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AGENDA
Saturday, August 21, 2021

AM Moderator: Masur
PM Moderator: Gilbert

#	Start		End	Presentation	Speaker
1	9:30 AM	-	10:00 AM	**Introduction**	*John Bennett, MD and Henry Masur, MD*
2	10:00 AM	-	10:15 AM	**How to Prepare for the Certification, Recertification, or Check-in Exam**	*Helen Boucher, MD*
3	10:15 AM	-	10:45 AM	**Preview Day 1**	*Henry Masur, MD*
4	10:45 AM	-	11:30 AM	**Core Concepts: Microbiology: What You Need to Know for the Exam**	*Robin Patel, MD*
5	11:30 AM	-	11:45 AM	**Microbiology Questions that Could Be on the Exam**	*Robin Patel, MD*
	11:45 AM	-	12:15 PM	***BREAK with FACULTY CHAT***	
6	12:15 PM	-	1:00 PM	**Core Concepts: Antibacterial Drugs I:**	*David Gilbert, MD*
7	1:00 PM	-	1:15 PM	**Antibacterial Drugs I: Key Points and Questions that Could be on the Exam**	*David Gilbert, MD*
8	1:15 PM	-	2:00 PM	**Board Review Day 1**	*Drs. Masur (Moderator), Bell, Bennett, Boucher, Gandhi, Gilbert, Patel, and Winthrop*
9	2:00 PM	-	2:45 PM	**Core Concepts: Antibacterial Drugs II**	*Helen Boucher, MD*
10	2:45 PM	-	3:00 PM	**Antibacterial Drugs II: Key Points and Questions that Could Be On The Exam**	*Helen Boucher, MD*
	3:00 PM	-	3:30 PM	***BREAK with FACULTY CHAT***	
11	3:30 PM	-	4:15 PM	**Core Concepts: Antifungal Drugs**	*John Bennett, MD*
12	4:15 PM	-	4:45 PM	**Core Concepts: Antiviral Drugs**	*Andrew Pavia, MD*
	4:45 PM	-	5:15 PM	***BREAK with FACULTY CHAT***	
13	5:15 PM	-	5:45 PM	**Nontuberculous Mycobacteria in Normal and Abnormal Hosts**	*Kevin Winthrop, MD*
14	5:45 PM	-	6:15 PM	**Syndromes in the ICU that ID Physicians Should Know**	*Taison Bell, MD*
15	6:15 PM	-	7:00 PM	**Photo Opportunity I: Photos and Questions to Test Your Board Preparation**	*Rajesh Gandhi, MD*
16	7:00 PM	-	7:30 PM	**Skin and Soft Tissue Infections**	*Helen Boucher, MD*
	7:30 PM	-	8:00 PM	***END OF THE DAY FACULTY CHAT***	

Sunday, August 22, 2021

AM Moderator: Pavia
PM Moderator: Masur

#	Start		End	Presentation	Speaker
17	9:30 AM	-	10:00 AM	**Daily Question Preview Day 2**	*Andrew Pavia, MD (Moderator)*
18	10:00 AM	-	11:00 AM	**Clinical Immunology and Host Defense**	*Steven Holland, MD*
19	11:00 AM	-	11:45 AM	**Respiratory Viral Infections including Influenza, Immunocompetent, and Immunocompromised Patients**	*Andrew Pavia, MD*
	11:45 AM	-	12:15 PM	***BREAK with FACULTY CHAT***	
20	12:15 PM	-	1:00 PM	**Board Review Day 2**	*Drs. Pavia (Moderator), Aronoff, Chambers, Nelson and Trautner*
21	1:00 PM	-	1:45 PM	**Bone and Joint Infections**	*Sandra Nelson, MD*
22	1:45 PM	-	2:30 PM	**Photo Opportunity II: More Photos and Questions to Test Your Board Preparation**	*John Bennett, MD*
	2:30 PM	-	3:00 PM	***BREAK with FACULTY CHAT***	
23	3:00 PM	-	4:00 PM	**Endocarditis of Native and Prosthetic Devices, and Infections of Pacers and Ventricular Assist Devices**	*Henry Chambers, MD*
24	4:00 PM	-	4:45 PM	**Zoonoses**	*David Aronoff, MD*
25	4:45 PM	-	5:00 PM	**Penicillin Allergies**	*Sandra Nelson, MD*
	5:00 PM	-	5:30 PM	***BREAK with FACULTY CHAT***	
26	5:30 PM	-	6:15 PM	**Staphylococcal Disease**	*Henry Chambers, MD*
27	6:15 PM	-	6:45 PM	**Helicobacter and Clostridioides Difficile**	*David Aronoff, MD*
28	6:45 PM	-	7:30 PM	**HIV-Associated Opportunistic Infections I**	*Henry Masur, MD*
	7:30 PM	-	8:00 PM	***END OF THE DAY FACULTY CHAT***	

Monday, August 23, 2021

AM Moderator: Whitley
PM Moderator: Bennett

#	Start		End	Presentation	Speaker
29	9:30 AM	-	10:00 AM	**Daily Question Preview Day 3**	*Richard Whitley, MD (Moderator)*
30	10:00 AM	-	10:30 AM	**Sexually Transmitted Infections: Genital Ulcers Diseases (GUD)**	*Khalil Ghanem, MD*
31	10:30 AM	-	11:00 AM	**CMV, EBV, HHV6 and HHV8 in Immunocompetent and Immunocompromised Patients**	*Camille Kotton, MD*
	11:00 AM	-	11:30 AM	***BREAK with FACULTY CHAT***	
32	11:30 AM	-	12:30 PM	**Sexually Transmitted Infections: Other Diseases and Syndromes**	*Khalil Ghanem, MD*
33	12:30 PM	-	1:00 PM	**HSV and VZV in Immunocompetent and Immunocompromised Hosts**	*Richard Whitley, MD*
34	1:00 PM	-	1:45 PM	**Board Review Day 3**	*Drs. Whitley(Moderator), Kotton, Dhanireddy, Ghanem, Rose, Thomas, and Tunkel*
	1:45 PM	-	2:15 PM	***BREAK with FACULTY CHAT***	
35	2:15 PM	-	3:00 PM	**Kitchen Sink: Syndromes Not Covered Elsewhere**	*Stacey Rose, MD*
36	3:00 PM	-	4:00 PM	**Immunizations: Domestic, Travel, and Occupational**	*Shireesha Dhanireddy, MD*
37	4:00 PM	-	4:45 PM	**Acute Hepatitis**	*David Thomas, MD*
	4:45 PM	-	5:15 PM	***BREAK with FACULTY CHAT***	
38	5:15 PM	-	5:45 PM	**Viral and Bacterial Meningitis**	*Allan Tunkel, MD*
39	5:45 PM	-	6:45 PM	**Chronic Hepatitis**	*David Thomas, MD*
40	6:45 PM	-	7:15 PM	**Brain Abscess, Cavernous Sinus Thrombosis, and Subdural and Epidural Empyema**	*Allan Tunkel, MD*
	7:15 PM	-	7:45 PM	***END OF THE DAY FACULTY CHAT***	

Tuesday, August 24, 2021

AM Moderator: Gulick
PM Moderator: Masur

#	Start		End	Presentation	Speaker
41	9:30 AM	-	10:00 AM	**Daily Question Preview Day 4**	*Roy Gulick, MD (Moderator)*
42	10:00 AM	-	10:30 AM	**Gastrointestinal Disease: Clinical Syndromes**	*Herbert Dupont, MD*
43	10:30 AM	-	11:15 AM	**Clinical Manifestations of Human Retroviral Diseases and Slow Viruses**	*Frank Maldarelli, MD*
44	11:15 AM	-	11:45 AM	**Gastrointestinal Disease: Etiologic Agents**	*Herbert Dupont, MD*
	11:45 AM	-	12:15 PM	***BREAK with FACULTY CHAT***	
45	12:15 PM	-	12:30 PM	**HIV Diagnosis**	*Frank Maldarelli, MD*
46	12:30 PM	-	1:15 PM	**Antiretroviral Therapy**	*Roy Gulick, MD*
47	1:15 PM	-	1:30 PM	**HIV Drug Resistance**	*Michael Saag, MD*
48	1:30 PM	-	2:00 PM	**Antiretroviral Therapy for Special Populations**	*Roy Gulick, MD*
	2:00 PM	-	2:30 PM	***BREAK with FACULTY CHAT***	
49	2:30 PM	-	3:15 PM	**Board Review Session 4**	*Drs. Gulick (Moderator), Bloch, Dorman, Dupont, Maldarelli, Saag, and Weinstein*
50	3:15 PM	-	4:00 PM	**Syndromes that Masquerade as Infections**	*Karen Bloch, MD*
51	4:00 PM	-	4:45 PM	**Tuberculosis in Immunocompetent and Immunosuppressed Hosts**	*Susan Dorman, MD*
	4:45 PM	-	5:15 PM	***BREAK with FACULTY CHAT***	
52	5:15 PM	-	6:00 PM	**Non AIDS-Defining Complications of HIV/AIDS**	*Michael Saag, MD*
53	6:00 PM	-	7:00 PM	**Hospital Epidemiology**	*Robert Weinstein, MD*
54	7:00 PM	-	7:15 PM	**Pharyngitis Syndromes Including Group A Strep Pharyngitis**	*Karen Bloch, MD*
	7:15 PM	-	7:45 PM	***END OF THE DAY FACULTY CHAT***	

Wednesday, August 25, 2021

AM Moderator: Marr
PM Moderator: Auwaerter

#	Start		End	Presentation	Speaker
55	9:30 AM	-	10:00 AM	**Daily Question Preview Day 5**	*Kieren Marr, MD (Moderator)*
56	10:00 AM	-	11:15 AM	**Infections in the Neutropenic Cancer Patient and Hematopoietic Stem Cell Recipients**	*Kieren Marr, MD*
57	11:15 AM	-	12:00 PM	**Fungal Disease in Normal and Abnormal Hosts**	*John Bennett, MD*
	12:00 PM	-	12:30 PM	***BREAK with FACULTY CHAT***	
58	12:30 PM	-	1:30 PM	**Infections in Solid Organ Transplant Recipients**	*Barbara Alexander, MD*
59	1:30 PM	-	2:00 PM	**Pneumonia: Some Cases that Could be on the Exam**	*Paul Auwaerter, MD*
60	2:00 PM	-	2:45 PM	**Board Review Session 5**	*Drs. Auwaerter (moderator), Alexander, Bennett, Marr, and Mitre*
	2:45 PM	-	3:15 PM	***BREAK with FACULTY CHAT***	
61	3:15 PM	-	4:15 PM	**Ticks, Mites, Lice and the Diseases They Transmit**	*Paul Auwaerter, MD*
62	4:15 PM	-	5:15 PM	**Worms and More Worms**	*Edward Mitre, MD*
	5:15 PM	-	5:45 PM	***BREAK with FACULTY CHAT***	
63	5:45 PM	-	6:15 PM	**Lyme Disease**	*Paul Auwaerter, MD*
64	6:15 PM	-	7:15 PM	**Lots of Protozoa**	*Edward Mitre, MD*
	7:15 PM	-	7:45 PM	***FINAL FACULTY CHAT***	

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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

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 2021**."
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/IDBR2021.
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 2021 IDBR App

Make the Most of Your On-Site Experience!*

Notetaking & Bookmarking
Annotate directly on audio synced 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!

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

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CLICK to launch.
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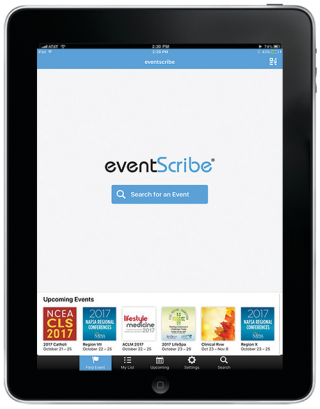

Search for an Event

Search:
2021 IDBR

2. Login to your event's App.

INFECTIOUS DISEASE BOARD REVIEW
AUGUST 21 – 25
TWENTY TWENTY-ONE
IDBR 2021

To start using the app, Login using your email address and badge number.

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!
If you have a laptop, you can access the presentations here:
https://tinyurl.com/IDBR2021

Instructions to Create an EthosCE User Account

EthosCE

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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
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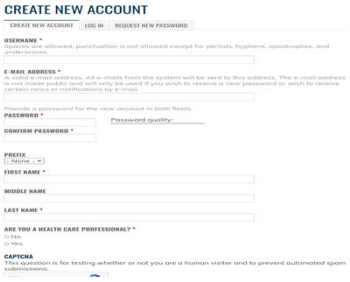
smhs.gwu.edu

EthosCE User Account



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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 - 71 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, 2021** in order **for the MOC points to count toward any MOC requirements that are due by the end of 2021.**

CEHP will continue to submit participant completion data for the course until **August 16, 2022**. **No ABIM MOC credit will be awarded for this activity after August 16, 2022**.

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 71 *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 71 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 71 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, 2021** in order **for the MOC points to count toward any MOC requirements that are due by the end of 2021.**

CEHP will continue to submit participant completion data for the course until **August 16, 2022. No ABIM MOC credit will be awarded for this activity after August 16, 2022**.

OVERVIEW OF ONLINE MATERIALS AND INSTRUCTIONS FOR CLAIMING CREDIT AND MOC

Online Only Lectures	CME Hours: 4	MOC Points: 4
• 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.		

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.

