- Mechanism:
  - Binds to LPS & Phospholipids of cell wall of GNB
  - Displaces divalent cations; resulting membrane disruption, and bactericidal activity
- Resistance is increasing, esp. Carbapenemase producing GNBs
  - Due to LPS target change and efflux pumps
  - Plasmid spread of mcr-1 gene
- Guideline reference: Pharmacotherapy 2019;39: 10

Activity vs Aerobic GNB

- Susceptible: *Enterobacterales, ESBLs, KPCs, non-fermenters (Acinetobact., Stenotroph., Ps. Aeruginosa*
- Intrinsic Resistance: M—*Moraxella*
  - *a----a vowel*
  - *P---Proteus*
  - *P---Providencia*
  - *S---Serratia*
- All gram + bacteria are "R"

Polymyxin Pharmacology

- Polymyxin B
  - Uncomplicated dosing
  - Non-renal clearance
  - Drug of choice except for UTI
- Colistin (pro-drug)
  - Complicated dosing
  - Renal excretion
    - Use for UTIs
    - Adjust dose for renal insufficiency
- Often used as part of combination therapy

Polymyxins: Adverse Effects

- Nephrotoxicity. Lower risk with polymyxin B
- Neurotoxicity. Wide range of problems:
  - Dizziness
  - Paresthesias
  - Vertigo
  - Confusion
  - Ataxia
  - Neuromuscular blockade

Trimethoprim-Sulfamethoxazole

- Mechanism of action:
  - Sequential blockade of two enzymes needed to synthesize folate
- Broad spectrum---Activity vs. GNB:
  - Enterobacterales
  - Non-Fermentative GNBs: *Burkholderia and Stenotrophomonas.*
    - *No activity vs Ps.aeruginosa*
    - Also , no activity vs:*Mycoplasma, Francisella tularensis, and Bacteroides fragilis*

TMP/SMX: Pharmacology

- Widely distributed to include CSF and Prostate
- Renal excretion by both tubular secretion and glomerular filtration
- Lots of Drug-Drug interactions

TMP/SMX: Adverse Effects

- Hyperkalemia due to TMP and /or ACEIs/ARB due to interference with tubular secretion
- Neutropenia
- Promotes folate deficiency; Dangerous in pregnancy----neural tube defects
- Derm.: Stevens Johnson syndrome; toxic epidermal necrolysis
- Aseptic meningitis

Nitrofurantoin for uncomplicated *E.coli* UTI*

- Pulmonary toxicity with chronic therapy: desquamative interstitial pneumonia with fibrosis
- Intrahepatic cholestasis and hepatitis
- DRESS syndrome: drug rash, eosinophilia, & systemic symptoms

*Cystitis only

Metronidazole

- Antibacterial and anti-protozoan activity requires a strict anaerobic environment
- "Gold Standard" for treatment of *Bacteroides species*
  - Other Drugs active vs *B.fragilis*: Pip/tazo, Amp/sulb, and Carbapenems
- Other clinical Indications: Bacterial vaginosis, Amebiasis, Giardiasis, and *Trichomonas vaginitis*
- Metro. "R" Anaerobes: *P. (Cutibacterium) acnes, Peptostreptococci, Eikenella* and *Actinomyces*

Metronidazole: Adverse Effects

- Metallic taste; "furry" tongue
- Disulfiram reaction (N/V, flushing, tachycardia, dyspnea) after alcohol
- Prolonged use: peripheral, autonomic , and/or optic neuropathy
- Aseptic meningitis
- After 3 weeks: confusion and cerebellar dysfunction

Is the patient's encepalopathy due to your antibiotic therapy ?

Antibiotic	Time to onset	Syndrome
Beta-Lactams	Within days *	Seizures; abnormal EEG
FQs, Macrolides	Within days	Delusions/Hallucinations; normal MRI
Metronidazole	Weeks	Cerebellar dysfunction with abnormal MRI

* High serum concentrations due to renal insufficiency
Reference: Neurology 2016; 86:963