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

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

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 L. 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

Steven M. Holland, MD*
Bethesda, Maryland

Camille Kotton, MD
Harvard Medical School
Boston, Massachusetts

Frank Maldarelli, MD, PhD*
Bethesda, Marylan

Edward Mitre, MD
Bethesda, Maryland

Sandra Nelson, MD
Massachusetts General Hospital
Boston, Massachusetts

Stacey Rubin Rose, MD
Baylor College of Medicine
Houston, Texas

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

Barbara W. Trautner, MD, PhD
Baylor College of Medicine
Houston, Texas

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)

- Taison Bell, MD
- Karen C. Bloch, MD, MPH, FIDSA, FACP
- Shireesha Dhanireddy, MD
- Susan Dorman, MD
- Herbert L. Dupont, MD
- Rajesh Gandhi, MD
- Khalil G. Ghanem, MD
- Roy M. Gulick, MD, MPH
- Steven M. Holland, MD
- Frank Maldarelli, MD
- Edward Mitre, MD
- Sandra Nelson, MD
- Stacey R. Rose, MD, FACP
- 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

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The following faculty members (speakers) disclosed commercial relationships:

FACULTY MEMBER (Speaker)	FINANCIAL DISCLOSURE(S)
Paul G. Auwaerter, MD	• Consulting: Pfizer, EMD Soreno, Medical-Legal • Equity: JNJ
Barbara D. Alexander, MD, MHS	• Consulting: Scynexis, Astellas • Research Grant (Institution): Leadiant • Clinical Trials (Site PI/Study PI): Astellas, Cidara, Scynexis, Shire, F2G • Royalties (Chapter Author): UpToDate
David M. Aronoff, MD	• Research Grant - Pfizer (C. difficile pathogenesis)
Helen Boucher, MD	• Editor: ID Clinics of North America, Antimicrobial Agents and Chemotherapy, Sanford Guide • 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)
Henry F. Chambers, MD	• Equity: Moderna • Data Monitoring Committee: Merck • Consultant: Janssen
David Gilbert, MD	• Consulting: Biomerieux • Grantee: Biofire (diagnostics)
Camille Kotton, MD	• Consulting: Biotest (CMV immunoglobulins), Hookipa (CMV Vaccine trial), Merck (CMV), Oxford Immunotec (CMV), Takeda (CMV)
Kieren A. Marr, MD	• Consulting: Cidara, Merck and Company, Sfunga Therapeutics • Ownership Interests: MycoMed Technologies

Robin Patel, MD	• Contracted Research: ContraFect, TenNor Therapeutics Limited, Hylomorph, BioFire, Shionogi • Consulting: Curetis, Specific Technologies, Next Gen Diagnostics, PathoQuest, Selux Diagnostics, 1928 Diagnostics, PhAST, Torus Biosystems, Mammoth Biosciences, Qvella, Netflix • Patent: Bordetella pertussis/parapertussis PCR; a device/method for sonication; an anti-biofilm substance issued
Andrew T. Pavia, MD	• Commercial Interests: Antimicrobial Therapy Inc, WebMD, Merck and Company
David Thomas, MD, MPH	• Data and Safety Monitoring Board: Merck • Advisory Board: Merck
Barbara W. Trautner, MD	• Consulting: Genentech (Tocilizumab for Covid pneumonia) • Research Funding: Genentech (Empacta trial)
Richard J. Whitley, MD	• Member of the Board of Directors and the Health Policy Advisory Board: Gilead Sciences • Chairperson: NIAID Covid-19 Vaccine DSMB, Merck Letermovir DMC and GSK IDMC (Zoster) • Scientific Advisory Board: Treovir, LLC • Member of the Board of Directors: Evrys Bio, Virios Therapeutics
Kevin L. Winthrop, MD	• Research: Insmed • Consulting: Insmed, Spero, Red Hills, Paratek

Saturday, August 21, 2021

AM Moderator: Masur
PM Moderator: Gilbert

#	Start		End	Presentation	Speaker
1	9:30 AM	-	10:00 AM	**Introduction**	*John Bennett, MD and Henry Masur, MD*
2	10:00 AM	-	10:15 AM	**How to Prepare for the Certification, Recertification, or Check-in Exam**	*Helen Boucher, MD*
3	10:15 AM	-	10:45 AM	**Preview Day 1**	*Henry Masur, MD*
4	10:45 AM	-	11:30 AM	**Core Concepts: Microbiology: What You Need to Know for the Exam**	*Robin Patel, MD*
5	11:30 AM	-	11:45 AM	**Microbiology Questions that Could Be on the Exam**	*Robin Patel, MD*
	11:45 AM	-	12:15 PM	***BREAK with FACULTY CHAT***	
6	12:15 PM	-	1:00 PM	**Core Concepts: Antibacterial Drugs I:**	*David Gilbert, MD*
7	1:00 PM	-	1:15 PM	**Antibacterial Drugs I: Key Points and Questions that Could be on the Exam**	*David Gilbert, MD*
8	1:15 PM	-	2:00 PM	**Board Review Day 1**	*Drs. Masur (Moderator), Bell, Bennett, Boucher, Gandhi, Gilbert, Patel, and Winthrop*
9	2:00 PM	-	2:45 PM	**Core Concepts: Antibacterial Drugs II**	*Helen Boucher, MD*
10	2:45 PM	-	3:00 PM	**Antibacterial Drugs II: Key Points and Questions that Could Be On The Exam**	*Helen Boucher, MD*
	3:00 PM	-	3:30 PM	***BREAK with FACULTY CHAT***	
11	3:30 PM	-	4:15 PM	**Core Concepts: Antifungal Drugs**	*John Bennett, MD*
12	4:15 PM	-	4:45 PM	**Core Concepts: Antiviral Drugs**	*Andrew Pavia, MD*
	4:45 PM	-	5:15 PM	***BREAK with FACULTY CHAT***	
13	5:15 PM	-	5:45 PM	**Nontuberculous Mycobacteria in Normal and Abnormal Hosts**	*Kevin Winthrop, MD*
14	5:45 PM	-	6:15 PM	**Syndromes in the ICU that ID Physicians Should Know**	*Taison Bell, MD*
15	6:15 PM	-	7:00 PM	**Photo Opportunity I: Photos and Questions to Test Your Board Preparation**	*Rajesh Gandhi, MD*
16	7:00 PM	-	7:30 PM	**Skin and Soft Tissue Infections**	*Helen Boucher, MD*
	7:30 PM	-	8:00 PM	***END OF THE DAY FACULTY CHAT***	

01

Introduction

Drs. Bennett and Masur

01 – Introduction

Speakers: Drs. Masur and Bennett

Introduction

Henry Masur, MD
John E. Bennett, MD

7/21/21

Disclosures of Financial Relationships with Relevant Commercial Interests

- **None**

The 2nd Annual Virtual Edition of IDBR

- **Goals**
  - **1. To prepare you for you certification or recertification ABIM Examination in ID…or to give you a comprehensive review**
  - **2. To expose you to faculty who are thought leaders in their areas of expertise**
  - **3. To provide a course that is as close to the live experience as possible….**
- **All Materials Are Available On Website until December 2022**
  - **Syllabus**
  - **Answers to daily questions, your test scores, and other material will be added daily**

Components of the Virtual Course

- **Preview Questions (Live)**
- **Lectures (Recorded with past few weeks)**
- **Faculty interaction sessions (Live)**
- **"Lunch" Board Review Sessions (Live)**
- **Scoring for all your ARS responses**
  - **Comparison to group metrics**

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 NOT tell you what has been on past exams…even if we know!!!

Three Sites to Know

- **Virtual Course Content**
  - You are logged in if you are listening!
- **SLIDO for Polling**
  - See next slide
- **Zoom for Faculty Chats**
  - You will be sent address

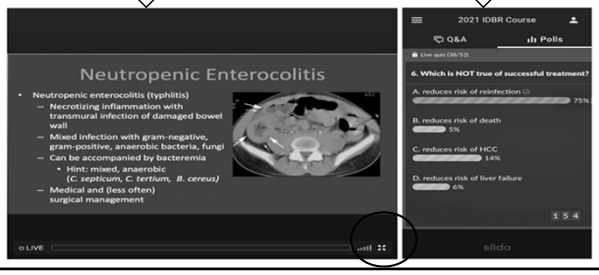
01 – Introduction

Speakers: Drs. Masur and Bennett

Browser Window

Virtual Lecture

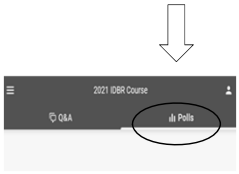
SLIDO



SLIDO for Polling or Faculty Questions

- **Go to SLIDO.COM or**
- **Download app from Apple Store**
- **Code - #4479**

To vote, go to **POLLS** tab (circled red).



ZOOM for Faculty Q and A During Breaks

- **These will be held on zoom, not the course website**
- **You must have a zoom account to participate**
  - https://zoom.us/signin
- **The zoom address for session will be posted during course**
- **Please mute unless you are asking a question**
- **Pose a question either electronically by SLIDO at any time, or live by hand raising during live zoom**

IDBR APP

- **Download the IDBR App from Apple store or Google Play store**
  - Download Eventscribe
  - Search for course by entering "2021IDBR"
  - Log in with the email and password that was emailed to you
  - Problems: email idbr@gwu.edu or call (202) 994-4285
- **You can use this app until 12/2022, on your cell phone or tablet to look at the syllabus-not the other material**

Which Will You Be?

How To Get The Most Out of Virtual Course

- **This is a Long Course**
  - **Decide how you learn best over 10+ hours x 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

Speakers: Drs. Masur and Bennett

IDBR Program for Certification/Recertification Preparation

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

- Virtual course for 5.0 days
  - Live Board Review Questions During Virtual Course
    - Rationales and daily scores published online 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 2021 Lectures (posted within a few days 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 5.0 days
  - Equally important as live lectures

Technical or Administrative Problems

– Telephone help line: (202) 994-4285

– Email help hotline: idbr@gwu.edu

CME and MOC

Total Possible: 114 CME and 114 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 - 114
    - Lectures – 43
    - Enduring Material 58 (online IDBR website)
- **MOC: one hour CME = 1 MOC credit**
  - You must first 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


Kieren Marr
Johns Hopkins


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

Lets Test The ARS (Audience Response System) Use SLIDO

Question 1
Why are you taking this course

1) Initial ABIM ID Certification
2) Recertification
3) Update in ID unrelated to ABIM Board Certification

Question 2

Where do you work

1) East coast, US
2) Midwest, US
3) South, US
4) West coast, US
5) Canada
6) Europe
7) Asia
8) Other

Question 3

Which parts of IDBR on line materials have you looked at prior to the course

1) Question sets only
2) Primers only
3) On line lectures only
4) Several of the above
5) None of the above

Let's Begin!

02

How to Prepare for the Certification, Recertification, or Check-in Exam

Dr. Helen Boucher

03

Daily Question Preview 1

Dr. Henry Masur (Moderator)

03 – Daily Question Preview: Day 1

Moderator: Henry Masur, MD

Daily Question Preview: Day 1

Moderator: Henry Masur, MD, FIDSA, MACP

PREVIEW QUESTION

1.1 **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

PREVIEW QUESTION

1.2 **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 "Resistant" to: all fluoroquinolones, aminoglycosides, pip/tazo, and all carbapenems**

PREVIEW QUESTION

1.2 **Which one of the following antibiotics is most likely to have activity vs. this KPC infection?**

A) Tigecycline

B) Ceftazidime-avibactam

C) Aztreonam

D) Ceftolozane-tazobactam

PREVIEW QUESTION

1.3 **40-year-old surgeon has surgical repair of torn anterior cruciate ligament of his knee. A single dose of cefazolin was given as a prophylactic antibiotic.**

- **Three days post-op: Purulent knee exudate. GNB on gram stain. Ceftriaxone (CTX) started**
- **Five days post-op: Growing Klebsiella (Enterobacter) aerogenes suscept. To CTX**
- **Ten days post-op: Knee still inflamed. Repeat culture: K.(E.) aerogenes resistant to CTX**

PREVIEW QUESTION

1.3 **Which one of the following is the most likely explanation of the Klebsiella(E.) aerogenes resistance to ceftriaxone?**

A) Spontaneous Mutation in Cephalosporin cell membrane binding protein

B) Activation of a Cephalosporin efflux pump

C) Activation of an inducible chromosomal cephalosporinase

D) Expression of constitutive plasmid cephalosporinase

03 – Daily Question Preview: Day 1

Moderator: Henry Masur, MD

PREVIEW QUESTION

1.4 What is the only cephalosporin active against MRSA

A) Cefpodoxime

B) Cefapime

C) Ceftaroline

D) Cefixime

E) Cefoxitin

PREVIEW QUESTION

1.5 Which quinolone has activity against MRSA

A) Ciprofloxacin

B) Moxifloxacin

C) Trovafloxacin

D) Delafloxacin

E) Levofloxacin

PREVIEW QUESTION

1.6 What is the major advantage of tedizolid compared to linezolid:

A) Longer half life

B) Better penetration of prostate

C) Better CSF Penetration

D) Wide spectrum of activity against anaerobes

E) More effective in clinical studies for VRE

PREVIEW QUESTION

1.7 In Staphylococcus aureus, the protein encoded by the mecA gene is which of the following:

A) Leukocidin

B) PBP 2a

C) Oxacillinase

D) IL28 TT

E) ESBL

PREVIEW QUESTION

1.8 Which of the following would be the best choice, among the drugs listed, to treat MSSA bacteremia:

A) Doripenem

B) Imipenem

C) Ceftriaxone

D) Cefazolin

E) Aztreonam

PREVIEW QUESTION

1.9 What is the mechanism of action for vancomycin resistance for Staphylococcus aureus

A) Mec A

B) Efflux pump

C) Change in vancomycin binding site on peptidoglycan

D) Porin

03 – Daily Question Preview: Day 1

Moderator: Henry Masur, MD

PREVIEW QUESTION

1.10 **Eosinophilic pneumonia is a complication of which of the following:**

A) Ceftaroline

B) Delafloxacin

C) Doripenem

D) Daptomycin

E) Linezolid

PREVIEW QUESTION

1.11 **A 47-year-old male with known HIV, poorly compliant with ARV, last CD4 20/mcl, presents with low grade fever and headache.**

Blood culture is growing a yeast, not yet identified.

PREVIEW QUESTION

1.11 **Starting micafungin would be a poor choice if the isolate is which of the following:**

A. Candida parapsilosis

B. Cryptococcus gattii

C. Candida auris

D. Candida krusei

E. Candida glabrata

PREVIEW QUESTION

1.12 **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

PREVIEW QUESTION

1.13 **A 37-year-old 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.

PREVIEW QUESTION

1.13 **Which of the following would be most appropriate?**

A) Voriconazole

B) Anidulafungin

C) Fluconazole

D) Liposomal amphotericin B

E) Itraconazole

03 – Daily Question Preview: Day 1

Moderator: Henry Masur, MD

PREVIEW QUESTION

1.14 **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

1.15 **A 50-year-old female alcoholic suffered a provoked dog bite. Bite was cleansed, tetanus toxoid given, and the dog placed under observation.**

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.

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

PREVIEW QUESTION

1.16 **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.

PREVIEW QUESTION

1.16 **Which one of the following organisms is the likely etiologic agent?**

A) Streptococci

B) Eikenella corrodens

C) Peptostreptococcus

D) Fusobacterium species

04/05

Core Concept - Microbiology: What You Need to Know for The Exam

Microbiology Questions That Could be on the Exam

Dr. Robin Patel

04 – Core Concepts: Microbiology
05 – Microbiology: What You Need to Know for The Exam
Speaker: Robin Patel, MD

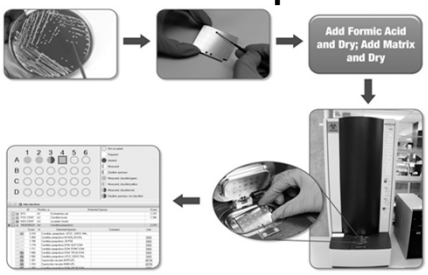
Core Concepts: Microbiology
What You Need to Know for the Exam

Robin Patel, MD
Professor of Medicine and Microbiology
Director, Infectious Diseases Research Laboratory
Mayo Clinic

Disclosures of Financial Relationships with Relevant Commercial Interests

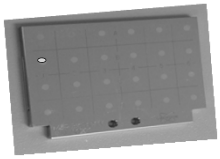
- Contracted Research: ContraFect, TenNor Therapeutics Limited, Hylomorph, BioFire, Shionogi
- Consultant: Curetis, Specific Technologies, Next Gen Diagnostics, PathoQuest, Selux Diagnostics, 1928 Diagnostics, PhAST, Torus Biosystems, Mammoth Biosciences, Qvella, Netflix
- Patent: Bordetella pertussis/parapertussis PCR; a device/method for sonication; an anti-biofilm substance issued

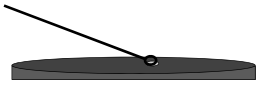
MALDI ToF Mass Spectrometry



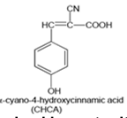
MAYO CLINIC

MALDI ToF Mass Spectrometry





1. **Add colony**
2. **Add matrix (1-2 µl)**



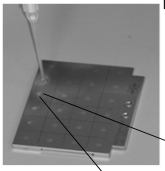
α-cyano-4-hydroxycinnamic acid (CHCA)

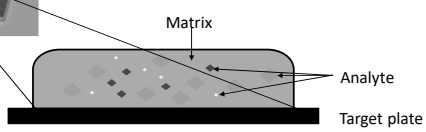
Dissolved in acetonitrile (50%) & 2.5% trifluoroacetic acid

3. **Dry – room air 5 min**

MAYO CLINIC

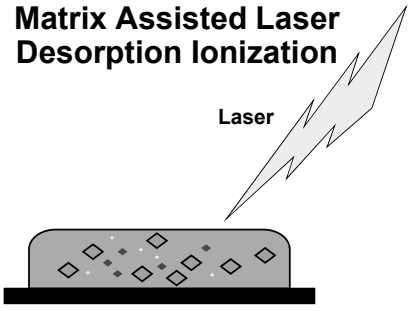
Matrix Assisted Laser Desorption Ionization





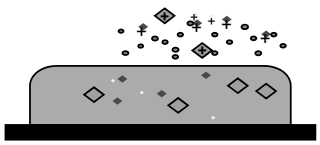
MAYO CLINIC

Matrix Assisted Laser Desorption Ionization



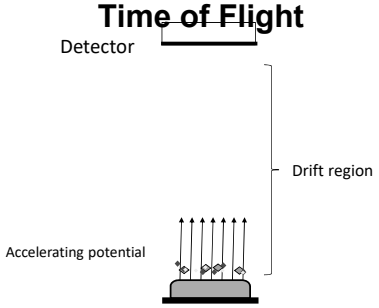
MAYO CLINIC

Matrix Assisted Laser Desorption Ionization



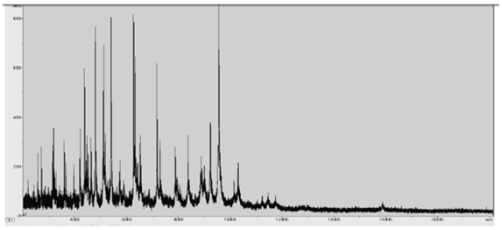
MAYO CLINIC

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

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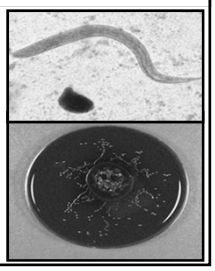
Strongyloides stercoralis

- **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
- *Burkholdheria pseudomallei*
  - (*Burkholdheria 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*

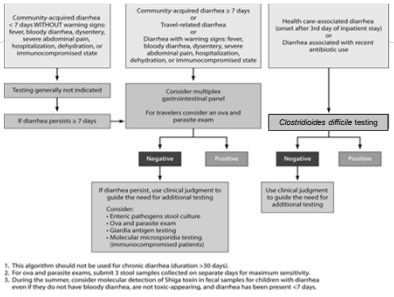
ORGANISMS ABOUT WHICH THE LABORATORY SHOULD BE NOTIFIED IF SUSPECTED

- **Avian influenza**
- ***Bacillus anthracis***
- ***Brucella* species**
- ***Burkholdheria pseudomallei***
- ***Burkholdheria mallei***
- ***Clostridium botulinum***
- ***Coxiella burnetii***
- ***Coccidioides immitis/posadasii***
- **Hemorrhagic fever viruses**
  (e.g., Ebola, 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		

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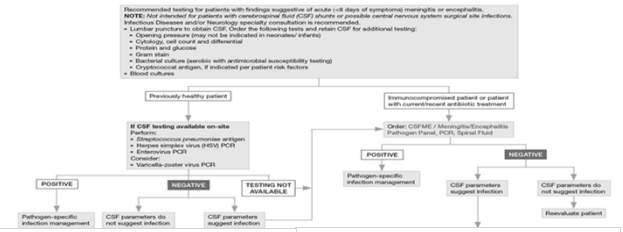
Meningitis/Encephalitis Panel Algorithm



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FDA-Approved Multiplex Respiratory Panels

Parameter	FilmArray	Verigene	NxTAG-RPP	eSensor RVP	ePlex
Analysis platform	FilmArray system or FilmArrayTorch	Verigene system	Luminex MAGPIX	eSensor	ePlex system
Acceptable specimens	NP swab	NP swab	NP swab	NP swab	NP swab
Number of targets	20	16	20	14	18
Pathogens					
Viruses					
Adenovirus	✓	✓	✓	✓(differentiates B/E from C)	✓
Coronavirus (229E, HKU1, NL63, OC43)					✓
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	High	Medium	Scalable
Time to result	~1 hour	~2.3 hours	~4 hours	~6 hours	~1.5 hours

Ramanan et al. Clin Microbiol Rev 2018;31:1-28

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Lower Respiratory Tract Panels

	Curetis Unyvero	BioFire
Bacteria		
Acinetobacter spp.	✓	
Acinetobacter calcoaceticus-baumannii complex		✓
Chlamydia pneumoniae	✓	✓
Citrobacter freundii	✓	
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)		✓
SARS-CoV-2		✓
Resistance genes		
bla_{KPC}	✓	✓
bla_{NDM}	✓	✓
bla_{IMP}		✓
bla_{OXA-23}	✓	
bla_{OXA-48}	✓	
bla_{OXA58}	✓	
$bla_{OXA58-like}$		✓
bla_{VIM}	✓	✓
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 aureus*, *Staphylococcus epidermidis* as well as *mecA/C* but not *mecA/C* and MREJ.

QUESTION #5

Which of the following is the interpretation of this finding?

A. Methicillin-susceptible *S. aureus* and methicillin-resistant *S. epidermidis*
B. Methicillin-susceptible *S. aureus* and methicillin-susceptible *S. epidermidis*
C. Methicillin-resistant *S. aureus* and methicillin-resistant *S. epidermidis*
D. Methicillin-resistant *S. aureus* and methicillin-susceptible *S. epidermidis*

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FDA-Approved Multiplex Panels for Detection of Select Organisms and Resistance Genes in Positive Blood Cultures

		FilmArray BCID2	VERIGENE®		GenMark $ePlex_{BC}$	
			Gram Positive Blood Culture Test	Gram Negative Blood Culture Test	Gram Positive BCP Panel	Gram Negative BCP Panel
Gram-positive bacteria	*Staphylococcus* species	✓	✓		✓	
	Staphylococcus aureus	✓	✓		✓	
	Staphylococcus epidermidis	✓	✓		✓	
	Staphylococcus lugdunensis	✓	✓		✓	
	Enterococcus species	✓	✓		✓	
	Enterococcus faecalis	✓	✓		✓	
	Enterococcus faecium	✓	✓		✓	
	Streptococcus pneumoniae	✓	✓		✓	
	Streptococcus anginosus group	✓	✓		✓	
	Streptococcus agalactiae	✓	✓		✓	
	Streptococcus pyogenes	✓	✓		✓	
	Enterococcus faecium	✓	✓		✓	
	Listeria species				✓	
	Listeria monocytogenes	✓			✓	
	Bacillus cereus group				✓	
	Bacillus subtilis group				✓	
	Lactobacillus species				✓	
	Lactobacillus casei group				✓	
	Micrococcus species				✓	
	Gram-Positive					✓
Gram-negative bacteria	Gram-Negative					✓
	Citrobacter freundii complex	✓		✓		✓
	Citrobacter koseri complex	✓		✓		✓
	Citrobacter species	✓				✓
	Enterobacter aerogenes	✓				✓
	Enterobacter cloacae complex	✓				✓
	Enterobacter species	✓				✓
	Escherichia coli	✓		✓		✓
	Escherichia coli O157	✓				✓
	Klebsiella oxytoca complex	✓		✓		✓
	Klebsiella pneumoniae group	✓				✓
	Klebsiella aerogenes	✓				✓
	Klebsiella oxytoca	✓				✓
	Klebsiella pneumoniae	✓				✓
	Proteus species	✓		✓		✓
	Proteus mirabilis	✓				✓
	Acinetobacter species			✓		✓
	Acinetobacter baumannii complex	✓				✓
	Pseudomonas aeruginosa group	✓				✓
	Haemophilus influenzae	✓				✓
	Neisseria meningitidis	✓				✓
	Serratia marcescens	✓		✓		✓
	Stenotrophomonas maltophilia	✓				✓
	Salmonella species	✓		✓		✓
	Salmonella enterica	✓				✓
	Klebsiella aerogenes	✓				✓
	Klebsiella pneumoniae group	✓				✓
	Proteus mirabilis	✓				✓

*Detected as *Enterobacter* species

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FDA-Approved Multiplex Panels for Detection of Select Organisms and Resistance Genes in Positive Blood Cultures, continued

		FilmArray BCID2	VERIGENE®		GenMark®		
			Gram-Positive Blood Culture Test	Gram-Negative Blood Culture Test	ePlex BCID-GP Panel	ePlex BCID-FP Panel	ePlex BCID-GN Panel
Yeasts	*Candida albicans*	✓				✓	
	Candida auris	✓				✓	
	Candida dubliniensis					✓	
	Candida famata					✓	
	Candida glabrata	✓				✓	
	Candida guilliermondii					✓	
	Candida kefyr					✓	
	Candida krusei	✓				✓	
	Candida lusitaniae					✓	
	Candida parapsilosis	✓				✓	
	Candida tropicalis	✓				✓	
	Cryptococcus gattii					✓	
	Cryptococcus neoformans					✓	
	C. neoformans/gattii	✓					
	Fusarium species					✓	
	Rhodotorula species					✓	
	Pan *Candida*				✓		✓
Resistance genes	*mecA*		✓		✓		
	mecC				✓		
	mecA/C	✓					
	mecA/C and MREJ	✓					
	vanA	✓	✓		✓		
	vanB	✓	✓		✓		
	bla_{KPC}	✓		✓			✓
	bla_{NDM}	✓		✓			✓
	bla_{VIM}	✓		✓			✓
	bla_{IMP}	✓		✓			✓
	bla_{OXA}	✓		✓			✓
	mcr-1	✓					

STAPHYLOCOCCI
METHICILLIN RESISTANCE

- 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
- *mecA/C* and MREJ specific for *Staphylococcus aureus*
- For serious infections, susceptibility to oxacillin confirmed using PBP2a testing or nucleic acid amplification test (NAAT) to detect *mecA* (and *mecC*)

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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)?

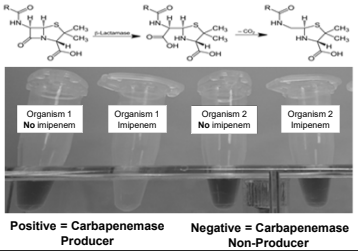
	Cefazolin	Cefotaxime	Ceftazidime	Piperacillin/ tazobactam	Imipenem	Aztreonam
a)	R	S	S	S	S	S
b)	R	R	R	S	S	R
c)	R	R	R	R	S	R
d)	R	R	R	R	R	R

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

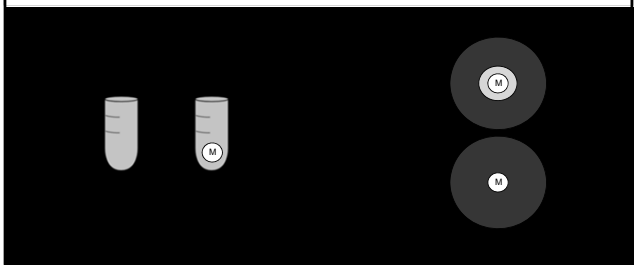


Positive = Carbapenemase Producer

Negative = Carbapenemase Non-Producer

- **β-lactam ring hydrolyzed by carbapenemase**
- **↓pH (detected by indicator dye color change red → yellow)**
- **Rapid (2 hours)**

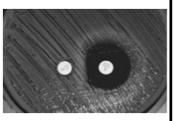
CARBAPENEMASE PRODUCTION TEST
MODIFIED CARBAPENEM INACTIVATION



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

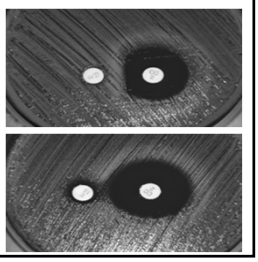
D. Erythromycin susceptibility, constitutive clindamycin resistance

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)

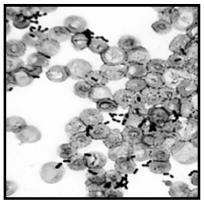
INDUCIBLE CLINDAMYCIN RESISTANCE (D-TEST)

- 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

06

Core Concept: Antibacterial Drugs I

Dr. David Gilbert

06 – Core Concepts: Antibacterial Drugs I

Speaker: David Gilbert, MD

Core Concepts: Antibacterial Drugs I

David N. Gilbert, MD
Professor of Medicine and Infectious Diseases
Oregon Health and Science University

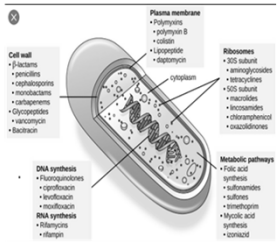
Disclosures of Financial Relationships with Relevant Commercial Interests

- Consultant: Biomerieux
- Research Grant on Diagnostics: Biofire

Overview

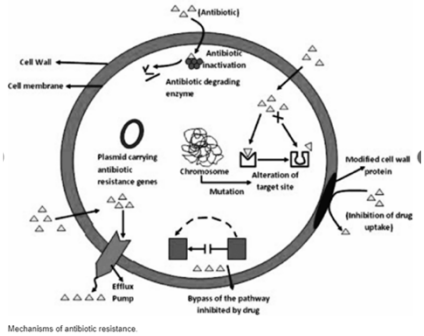
- First Lecture: Beta-lactams, FQs, AGs, Metronidazole
- Then , ARQs focused on clinical application
- A second on line lecture on to finish antibacterials used for infections due to Gram-negative bacteria: Polymyxins, Nitrofurantoin, Fosfomycin, Tetracyclines, TMP/SMX
- Dr. Boucher will discuss antibiotics primarily active vs Gram-Positive bacteria

Mechanisms of Action of Antibacterials

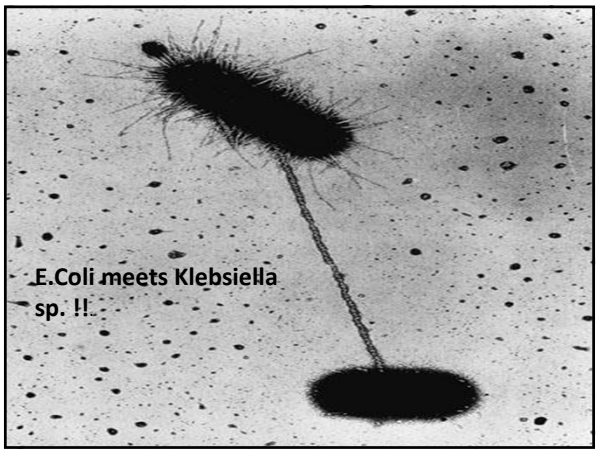


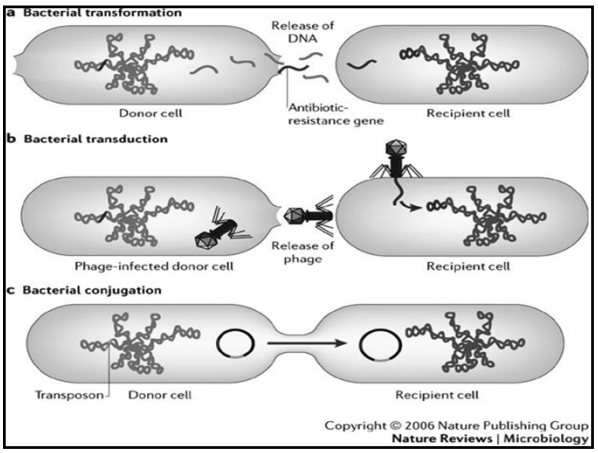
Major Gene-Expressed Mechanisms of Resistance to Antibacterials

- **Enzymatic inactivation**
- **Target site absent: intrinsic resistance**
- **Target site modification or protection (high level of resistance)**
- **Excessive binding sites**
- **Altered cell wall permeability**
- **Drug efflux (low level resistance)**



Mechanisms of antibiotic resistance





Combination vs Mono-Antibacterial Therapy

- **Combination therapy:**
  - **Decreases risk of selection of resistant subpopulations**
  - **Empirically in patient at risk of MDR GNB infection;**
    - **Increases likelihood of at least one active drug**
  - **Required for efficacy: e.g. Enterococcal Infective Endocarditis ; M.tbc.**
  - **Adjunctive:**
    - **Addition of clindamycin for toxic shock**
    - **Addition of rifamycin for penetration of biofilms on prostheses**

If choice of treatment is based on comparative
risk of adverse effect between a beta – lactam and
Other antibiotic classes active vs Aerobic GNBs,

The best answer is usually the BETA-Lactam !

Beta-Lactams

- **Penicillins**
- **Cephalosporins**
- **Carbapenems**
- **Monobactams (e.g.,Aztreonam)**
- **Share: presence of a beta-lactam ring, potential for causing seizures, and allergenicity**

To survive bacteria are constantly mutating

- **More than 2800 beta-lactamases reported**
- **Promiscuity is rampant among bacteria**
- **Not unusual to detect other mechanisms of resistance: e.g.,**
  - **Target change &/or Target Protection**
  - **Active efflux pumps**
  - **Decrease in permeability**
  - **Phenotypic antibiotic suscept. Testing does not identify specific mechanism(s) of resistance**
- **IF patient fails clinically and/or failure to eradicate pathogen, whole genome sequencing can identify specific mechanisms**
- **NO surprise, hard to write "resistance " test questions**

Ambler Molecular Classificaton of Beta-Lactamases*

Class	Subtypes	B-L-ase 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	Oxa-48 Some ESBLs Serine carbapenemases (e.g., KPCs)	None Clavulanic Avibactam & Vaborbactam	Penicillins, Carbapenems, ESCs, & Aztreonam ESCs and Carbapenems

*Ambler: Based on nucleotide sequencing

Antibacterial activity of Piperacillin-Tazobactam

- Active vs.:
  - Majority of *Enterobacterales (Enterobacteriaceae*)
  - *Bacteroides fragilis*
  - Maybe *Pseudomonas aeruginosa* if HIGH dose and prolonged infusion
  - Failed vs ESBL producing *Enterobacterales* as compared to meropenem (Merino trial)
- Better than ampicillin-sulbactam for empiric therapy due to 50% resistance of *E.coli*

Beta-Lactam Efficacy associated with time above MIC

- For Exam, pick regimen with prolonged or continuous infusion
- Supportive data for prolonged/continuous infusion for multiple beta-lactams:e.g.,
  - Ampicillin-sulbactam
  - Cefazolin
  - Cefepime
  - Ceftazidime
  - Doripenem
  - Meropenem
  - Piperacillin-tazobactam
  - Vancomycin

Ref.: Sanford Guide to Antimicrobial Therapy, 2021

Comparison of activity of Piperacillin-tazo. Vs Ampicillin-sulbactam

Target Bacteria	Ampicillin-sulbactam	Piperacillin-tazobactam
E.coli	+/-	++
Aeromonas sp.	+/-	+
Klebsiella sp.	+	+
ESBL producing E.coli; Klebsiella sp.	0	+/- or 0
Citrobacter, Morganella, Providencia sp.	0	+
Pseudomonas aeruginosa	0	+ (dose dependent)
Anaerobic GNB (*B.fragilis*)	+	+
In short: Prefer Pip/tazo for empiric therapy.		

Ampicillin-Sulbactam

Use as a source of sulbactam in combination therapy of MDR *Acinetobacter*

- **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

Piperacillin-tazobactam: AEs

- Common to All beta-lactams:
  - Allergy, seizures, neutropenia, thrombocytopenia
  - Drug-drug interactions: Rare
- Pip-tazo AE issues:
  - Sodium overload--36-90 meq of sodium in a full daily dose ; can aggravate CHF management
  - Pseudo-enhancement of vancomycin-induced nephrotoxicity

Cephalosporin "Generations"

Generation	Spectrum	Comment
First (Cefazolin)	*MSSA; E.coli, Kleb.sp.*	No activity versus enterococci
Second(Cefoxitin, Cefotetan)	Original target *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 activity vs. enterococci
Sixth (Ceftolozane/Tazo)	ESBL producing GNBs; Also antipseudomonal	No activity Vs. *Bacteroides* species
Seventh (Ceftaz/Avibactam)	(ESBL producing GNBs) & KPCs	Inconsistent activity vs *Bacteroides species*

Cephalosporin "Generations"

Generation	Spectrum	Comment
Eighth: Cefiderocol	Carbapenemase producing Enterobacterales and Non-fermenters*	No useful activity vs Gram positives and anaerobic bacteria

- *Non-fermenters: *Acinetobacter sp. ,Burkholderia sp., Ps.aeruginosa,*
- *Stenotrophomonas*

What you need to know about GNB producing ESBLs:

- Phenotypic Detection by micro. lab based on:
  - In vitro "R" to penicillin, cefazolin, ceftriaxone, ceftazidime, azreonam (see Dr. Patel's lecture)
  - Partial reversal of "R" by BLIs (Clav/Tazo)
  - Similar Resistance Pattern Could be due to:(Decreased permeation + Efflux pump) or AmpC production
- Preferred therapy: Meropenem
  - Alternative: Ceftolozane-tazobactam, Cefepime (if low MIC)
  - Others: Plazomicin, FQs +/-, Polymyxins
  - Avoid Piperacillin-tazobactam

If I say Amp C, you think:All cephs destroyed except ceftolozane-tazobactam or ceftazidime/avibactam.

Bacteria with Amp C Genes come 2 ways:

Chromosomal & Inducible

- M: *Morganella*
- *Y: Yersinia*
- *S: Serratia*
- *P:*
- *Pseudo/Proteus/Provid.*
- *A: Aeromonas/Acinetobact.*
- *C: Citrobacter*
- *E: Enterobacter species*

(19%)

On plasmid; constitutive

- *Escherichia coli*
- *Klebsiella species*

Treatment: Carbapenem. Maybe Pip/Tazo.; Beware of cefepime with MIC of 4 -8.
AAC 2015;59:7558
JAC 2016;71:296

Microlab cannot detect unless induced by treatment. !!!!

Parenteral Carbapenem Sparing Cephalosporins Active vs GNB producing ESBL and/or AmpC

	Cephalosporin active Vs:	
	AmpC producers	ESBL producers
Ceftazidime	Variable	Variable
Cefepime	If low MIC ; Big dose	I 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

[redacted]

- **F**osfomycin
- **A**moxicillin-clavulanate
- **N**itrofurantoin

Testable Cephalosporin AEs

- **Cross Allergenicity: Ceftazidime and Aztreonam have same side chain**
- **Ceftriaxone: Crystals in Biliary tree (Pseudo-cholelithiasis)**
- **Cefepime: Non-convulsive status epilepticus**
- **No Drug-Drug interactions**

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

Carbapenems: Spectrum of antibacterial activity

Active versus:	NOT ACTIVE versus
MSSA and Enterobacterales +/- ESBLs	*MRSA*
*Pseudomonas aeruginosa**	*Stenotrophomonas maltophila*
Bacteroides fragilis	*Acinetobacter (variable)*
Enterococcus faecalis	*Enterococcus faecium*
Listeria monocytogenes	

*Resistance can emerge during therapy via porin closure and efflux pumps

The Major Families of Carbapenemases

Non-Metallo (Serine at active site)	Metallo (Zinc at active site)
KPC (Class A)	VIM (Class B)
OXA-48 et al (Class D)	New Dehli Metallo-Blasé (Class B)
	IMP (Class B)

KPC=Klebsiella-producing carbapenemases; OXA=oxacillinase; IMP=Imipenemase; VIM=Verona integron-encoded metallo Blamase; NDM= New Dehli metallo BLamase

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 is a phenotypic marker for production of ESBLamases**
  - **In vitro active vs GNB that produce metallo-carbapenemases; however, inactivated by concomitant production of ESBLs**
    - **Use Ceftazidime-avibactam plus aztreonam to treat GNB co-producing ESBL and metallo-Carbapenemase**

Beta-Lactam Treatment of Carbapenemase Producing GNBs

- **Class A (KPCs-Klebsiella-Producing Carbapenemases):**
  - **Ceftazidime-avibactam**
  - **Meropenem-vaborbactam; Imipenem-cilistatin-relebactam**
  - **Cefiderocol**
- **Class B (Metallo-carbapenemases):**
  - **Ceftazidime-avibactam + Aztreonam**
  - **Cefiderocol**
- **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!**

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 includes:**
  - **XDR Enterobacterales**
  - **XDR Non-fermenters (Steno, Pseudo, Acinto)**
  - **No activity vs gram + bacteria or anaerobic bacteria**

Aztreonam Activity vs Carbapenemase-Producing GNB

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***

Primary & Alternative Rx of ESBL and Carbapenemase Producing Enterobacterales*

Resistant	Sensitive	Presumed Mechanism	Primary Treatment	Alternative Treatment
CTX & Aztreonam	Mero, P/T, Ceftolo-Tazo	ESBL**	Mero: Extended Infusion	Ceftolo-tazo, FQ, TMP/SMX
Ertapenem	Meropenem	Serine Carba-penemase	Meropenem	Ceftz-Avi
Erta + Mero	Ceftz-Avi	Serine Carbapenem ase	Ceftaz –Avi	Mero-vaborbactam ; Imipenem-relabactam
Ceftaz-Avi, Cpenems, azithromycin	Cefiderocol, Plazomicin, Polymyxin	Metallo (Zn) Carba-penemase	Ceftaz-Avi + Aztreonam	Cefiderocol; Eravacycyline if IAI

*IDSA Guideline:CID 2021;72:1109; **If chromosomal, not detected until induced

*"Difficult to Rx" Resistance of Ps.aeruginosa **

Preferred Therapy	Alternative Therapy
Ceftolozane-tazobactam	Aminoglycoside monotherapy (Gentamicin, Plazomicin et al)
Ceftazidime-avibactam	
Imipenem-cilastatin-relebactam	
Cefiderocol	
In addition, need Source Control	

*DTRx defined as "R" to Pip/tazo, ceftazidime, cefepime, Aztreonam, Meropenem, Imipenem-cilastatin, and FQs.
Reference: IDSA 2020 Guideline on Rx of Antimicrobial Resistant Gram-Negative Infections: CID 2021;72: 1109

IN SUMMARY: Rx

- ESBL production: Meropenem
- AmpC induced production risk: Avoid cephalosporins; Meropenem
- Serine-based Carbapenemase: Ceftazidime –avibactam, Meropenem-vaborbactam, or Imipenem-cilastatin-relebactam
- Metallo-based carbapenemase production: Ceftazidime-avi + Aztreonam

PK/PD.

- **Concentration-dependent killing and long persistent (post-antibiotic) effect ?**
  - ***AGs, daptomycin, FQs, telithro***
- **Killing dependent on time above MIC, no persistent effect?**
  - ***Penicillins, cephalosporins, aztreonam, and carbapenems***
- **Killing depends on time above MIC and a persistent effect?**
  - ***Vanco., macrolides, tetra, linezolid, clinda***

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; FDA Safety Warning.
- Conclusions:
  - Uncomplicated infections(bronchitis)---AVOID
  - Severe infections---RISK vs Benefit

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

Preferred FQs vs: ?

- For aerobic GNB: Ciprofloxacin
- For *Pseudomonas aeruginosa*: Ciprofloxacin
- For respiratory pathogens: Levofloxacin, delafloxacin , and Moxifloxacin
- For Anaerobic bacteria: Moxifloxacin
- For Mycobacteria: Moxifloxacin
- For MRSA : Delafloxacin

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

FQs and *Clostridioides difficile*

- Most common drug class to cause *C.difficile*
- Second are the cephalosporins
- Third is clindamycin

FQs and Acute Liver Injury

- Compared to clarithromycin, increased risk for acute liver injury within 30 days of prescription use of moxifloxacin or levofloxacin (ORs 2.2 and 1.85)
- No increased risk after use of ciprofloxacin

FQs and Neurologic AEs

- **Altered mental status**
- **Peripheral neuropathy**
- **Seizure**
- **Pseudotumor cerebri**
- **Exacerbation of myasthenia gravis**

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.**
- **Moxifloxacin: Highest association; Delafloxacin the lowest.**

FQ Drug-Drug Interactions

- **Cipro inhibition of cytochrome P450 resulting in impaired drug elimination**
- **NSAIDs plus FQs displace GABA from its receptors: Lowers seizure threshold**
- **Rifampin and rifapentine lower serum level of moxifloxacin; of import for combined therapy of Mycobacteria**

FQs and Chelation-Related AEs

- **Aortic aneurysm and aortic dissection**
- **Tendinopathy (Tendon rupture)**
  - **OR 8.3 if over age 60 and**
  - **OR 9.1 if using oral steroid**
- **Arthropathy**

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**
- **Monotherapy vs Tularemia and Plague**

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 & FQs 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 with TID AG therapy

AG: Shared Adverse Effects

- Nephrotoxicity: Acute tubular necrosis
- Ototoxicity:
  - Cochlear (genetic predisposition & non-reversible)
  - Vestibular (irreversible but host can compensate)
- Neuromuscular blockade (neomycin)

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, part of combo therapy of H.pylori*
- Metro. "R" Anaerobes: *P. (Cutibacterium) acnes, Peptostreptococci, Eikenella* and *Actinomyces*

Metronidazole: Adverse Effects

- Metallic taste; "furry" tongue
- Disulfiram (Antabuse) reaction (N/V, flushing, tachycardia, dyspnea) after alcohol use
- 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/Hallucination; normal MRI
Metronidazole	Weeks	Cerebellar dysfunction with abnormal MRI

* High serum concentrations due to renal insufficiency
Reference: Neurology 2016; 86:963

What do you need to know ?

- In the USA there are roughly 210 FDA-approved antibacterials
- As of 2020, there are 43 anti-bacterials in the clinical development pipeline*
- What do you need to know for the certifying examination ?

* WHO;2021. License: CC BY-NC-SA 3.0 | GO

What do you need to know ?

- Major mechanisms of antibacterial activity
- Spectrum of antibacterial activity
- Mechanisms and "language" of antibacterial resistance
- Drug Pharmacology: PK/PD, Distribution, Drug-drug interactions, Excretion, Unique toxicities (Allergy lecture to follow)
- Pertinent Clinical Microbiology (see Dr. Patel's lecture): Phenotypic patterns of resistance to beta-lactams
- Useful acronyms: SPACE-M, KPCs, NDM-CP, PEACHES

How do bacteria acquire genes that control resistance mechanisms?

- Transduction via bacteriophages (bacterial viruses): species specific
- Transformation: scavenge and incorporate naked DNA of dead bacteria
- Conjugation: cytoplasmic bridges between species with transfer of plasmids
- Spontaneous mutations

What is a plasmid?

- Extra chromosomal circular DNA
- Can replicate independent of chromosomal DNA
- Replication can be constitutive or induced
- Exchanged between species by conjugation
- Can carry genes for multiple antibacterial resistance determinants and virulence factors

What is a transposon?

- **Mobile short stretch of DNA**
- **Can move between different points within a genome by a process termed transposition.**
- **Not capable of self-replication**

What is an integron?

- **Collects genes from transposons and forms chunks of DNA called cassettes**
- **Integrons allow transposons/cassettes to move from chromosome to plasmid DNA .**
- **Then the plasmid DNA can spread via conjugation from one genus to another.**
- **Mobile genetic elements= plasmids, transposons, integrons**

Conjugative Plasmids

- **Increasingly common**
- **Carry multiple resistance genes expressed in vitro as resistance to beta-lactams, FQs, Aminoglycosides, other drugs.**

Beta-Lactam – Beta-Lactamase Inhibitor (BLI) Combinations

- **The six current BLIs are: Clavulanic acid, Tazobactam, Sulbactam, Avibactam,Relebactam, and Sulbactam . Not All are beta-lactams.**
- **BLIs demonstrate irreversible ("suicide") binding to bacterial beta-lactamases**
- **To date, there are 3 BLIs combined with a penicillin, 1 combined with a cephalosporin, and 2 combined with a carbapenem.**
- **Sulbactam is the only BLI with clinically useful antibacterial activity: active vs. Acinetobacter sp.**

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 of Pip/tazo.**
- **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**

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**

Ceftriaxone "R" *E. coli*

- 25% "R" of organisms in the order *Enterobacterale* worldwide; In Asia, 50% of *E.coli* are resistant to ceftriaxone
- Most common mechanisms of resistance:
  - 1. Production of Extended spectrum beta-lactamase (ESBLs)
  - 2. If *Enterobacter species*: could be Production of Amp C cephalosporinase
  - Carbapenems effective in presence of both mechanisms
- Are there any carbapenem sparing cephalosporins ?

Collateral Damage from Carbapenem Therapy for ESBLs

- Selection of CP "R" strains of Enterobacterales, and/or Non-Fermenters (e.g., *Acinetobacter sp.*)
- Selection of vanco "R" enterococci, MRSA, Candida species
- Nonetheless, based on the MERINO trial, Meropenem is Drug of Choice for treatement of ESBL producing Enterobacteraceae

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

ARQ #2

- 40 y.o. surgeon has surgical repair of torn anterior cruciate ligament of his knee. Single dose of cefazolin as prophylactic antibiotic.
- Three days later: Purulent knee exudate. GNB on gram stain. Ceftriaxone (CTX) started empirically
- At five days: Growing *Klebsiella (Enterobacter) aerogenes* suscept. To CTX
- At Ten days: Knee still inflamed. Repeat culture: *K.(E.) aerogenes* resistant to CTX

ARQ #2

- Which one of the following is the most likely explanation of the *Klebsiella(E.) aerogenes* resistance to ceftriaxone ?
  - A.Mutation in Cephalosporin cell wall binding protein
  - B. Activation of a Cephalosporin efflux pump
  - C. Activation of an inducible chromosomal cephalosporinase
  - D. Expression of constitutive plasmid cephalosporinase

Empiric therapy for Enterobacter (Klebsiella) sp.

- Avoid cephalosporins (except ceftolozane/tazo), penicillins, BL/BLIs due to induction of Amp C resistance, and documented poor clinical outcomes in patients &/or animal models.
- Carbapenems current choice

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

- **Broad spectrum synthetic bactericidal antibiotics that inhibit DNA synthesis of both intracellular and extracellular bacteria**
- **Increasing antibacterial resistance**
- **Increasing recognition of serious adverse events**
- **Benefit needs to exceed risk**

07

Antibacterial Drugs I: Key Points and Questions that Could be on the Exam

Dr. David Gilbert

07 – Antibacterial Drugs I: Key Points and Questions that Could be on the Exam

Speaker: David Gilbert, MD

Antibacterial Drugs I: Key Points and Questions That Could be on the Exam

David N. Gilbert, MD
Professor of Medicine and Infectious Diseases
Oregon Health and Science University

Disclosures of Financial Relationships with Relevant Commercial Interests

- Consultant: Biomerieux
- Research Grant on Diagnostics: Biofire

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 "Resistant" to: all fluoroquinolones, aminoglycosides, pip/tazo, and all carbapenems**

ARQ #1

- **Which one of the following antibiotics is most likely to have activity vs. this KPC infection ?**
  - **A. Tigecycline**
  - **B. Ceftazidime-avibactam**
  - **C. Aztreonam**
  - **D. Ceftolozane-tazobactam**

ARQ #2

- **Which one of the following would you recommend for empiric therapy of *Pseudomonas aeruginosa pneumonia* ?**
  - **A. Ampicillin-sulbactam**
  - **B. Ertapenem**
  - **C. Piperacillin-tazobactam**
  - **D. Fosfomycin**

ARQ #3

- **40 y.o. surgeon has surgical repair of torn anterior cruciate ligament of his knee. A single dose of cefazolin was given as a prophylactic antibiotic.**
- **Three days post-op: Purulent knee exudate. GNB on gram stain. Ceftriaxone (CTX) started**
- **Five days post-op: Growing *Klebsiella* (*Enterobacter) aerogenes* suscept. To CTX**
- **Ten days post-op: Knee still inflamed. Repeat culture: *K.(E.) aerogenes* resistant to CTX**

ARQ #3

- **Which one of the following is the most likely explanation of the *Klebsiella*(*E.) aerogenes* resistance to ceftriaxone ?**
  - **A. Spontaneous Mutation in Cephalosporin cell membrane binding protein**
  - **B. Activation of a Cephalosporin efflux pump**
  - **C. Activation of an inducible chromosomal cephalosporinase**
  - **D. Expression of constitutive plasmid cephalosporinase**

ARQ #4

- **A COPD KPC pneumonia patient is started on Ceftazidime-avibactam with a good initial clinical response.**
- **Patient is Extubated and sent to general nursing unit**
- **Two days later, despite continuing Ceftaz/avibactam, return of respiratory distress with increased sputum production, fever, elevated WBC, new CXR infiltrates**
- **Repeat sputum culture again positive for KPC but now resistant to Ceftazidime-avibactam**

ARQ #4

- **Which one of the following treatment regimens would you select ?**
  - **A . Meropenem-vaborbactam**
  - **B. Tobramycin**
  - **C. Polymyxin E (colistin)**
  - **D. Ertapenem + Imipenem-cilastatin**

ARQ ? #5

- **63 y.o. female presents with nausea, vomiting, fever, flank pain and dysuria.**
- **Known to have IDDM and obstructing ureteral calculi**
- **Urinanalysis notable for many WBCs and pH of 9**
- **Urine and blood cultures and removal of calculi are pending.**
  - **Based on the most likely etiologic bacteria, what is your choice for empiric therapy ?**
    - **A. Polymyxin E (Colistin)**
    - **B. Eravacycline**
    - **C. Gentamicin**
    - **D. Delafloxacin**

ARQ ? #6

- **A 45 y.o. married monogamous male requires a trans-rectal prostate biopsy for evaluation of an elevated PSA. As instructed , he took one "prophylactic" dose of levofloxacin, 750 mg, po with a multivitamin prior to driving to the hospital.**
- **18 hrs. post-biopsy he returns with urinary frequency, dysuria,, decreased urinary stream, and perineal pain.**
- **On exam: Temp 38 degrees C. Prostate is tender.**
- **Urinanalysis: Positive for microscopic pyuria and hematuria. Urine and blood cultures are pending.**

ARQ ? #6

- **Which one of the following would you select for empiric IV therapy ?**
- **A. Ceftriaxone**
- **B. Moxifloxacin**
- **C. Aztreonam**
- **D. Trimethoprim-sulfamethoxazole**

ARQ Q #7

- **A 51 y.o. male alcoholic with known cirrhosis is admitted with seizures.Two days ago, he had witnessed aspiration of oropharyngeal and gastric contents during a protracted seizure. He is now producing purulent sputum. He is febrile, the WBC is 16,000, and the serum procalcitonin is 3.0 ng/ml with a serum creatinine of 2.**
- **The sputum culture is positive for multi-drug resistant Serratia species**
- **The seizures are controlled with fosphenytoin and Keppra**
- **The Serratia is sensitive to all of the following antibacterials.**

ARQ Q # 7

- **Which one of the following antibacterials can lower the seizure threshold ?**
- **A. Levofloxacin**
- **B. Piperacillin-tazobactam**
- **C. Tobramycin**
- **D. Polymyxin B**

08

Board Review Session 1

Drs. Masur (Moderator), Bell, Bennett, Boucher, Gandhi, Gilbert, Patel, and Winthrop

8 – Board Review Day 1

Speaker: Drs. Masur (Moderator), Bell, Bennett, Boucher, Gandhi, Gilbert, Patel, and Winthrop

Board Review: Day 1

Moderator: Dr. Masur
Faculty: Drs. Bell, Bennett, Boucher, Gandhi, Gilbert, Patel, and Winthrop

BOARD REVIEW DAY 1

#1 **A 50-year-old woman presents with fevers and general malaise of three weeks' duration. She was given a three-day course of amoxicillin, but her symptoms persisted.**

On physical examination, a new murmur of mitral regurgitation is noted; subsequent echocardiography shows severe mitral regurgitation with a mobile 3 mm vegetation on her mitral valve.

- **Three sets of blood cultures are negative after five days of incubation**
- **Serologies for *Bartonella* species and *Coxiella burnetii* are negative**
- **She undergoes mitral valve replacement**
- **The valve is sent for diagnostic evaluation**

BOARD REVIEW DAY 1

#1 **In addition to histopathologic evaluation, which of the following is most likely to be helpful to perform on her valve?**

A) *Bartonella* PCR

B) Fungal culture

C) 16S ribosomal RNA gene PCR/sequencing

D) *C. burnetii* PCR

E) Mycobacterial culture

BOARD REVIEW DAY 1

#2 **A 79-year-old female with history of well-controlled non-insulin dependent diabetes mellitus (NIDDM) and hyperlipidemia is evaluated for abdominal pain and vomiting of 1-day duration.**

There is no known history of gallstone disease.

This patient has no exposure to health care facilities, no antibiotic exposure, and has had no acute illnesses in the past two years.

She is an accountant and has not traveled out of the country.

BOARD REVIEW DAY 1

#2 **On exam, the patient had temperature of 102 F, blood pressure 94/65, heart rate of 126 beats/min, icteric sclera, and tenderness to palpation in the right upper quadrant. WBC 18,000 cells/L with 23% bands, amylase = 100 (nl 23-85) U/L, lipase = 160 (nl 0-160) U/L, AST 55 (nl 10-40) U/L, ALT 80 (nl 7-56) U/L, ALK 650 (nl 20-140) U/L. TBili is 5.7 mg/dL, creatinine is 2.7 (baseline 1.0-1.3).**

Abdominal ultrasound revealed dilated bile ducts with stones.

BOARD REVIEW DAY 1

#2 **Which one is the following options is the most appropriate antimicrobial therapy for this patient?**

A) Piperacillin-tazobactam

B) Ampicillin-sulbactam

C) Meropenem plus fluconazole

D) Plazomicin plus vancomycin

E) Cefepime plus clindamycin

8 – Board Review Day 1

Speaker: Drs. Masur (Moderator), Bell, Bennett, Boucher, Gandhi, Gilbert, Patel, and Winthrop

BOARD REVIEW DAY 1

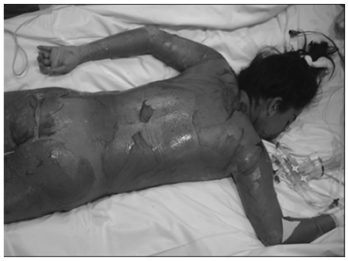
#3 **A 36-year-old woman presented with a fever and skin eruption two weeks after starting lamotrigine for depression. She had also had a mild, nonproductive cough for about ten days preceding the initiation of lamotrigine for which she was given trimethoprim-sulfamethoxazole by her family physician.**

On examination, she has a temperature of 38.3C, oral ulcers, and ulcerating skin lesions over 75% of her body. Her conjunctiva are inflamed.

Her lungs are clear, as is her chest radiograph. Her CBC shows a slight leukocytosis.

BOARD REVIEW DAY 1

#3



Arch Dermatol. 2008;144(6):724-726

BOARD REVIEW DAY 1

#3 **The most likely diagnosis is:**

A) Erythema multiforme

B) Stevens Johnson syndrome

C) Toxic epidermal necrolysis

D) Scalded skin syndrome

E) Disseminated herpes simplex

BOARD REVIEW DAY 1

#4 **A 56-year-old commercial crab fisherman on the Chesapeake Bay is seen for a painful, red hand.**

Three days ago he noticed a red dot on his index finger that was became increasingly painful. The lesion progressed to a red-purple involvement of his entire index finger, his middle finger, and most of the dorsum of his hand looking like a cellulitis.

He is afebrile and says the involved area is quite painful but only slightly tender to the touch.

He says the finger joints feel stiff although there is no joint swelling on exam.

BOARD REVIEW DAY 1

#4 **Which one of the following is the most likely cause of his problem?**

A) *Erysipelothrix rhusiopathiae*

B) *Mycobacterium chelonae*

C) *Sporothrix schenckii*

D) *Aeromonas*

E) *Pseudomonas aeruginosa*

BOARD REVIEW DAY 1

#5 **A 57-year-old medical school research scientist is seen for a febrile illness. Four days ago he was bitten on his hand by a laboratory rat.**

Last evening he had a fever, and today he has fever, chills, myalgias, and a painful left knee. On exam he is febrile. The bite wound is largely healed and has no evidence of infection.

His left knee is swollen with obvious effusion and some pain on both active and passive motion.

He has a petechial rash over both shins, and it is also present on the soles of his feet.

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Speaker: Drs. Masur (Moderator), Bell, Bennett, Boucher, Gandhi, Gilbert, Patel, and Winthrop

BOARD REVIEW DAY 1

#5 **Which one of the following is the most likely cause of his illness?**

A) *Leptospira interrogans*

B) *Spirillum minus*

C) *Streptobacillus moniliformis*

D) Hantavirus

E) *Pasteurella canis*

BOARD REVIEW DAY 1

#6 **A 66-year-old patient in the ICU is day 6 post-operative following a pancreatectomy for pancreatic carcinoma.**

He is recovering uneventfully with improving renal and hepatic function.

On the evening of his 6th post-operative day, he develops a fever of 38.5 C

The surgeons draw three cultures from an indwelling port that was placed preoperatively for chemotherapy that has not yet started. No other blood cultures were drawn.

Piperacillin-tazobactam is started.

BOARD REVIEW DAY 1

#6 **On Day 7 the patient remains intermittently febrile but is otherwise stable with no new findings.**

Labs are remarkable only for a WBC that continues to decline following surgery and is now 7800 cells/uL with 70% neutrophils

An ID consult is requested because after 14 hours of incubation, all three blood cultures are growing Gram-positive cocci in clusters.

BOARD REVIEW DAY 1

#6 **The patient has been stable but still has a low-grade fever. The port and the peripheral IV look fine, there are no other concerning physical findings or lab values.**

The organisms have been identified as Staphylococcus epidermidis with an oxacillin MIC of 1 mcg/ml.

The surgeon is very eager to retain the port. Because the patient is stable and will be hospitalized for starting his chemotherapy, you ask for port and peripheral blood cultures.

At 48 hours, the port cultures are positive but peripheral cultures are negative.

BOARD REVIEW DAY 1

#6 **You recommend stopping the piperacillin-tazobactam. What else would you recommend?**

A) Vancomycin should be started, and the port should be removed

B) Nafcillin or oxacillin should be started, and the port should be removed

C) Start vancomycin through the port

D) Start nafcillin or nafcillin through the port

E) Remove port. No antibiotic needed

BOARD REVIEW DAY 1

#7 **A 57 y/o man presents with 1 week of fever, chills, and low back pain.**

A transesophageal echocardiogram shows a 6 mm mobile mass on the mitral valve.

MRI of the spine shows evidence of discitis between the 3rd and 4th lumbar vertebrae.

Admission blood cultures are positive for S. aureus resistant only to penicillin.

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Speaker: Drs. Masur (Moderator), Bell, Bennett, Boucher, Gandhi, Gilbert, Patel, and Winthrop

BOARD REVIEW DAY 1

#7 He is treated with nafcillin 2 gm IV every 4 hours with resolution of fever but little change in his back pain.

Follow-up blood cultures form hospital days 4 and 5 are negative.

The white blood cell count, 18,000/mm^3 with 90% neutrophils on admission, but on hospital day 10, the white blood cell count is 3,000/mm3 with 30% neutrophils.

Renal function is normal.

BOARD REVIEW DAY 1

#7 Which of the following options is most appropriate for this patient?

A) Cefazolin 2 gm IV every 8 hours

B) Ceftriaxone 2 gm IV every 12 hours

C) Linezolid 600 mg IV every 12 hours

D) Nafcillin 1 gm IV every 4 hours

E) Vancomycin 1 gm IV every 12 hours

BOARD REVIEW DAY 1

#8 A 72 y/o US born, white female reports a history of needing antibiotic therapy for repeated respiratory infections over the last 12 months.

With each treatment she improves to near her baseline, but within several weeks her cough has worsened again, became more productive, and she complains of fatigue.

Overall, she notes a decline in exercise capacity, 10 lbs weight loss, and progressive fatigue the last 6 months.

BOARD REVIEW DAY 1

#8 She is a life-long non-smoker and has no risk factors for tuberculosis. She is otherwise healthy and takes no medications.

Her chest radiograph is normal, but a chest computed tomograph (CT) reveals right middle lobe bronchiectasis with scattered tree-bud infiltrate, mucous plugging, and a small right upper lobe cavity with a fungus ball present within the cavity.

BOARD REVIEW DAY 1

#8 The most likely cause of her syndrome and progressive decline is:

A) Mycobacterium gordonae

B) Chronic necrotizing aspergillosis

C) Mycobacterium tuberculosis

D) Mycobacterium avium complex

E) Nocardia farcinica

BOARD REVIEW DAY 1

#9 A 72-year-old man develops fever, abdominal pain, and unstable blood pressure after a subtotal colectomy for carcinoma of the colon.

Empiric therapy with piperacillin-tazobactam and vancomycin is initiated.

Within hours, the Clinical Microbiology laboratory reports that the patient's blood cultures are positive for enteric Gram-negative rods, preliminarily identified as ***Klebsiella pneumoniae***.

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BOARD REVIEW DAY 1

#9 ***In vitro*, the *K. pneumoniae* is:**

- **Susceptible to: piperacillin-tazobactam, meropenem, cefepime, and colistin**
- **Resistant to: ciprofloxacin, ceftriaxone and aztreonam**

BOARD REVIEW DAY 1

#9 **Which one of the following antibiotics would you recommend for specific therapy?**

A) Continue piperacillin-tazobactam

B) Ceftazidime-avibactam

C) Gentamicin

D) Cefepime

E) Meropenem

BOARD REVIEW DAY 1

#10 **A 26-year-old male with HIV infection (CD4=50 cells/uL, Viral Load 500,000 IU/mL) presents with severe right upper quadrant pain, nausea, vomiting and low-grade fever that suddenly occurred over the past 2 days.**

The patient has not been adherent to his antiretroviral therapy over the past several years.

He has had diarrhea (6 watery stools per day) for 8 months, and has lost 20 lbs during that period. The stools are brown, without blood or obvious mucous.

BOARD REVIEW DAY 1

#10 **He lives in Washington, D.C., works as a tour guide, and eats often at a variety of downtown food carts.**

He has multiple sex partners and is not consistent about safe sex practices.

He intermittently uses methamphetamines.

On exam he has normal vital signs (no fever at the time of examination) but severe right upper quadrant pain that is worse with palpation.

BOARD REVIEW DAY 1

#10 **CBC: WBC 4400, Platelets 270,000, Hct 43%**

Chemistries: liver function tests were moderately elevated: AST 435 IU/L, ALT 530 IU/L, Alk Phos 561 IU/L, Total Bili 2.4 (mg/dl)

Urine toxicology screen positive for marijuana and amphetamines.

Stool PCR, cultures, and ova and parasite exams are pending.

MRCP (Magnetic resonance cholangiopancreatography) reveals of bile duct stricture and moderate ductal dilation with no masses or adenopathy. Ultrasound and CT scan revealed similar findings and also jejunal thickening and thickening of the gall bladder wall.

BOARD REVIEW DAY 1

#10 **What is the most likely cause of this syndrome?**

A) Methamphetamines

B) CMV

C) Lymphoma

D) Cryptosporidiosis

E) Calculous cholecystitis

8 – Board Review Day 1

Speaker: Drs. Masur (Moderator), Bell, Bennett, Boucher, Gandhi, Gilbert, Patel, and Winthrop

BOARD REVIEW DAY 1

#11 **Which of the following is considered a serious hazard to laboratory staff if not handled appropriately?**

A) *Neisseria gonorrhoeae*

B) *Haemophilus ducreyi*

C) *Cryptococcus neoformans*

D) *Coccidioides immitis*

E) *Corynebacterium diphtheriae*

BOARD REVIEW DAY 1

#12 **75-year-old male with diabetes mellitus and ankylosing spondylitis treated with prednisone 20 mg daily, admitted with 3 weeks of fevers to 39°C, lethargy, and weight loss of 10 lbs**

He underwent transurethral resection of a bladder cancer three months prior, and recently completed a six-week course of intravesical Bacille Calmette Guerin (BCG) administered once weekly.

He lives in Tucson, Arizona. Urinalysis shows protein, nitrite, and leukocytes; routine bacterial culture is negative. Chest X-ray is normal. Chest CT scan shows innumerable tiny (1-4 mm) nodules.

BOARD REVIEW DAY 1

#12 **What diagnostic procedure is most likely to reveal the diagnosis?**

A) Bacterial blood culture

B) Silver stain of induced sputum

C) Ziehl-Neelsen stain of induced sputum

D) Trans-bronchial biopsy

E) Serum antibody testing for Coccidioides

BOARD REVIEW DAY 1

#13 **A previously healthy 60 y/o man presented with a few hours of severe pain in the right upper extremity.**

The exam was normal and he was discharged.

Over the next few hours, he developed progressive swelling of the right upper extremity. There was no history of trauma.

On exam, he appeared anxious, with cold and clammy skin.

BOARD REVIEW DAY 1

#13 **BP55/30. The right upper extremity was diffusely swollen with a deep-red discoloration; there were several bullae (shown).**

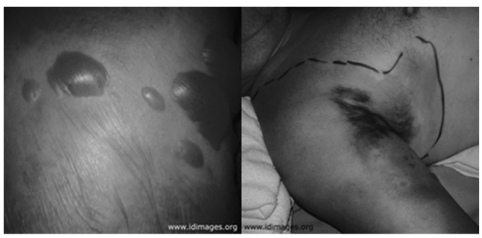
No pulses were palpable in the right upper extremity.

WBC 8,900 (47% polys, 38% bands).

An X-ray showed air in the soft tissues

BOARD REVIEW DAY 1

#13



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Speaker: Drs. Masur (Moderator), Bell, Bennett, Boucher, Gandhi, Gilbert, Patel, and Winthrop

BOARD REVIEW DAY 1

#13 **The most likely diagnosis is which of the following:**

A) Vibrio vulnificus

B) Group A streptococcal necrotizing fasciitis

C) Mixed aerobic/anaerobic necrotizing fasciitis

D) Clostridial gas gangrene

E) Ecthyma gangrenosa

BOARD REVIEW DAY 1

#14 **49-year-old man with AIDS (CD4 count 43, HIV RNA 225,000) presented with 4 weeks of pain on defecation.**

His physical exam was notable for a tender, boggy prostate. The urinalysis showed 5-10 WBC/hpf. The urine culture was without growth.

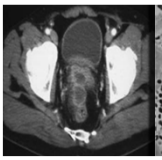
A pelvic CT scan showed a prostate abscess.

Aspirate of the abscess revealed the findings below.

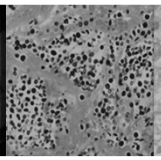
BOARD REVIEW DAY 1

#13

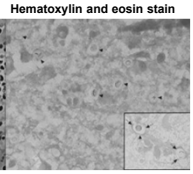
Pelvic CT



Silver stain. 4-8 mM



Hematoxylin and eosin stain



BOARD REVIEW DAY 1

#14 **Which of the following is the correct diagnosis?**

A) *Blastomyces dermatitidis*

B) *Pneumocystis jirovecii*

C) *Histoplasma capsulatum*

D) *Candida albicans*

E) *Cryptococcus neoformans*

BOARD REVIEW DAY 1

#15 **A 38-year-old male with HIV is asymptomatic, but his clinic physician drew a serum cryptococcal antigen test, which has come back positive.**

On evaluating the patient you find nothing remarkable by history or examination.

The patient has not been willing to take any medicines for HIV infection but is now willing to start antiretrovirals.

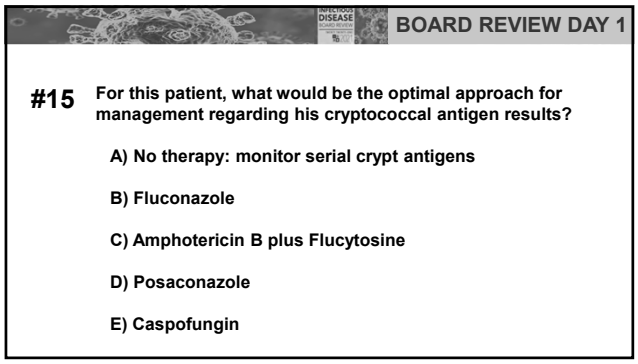
BOARD REVIEW DAY 1

#15 **Lab tests:**

- **Immunoblot: positive for HIV-1, negative for HIV-2**
- **CD4 count: 45 cells/mm3**
- **HIV viral load: 400k copies/ml**
- **CBC: normal**
- **Chemistry panel: normal**
- **LP: 0 cells, normal protein, and glucose, negative Cryptococcal antigen**
- **Serum Crypt antigen: 1:32**

8 – Board Review Day 1

Speaker: Drs. Masur (Moderator), Bell, Bennett, Boucher, Gandhi, Gilbert, Patel, and Winthrop



09

Core Concepts: Antibacterial Drugs II

Dr. Helen Boucher

09 – Core Concepts: Antibacterial Drugs II

Speaker: Helen Boucher, MD

Core Concepts: Antibacterial Drugs II

Helen Boucher, MD, FACP, FIDSA
Professor of Medicine
Tufts University School of Medicine

Disclosures of Financial Relationships with Relevant Commercial Interests

- Editor
  - ID Clinics of North America
  - Antimicrobial Agents and Chemotherapy
  - Sanford Guide
- 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)

Overview of Antibacterial Mechanisms

To Orient You: Little is Testable

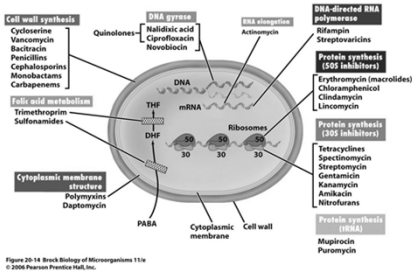


Figure 20-14 Brock Biology of Microorganisms 11/e
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3

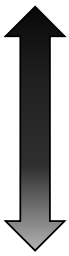
Cell Wall Active Agents

- **Penicillins**
- **Cephalosporins**
- **Carbapenems**
- **Vancomycin**
- **Daptomycin**
- **Polymyxins**

4

β-lactam Spectrum

- **Penicillins**
- **Semi-synthetic penicillins**
- **1st gen cephalosporins**
- **2nd gen cephalosporins**
- **3rd gen cephalosporins**
- **4th gen cephalosporins**
- **Carbapenems**
- **Monobactams**



Gram-positive

Gram-negative

5

β-lactam Antibiotics Share Mechanism of Action

— **Why are there different spectrum of activity for penicillins, cepahalosporins, carbapenems?**

- **Broad and narrow susceptibility to beta-lactamases**
- **Different penicillin binding proteins**
- **Selective efflux pumps**
- **Ability to reach target site**

6

β-lactam Adverse Effects

- **Anaphylaxis / allergy**
  - **See lecture by Sandy Nelson**
- **Seizures**
  - **Imipenem, cefepime**
- **Myelosuppression, leukopenia, hemolytic anemia**
- **Hypersensitivity hepatitis: e.g. Oxacillin**
- **Biliary stasis/sludging**
  - **Ceftriaxone**
- **Renal**
  - **Interstitial nephritis**

7

Penicillins

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Rx	Spectrum	Additional Adverse Events
Penicillin (oral/IV)	Group A strep; Syphilis	
Oxacillin/nafcillin (IV)	MSSA	AIN
Amoxicillin (oral) **Ampicillin** (IV)	Amox and amp have similar spectrum and are both broader than penicillin More active against H. flu, E. coli, Enterococcus, Listeria	
Amoxicillin clavulanate (oral) **Ampicillin sulbactam** (IV)	Broader spectrum than amox/amp due to addn of a beta-lactamase inhibitor; improved bioavilability (BID) Some activity against S. aureus; more active against H. flu and other gram negatives due to stability to some beta-lactamases NOT active against Pseudomonas Active against oral and gut anaerobes	Delayed hepatotoxicity (amox/clav)
Piperacillin tazobactam (IV)	Broader than amp/sulbactam Active against gram positive organisms including streptococci Broad activity against gram negatives incl Pseudomonas	

8

Question

- What is the only cephalosporin active against MRSA

- A) Cefpodoxime
- B) Cefapime
- C) Ceftaroline
- D) Cefixime
- E) Cefoxitin

9

Cephalosporins

- **Bactericidal**
  - **inhibit bacterial cell wall synthesis**
- **Time dependent killing**
- **Resistance due to susceptibility to β-lactamases**
- **Fewer allergic reactions than PCN**
- **CSF penetration with third generation**
- **Most renally excreted**

10

Key Points About Cephalosporin Activity

- **Enterococci**
  - **None are active**
- **MRSA**
  - **Only ceftaroline active**
- **Anaerobic activity**
  - **Only Cephamycins active**
    - **(e.g., cefoxitin, cefotetan)**
    - **Now high levels of resistance**

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Cephalosporins

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Rx	Spectrum	Additional Adverse Events
1st Gen Ceph **•Cefazolin** **•Cephalexin**	Staph and strep MSSA Some gram negatives including E. coli, Klebsiella, Proteus although 1st generation cephalosporins are very susceptible to beta-lactamases	
2nd Gen Ceph **•Cephamycin** **•Cefuroxime**	Gram positive cocci H. flu, E. coli, Klebsiella Cephamycin – active vs anaerobes, in vitro vs ESBLs (no clinical data)	
3rd Gen Ceph **•Ceftriaxone**	Streptococci pneumoniae (excellent) Gram negative rods but NOT Pseudomonas Excellent CSF penetration Drug of choice for bacterial meningitis	Biliary sludge
4th Gen Ceph **•Cefepime**	Broad gram positive and broad gram negative activity, including Pseudomonas Often used as empiric therapy in hospitalized patients (however may need to add vancomycin to treat MRSA)	Potential neurotoxicity, especially in patients with renal failure
5th Gen Ceph **•Ceftaroline**	Broader than amp/sulbactam; ceftriaxone-like Prodrug Active against gram positive organisms including streptococci and broad activity against gram negatives not incl Pseudomonas	

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Ceftaroline Fosamil – a Prodrug (IV and IM, Not PO)

- Activity
  - Gram-positive including MRSA and MDR *S. pneumoniae*
    - Some activity vs *E. faecalis*; not *E. faecium*
  - Limited activity vs. anaerobes
    - Active vs *Cutibacterium (formerly Propionobacterim) acnes, Actinomyces* spp.

Lodise & Low, Drugs, 2012; Saravolatz et al. CID 2011: 52: 1156

13

Ceftaroline Fosamil – a Prodrug (IV and IM, Not PO)

- Activity
  - Active vs Gram-negative pathogens
    - *E. coli*, *Klebsiella* spp., *H. influenzae* (incl B-lactamase positive), *M. catarrhalis*
  - Not *Pseudomonas* or ESBL+ GNB
  - Spectrum similar to ceftriaxone
- Bactericidal, time dependent killing

Lodise & Low, Drugs, 2012; Saravolatz et al. CID 2011: 52: 1156

14

Ceftaroline Clinical Use

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- Acute bacterial skin and soft tissue infections
- Community Acquired Pneumonia
- *S. aureus* bloodstream infection
  - Controversial-see Chambers Lecture
- Controversy over dosing regimen
  - 600mg twice daily – FDA-approved regimen

Lodise & Low, Drugs, 2012; Saravolatz et al. CID 2011: 52: 1156; File et al. CID 2010; 51: 1395; Zasowski et al, AAC 2017;61(2),e02015-16; Geriak et al. AAC 2019; 63(5); Kalil et al. AAC 2019; 63(11)

15

Ceftaroline Safety and Monitoring

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- Hypersensitivity 1-3%, rash 3%
- GI - nausea, vomiting, diarrhea 5%
- Hematologic toxicity (class effect)
  - Eosinophilia
  - Positive Coomb's test, rarely clinically significant
- Hepatotoxicity – LFT abn 1-7%
- Nephrotoxicity rare
- Neurotoxicity – tremor, confusion, seizure, encephalopathy
  - Worse with renal failure

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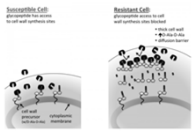
Vancomycin

- Bactericidal (slowly)
  - inhibits bacterial cell wall synthesis
- Active against:
  - Gram Positive Aerobes
    - Streptococcus
    - Staphyloccus
    - Enterococcus
  - Gram Positive Anaerobes
    - Clostridia
    - Propionibacteria
    - Peptostreptococci
    - Actinomyces

17

Vancomycin Resistance



- VISA
  - Thick walls, generous binding sites…
- Vancomycin resistance
  - Not in Streptococcus
  - RARE in Staphylococcus
  - Common in Enterococcus
    - Rare in *E. faecalis* (4% in 2014)
    - Common in *E. faecium* (71% in 2014)
    - Mechanism
      - Change in vancomycin binding site on peptidoglycan

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Vancomycin for MRSA Bloodstream Infection

- Controversy re: optimal therapy –see Dr. Chambers lecture
- Vancomycin trough only monitoring no longer recommended
  - Target AUC/MIC_{BMD} ratio of 400 to 600
    - (assume vancomycin MIC_{BMD} = 1 mg/L)
- Loading dose for seriously ill adults
  - 20–35 mg/kg can be considered
  - Pediatric doses higher
    - 60-80 mg/kg/day divided q 6-8 hours

Dosing Calculator helps!

https://www.idsociety.org/practice-guideline/vancomycin/

Vancomycin ADRs / Interactions

Adverse Drug Reactions

- Nephrotoxicity
  - Duration > 14d
  - Dose > 4g / day
  - Trough > 20
- Ototoxicity
- Histamine Release Syndrome

Drug Interactions

- Increased nephrotoxicity when given with other nephrotoxins
  - Aminoglycosides
  - NSAIDs
  - Contrast
  - Cyclosporine
  - Tacrolimus
  - Loop Diuretics
  - ACE inhibitors

20

Daptomycin (IV)

- Antimicrobial Class: Lipopeptide
- Broad spectrum gram + activity
  - Including MRSA
- Rapidly bactericidal
- Concentration-dependent killing
- Indications
  - cSSSI
  - *S. aureus* bloodstream infection
  - Right-sided endocarditis

Fenton C et al. *Drugs* 2004; 64: 445-55, Tedesco KL, Rybak MJ. *Pharmacother* 2004; 24:41-57, Mangili A et al. *Clin Infect Dis* 2005; 40:1058-60, Fowler VG et al. *New Engl J Med* 2006; 355:653-665

21

Daptomycin for *S. aureus* Bacteremia and Right IE

- Pneumonia
  - Do not use: surfactant binding inactivates drug
- Monitoring
  - CPK twice weekly
  - Discontinue if myopathy or CPK> 5x ULN
- Toxicity
  - Eosinophilic Pneumonia
    - Rx supportive care and steroids
  - Falsely prolonged Prothrombin Time
  - Muscle inflammation
    - CPK increase, myopathy, myositis
    - Risk factors: renal failure, statins, obesity

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Vancomycin and Daptomycin

Drug	MOA	MOR	Spectrum	Adverse Event
Vancomycin	Inhibits cell wall synthesis (not a beta lactam)	Change in cell wall terminus from D-ala-D-ala to D-ala-D-lactate (high level resistance)	Gram positive cocci only including MRSA	• Histamine release syndrome • Kidney toxicity
Daptomycin	Cell membrane depolarization Potassium efflux	• Decreased binding of drug to cell membrane • Altered cell membrane potential	Resistant gram positive cocci including MRSA and VRE Inactivated by surfactant (not used for pneumonia)	• Skeletal muscle toxicity

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Oritavancin and Dalbavancin

Long Acting Glycopeptides

- Mechanism of Action
  - Similar to vancomycin
  - Inhibition of cell wall synthesis
- Dosing
  - Oritavancin: IV only: 1 dose (1200 mg over 3hours)
  - Dalbavancin: IV only: 1000mg, then 500mg every 7 days …..OR 1500mg x 1
- Approved
  - Skin and Soft Tissue
  - Oritavancin FDA warning against use in osteomyelitis
  - Dalbavancin also used for osteomyelitis, right sided endocarditis
- Toxicity
  - Oritavancin prolongs aPTT (artificially), PT, and activated whole blood clotting time (ACT) for 5 days

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Oritavancin - Lipoglycopeptide With Long Half-life

- Mechanism of action
  - inhibition of cell wall synthesis and disrupts bacterial membrane
  - Gram-positive spectrum
    - *S. aureus*, MRSA, VISA, VRSA, GAS, *S. anginosus* group
    - *E. faecalis* , *E. faecium*/VRE (active vs VanA, VanB, Van C, Van D)
- Bactericidal
- IV only, 1 dose
  - 1200 mg over 3 hours
- Cytochrome P450 enzyme – warfarin interaction
- FDA approved
  - ABSSSI

HF Chambers NEJM 2014; 370(23): 2238. WWW.FDA.GOV,
Arias et al CID 2012: 54 (Suppl 3): S233; GR Corey et al. NEJM 2014; 370(23): 2180-2190

25

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Dalbavancin - Lipoglycopeptide With Long Half-life

- Gram-positive spectrum
  - *S. aureus*, MRSA, VISA, GAS
  - Low MRSA MICs
  - Enterococci – inactive vs VanA
- Mechanism of action – cell wall synthesis inhibit
- Bactericidal
- IV only (dose over 30 min), long half-life (app 8.5 days)
- Dosing
  - 1000mg, then 500mg every 7 days OR 1500mg x 1
  - Decrease dose by 25% for CrCl <30ml/min, not dialysis
- FDA approved ABSSSI

Dowell et al. *Critical Care* 2008, 12(Suppl 2):P26. www.fda.gov
Nailor and Sobel. Infect Dis Clin N Am 23(2009): 965. Jauregui et al. CID 2005; 41: 1407; Dunne et al CID 2016
HW Boucher, M Wilcox, GH Talbot, S Puttagunta, AF Das, MW Dunne. NEJM 2014; 370(23): 2169

26

Lipo/glycopeptide Testable Toxicities

- Vancomycin: Nephrotox.; Histamine Release
- Daptomycin: CPK elevation, myopathy, rhabdomyolysis; Eosinophilic pneumonia
- Telavancin: Nephrotoxicity
- Oritavancin: LFT elevation; False prolongation of aPTT
- Dalbavancin: LFT elevation

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Dalbavancin

- Other uses
  - Limited data, varying dosing regimens
    - Endocarditis and osteomyelitis
    - Persons who inject drugs
- Case reports of failure with emergence of VISA, presumably associated with low-level drug exposure
  - One patient had VISA detected in urine while on dalbavancin for CLASBI
  - One patient was pregnant and had failure of therapy for IE

- Steele JM et al. J Clin Pharm Ther. 2018;43:101-103.
- Werth BJ et al. Clin Microbiol Infect. 2018;24:429.e1-429.e5.

28

Question

- Which quinolone has activity against MRSA

- A) Ciprofloxacin
- B) Moxifloxacin
- C) Trovafloxacin
- D) Delafloxacin
- E) Levofloxacin

29

Antibiotics Active Intracellularly

- Fluoroquinolones
- Tetracyclines
- Linezolid
- TMP/SMX
- Pleuromutilins

30

Fluoroquinolone Mechanism of Action

- Topoisomerase inhibitors
  - Inhibits DNA gyrase and topoisomerases II and IV
  - Gyrase more for gram negs, topos for gram pos
- Resistance
  - Target site mutations
  - Drug permeability mutations
  - Occurs spontaneously on therapy

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Fluoroquinolones Spectrum of Gram Positive Activity

	Gram-positive	Gram-negative	Anaerobes
Cipro	Poor strep Some MSSA	Best FQ for •Pseudomonas •E coli	Some
Levo	Good strep Some MSSA	Best for Stenotrophomas	Some
Moxi	Good strep Good MSSA	Not effective Don't use for UTI	Best

Dr. Gilbert will address Gram-negative activity

32

Fluoroquinolone Pharmacokinetics

- High oral bioavailability
  - >95% for moxi / levo, 70-80% for cipro
- Widely distributed to tissues
  - Lower than serum but therapeutic concentration in CSF, saliva, bone, and ascitic fluid
- Elimination
  - Levo / cipro: renal through tubular secretion
  - Moxi: >60% hepatic/ biliary unchanged

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Fluoroquinolone Adverse Effects

- *C. difficile*
- Arthropathy/cartilage toxicity / tendonitis
  - FDA Warning for rare tendon rupture
    - Increased risk: advanced age, poor renal function, concomitant steroids
- Altered mental status (HA, dizziness, insomnia)
- Dysglycemia-FDA warning especially for older adults and diabetics
  - Hypo and hyperglycemia
- Aortic aneurysm and aortic dissection-FDA warning
  - Association is controversial
- QTc Prolongation:
  Moxi > levo ? Cipro
  - Increased risk:
    - Concomitant QTc prolongers, cardiomyopathy, bradycardia, low K+ and Mg++

34

Delafloxacin

- Broad spectrum fluoroquinolone
- Potential advantages:
  - MRSA activity
  - Broad spectrum including Pseudomonas
- Dosing IV and oral twice daily
- Approved for skin and soft tissue infections

Saravolatz LD and Stein GE. Clin Infect Dis. 2019;68(6):1058–62

35

Tetracyclines: Major Clinical Uses

- Acne (minocycline)
- Respiratory tract infections
  - Atypical pneumonia
- Sexually Transmitted Diseases
  - Syphilis (*T. pallidum*) – alternative therapy
  - *Chlamydia* spp.
- Tick-Borne Illnesses
  - Lyme disease
  - Anaplasmosis
  - Ehrlichiosis
  - Rocky Mountain Spotted Fever
- Community Acquired MRSA infections

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Tetracyclines: Adverse Effects

- Gastrointestinal
  - Nausea
  - Esophageal ulceration
  - Hepatotoxicity
- Skin
  - Photosensitivity
- Children
  - Yellow brown tooth discoloration if age <8 yrs for tetracyclines
  - Doxycycline therapy OK for ≤21 days in children of all ages
    - Ref: Redbook 2018 and Am Academy Pediatrics
- Pregnancy
  - Tetracyclines cross the placenta; accumulate in fetal bone/teeth
  - Most tetracyclines contraindicated in pregnancy

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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	1mg/kg IV q 12h (over 60 minutes)
	No dose adjustment for renal/hepatic impairment	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

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Question

- What is the major advantage of tedizolid compared to linezolid
- A) Longer half life
- B) Better penetration of prostate
- C) Better CSF Penetration
- D) Wide spectrum of activity against anaerobes
- E) More effective in clinical studies for VRE

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Linezolid and Tedizolid Oxazolidinone Drug Class

- Mechanism
  - binds 50s ribosome/prevents formation of initiation complex
- Spectrum of activity
  - Gram positive cocci including MRSA and VRE
    - Linezolid resistant *Staph aureus* reported
  - Mycobacteria
- Resistance is rare; target change
- Linezolid bid; Tedizolid qd
- FDA approvals for Linezolid:
  - Skin and Soft Tissue, Pneumonia, VRE
  - NOT Bloodstream infection (Black Box Warning)

Shinabarger DL et al. *Antimicrob Agents Chemother* 1997; 41: 2132-36; Swaney Sm et al. *Antimicrob Agents Chemother* 1998; 42: 3251-55; French G. *Int J Clin Pract* 2001; 55: 59-63

40

Linezolid Adverse Events

- Adverse events related to mitochondrial toxicity:
  - Cytopenias
    - Monitor CBC
  - Peripheral and optic neuropathy
  - Rare:
    - Lactic acidosis, serotonin syndrome (w SSRIs)
- ↑ mortality with catheter-associated bacteremia

Tsiodras S et al. *Lancet* 2001;358: 207-208; Pillai SK et al. *Clin Infect Dis* 2002; 186: 1603-7; Wilson P et al. *J Antimicrob Chemother* 2003;51:186-88; Medwatch March 16, 2007

41

Tedizolid - Oxazolidinone Drug Class Once Daily Dosing, Lower Dose

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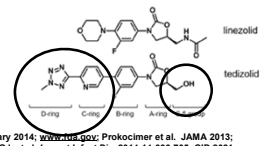
- Non-antibiotic antibacterial; a MAO inhibitor
  - Inhibits protein synthesis, bactreiostatic
    - Binds peptidyl transferase region of bacterial ribosome prevents binding of amino acyl tRNA
- Gram-positive spectrum
  - *S. aureus*, MRSA, VISA, GAS, *S. agalactiae*, *S anginosus* group, *E. faecalis* (vanco-susceptible only)
- IV and oral
- Half-life 12 hours, once daily dosing
- 200 mg daily x 6 days
  - No dose adjustment for age, renal/hepatic impairment
- FDA approved ABSSSI
- HABP/VABP Study Failed



Moellering CID January 2014; www.fda.gov; Prokocimer et al. JAMA 2013; Moran GJ, et al. *Lancet Infect Dis*. 2014;14:696-705; CID 2021

42

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Sulfonamides & TMP/SMX

- 1st clinically used antibiotic: sulfanilamide
  - Identified as anti-streptococcal in 1932
  - Initially an industrial dye
  - Changed the face of WWII
- Combined with trimethoprim 1968
- Off-shoot: methotrexate
  - Used for various hematologic, oncologic, and rheumatologic conditions

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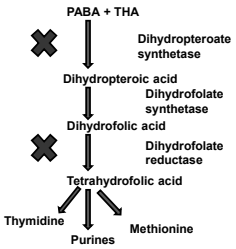
TMP/SMX Mechanism of Action

- Together inhibit folic acid synthesis
- Sulfamethoxazole
  - Competitively inhibit incorporation of para-amino benzoic acid (PABA) into tetrahydropteroic acid (THA)
    - SMX has higher affinity for THA than PABA does
- Trimethoprim
  - Inhibits dihydrofolate reductase (DFHR)
  - 50,000 to 100,000 times more active against bacterial DFHR than human enzyme



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TMP/SMX Resistance Mechanisms

Sulfamethoxazole

- PABA overproduction
  - Caution with OTC PABA supplements
- Structurally mutated dihydropteroate synthetase
- Decreased bacterial cell permeability

Trimethoprim

- Novel plasmid-mediated DFHR
- Altered cell permeability
- Loss of binding capacity
- Overproduction of or alterations in dihydrofolate reductase

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TMP-SMX Adverse Effects

- Anaphylaxis
- Skin rashes
- Bone marrow toxicity
- Kernicterus
- Hemolysis (G6PD def)
- Hepatitis

HIGH PLASMA PROTEIN BINDING

- Gastrointestinal effects
- "Nephrotoxicity"
- Fever
- Drug-drug interactions
- Hyperkalemia

COMPETES FOR TUBULAR SECRETION

46

TMP/SMX Spectrum of Activity - Typical Bugs

- Gram Positive
  - Staphylococci: great
  - Streptococci: controversial
  - Enterococcus: not effective
- Gram Negative
  - *E. coli*: ok, increasing resistance
  - Enterobacterales: relatively effective
  - Pseudomonas / Acinetobacter: not effective
  - Stenotrophomonas: often drug of choice

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TMP/SMX Spectrum of Activity - Odd Bugs

- *Stenotrophomonas maltophila*
- *Listeria monocytogenes*
- *Nocardia*
- *Moraxella catarhallis*
- *Pneumocystis jirovecii*
- *Toxoplasmosis gondii* (but not superior to pyr/sulf)
- *Chlamydia* (but enough resistance that its not used for STDs)
- Atypical *mycobacteria*

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Lefamulin

- Pleuromutilin antibiotic with IV and PO formulation
  - Protein synthesis inhibitor
  - Bacteriostatic
- FDA Approved community acquired bacterial pneumonia
  - Non-inferior to moxifloxacin for CABP in two studies
    - 5 days of po lefamulin vs. 7 days of po moxifloxacin

File CID 2019

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Macrolides (Erythro, Clarithro, Azithro)

Protein Synthesis Inhibitor Binds 50s Ribosome

Spectrum:

CABP Pathogens:
- Streptococcus pneumoniae
- Haemophilus influenzae
- Moraxella catarrhalis
- Leigonella spp.
- C. pneumoniae
- Streptococcus groups A, C, and G

Strep Pneumo Resistance
- Rising rates in US
  - Don't use macrolides if local rates of resistance > 25%

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Macrolide Spectrum

STDs
- *Haemophilus ducreyi (chancroid)*
- *Chlamydia spp.*

GI pathogens
- *Campylobacter spp.*
- *Helicobacter pylori*
- *Salmonella typhi*
- *Shigella spp.*

Miscellaneous Bugs
- *Arcanobacter spp.*
- *Bartonella henselae (cat-scratch)*
- *Bordetella pertussis*
- *Atypical mycobacteria*
- *Borrelia burgdorferi*
- *Babesia microti*

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Macrolide Adverse Drug Reactions

- QTc Prolongation
  - Ery ≥ clarith > azith
- GI intolerance: nausea, bloating, diarrhea
  - Ery >> clarith >> azith
  - Dose related
  - Activity at motilin (peristalsis) receptors
  - Rare cholestatic hepatitis
- Pregnancy risk

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Clindamycin Adverse Events

- Allergic reactions:
  - Rash, fever, erythema multiforme, anaphylaxis
- Elevated AST/ALT
  - rare progression to severe liver injury
- Diarrhea
  - can cause severe *C. difficile* toxin-mediated colitis
- Reversible neutropenia, thrombocytopenia, and eosinophilia
- Taste disturbance

Sanford Guide, Brit J Clin Pharmacol 64:542, 2007; Clin Med Insights Case Rep 2019 Dec 25;12:1-4

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Clindamycin

- Mechanism of action
  - Protein Synthesis Inhibitor
  - Binds 50s Ribosome

Hidden-for reference only in syllabus

Clin Infect Dis. 2014; 59:698-705J Antimicrob Chemother. 2019 Jan 1;74(1):1-5

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Protein Synthesis Inhibitors - Summary

Hidden-for reference only in syllabus

Drug	Mech of Action	Mech of Resist	Spectrum	Clinical Uses	Major Adverse Effect
Linezolid	50s	Mutation in ribosome	Gram + (resistant)	MRSA, VRE	Pancytopenia Serotonin syndrome
Tetracyclines (Doxycyline)	30s	Target site modification Efflux	Comm acq MRSA, atypical pneumonia pathogens, Lyme, rickettsia and other tick borne pathogens, Treponema pallidum	Lyme, RMSF, Comm Acq MRSA, acne, CABP	Enamel hypoplasia, photosensitivity Esophageal ulceration
Aminoglyco-sides	30s	Inactivating enzymes Efflux Ribosomal mutations	GNRs	serious gram negative infx	Nephrotoxicity Oto-vestib toxicity
Macrolides	50s	Target site modification Efflux	Gram + Atypical PNA pathogens	Atypical pneumonia, resp infx	p450 drug interactions GI upset QT prolongation
Clindamycin	50s	Target site modification Efflux Inactivate drug	Gram +, Anaerobes	Oral and intra-abd infx	*C. difficile* colitis

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Thank You!

- **Henry Masur**
- **Sue Cammarata**
- **G. Ralph Corey**
- **Sara Cosgrove**
- **Mike Dudley**
- **Mike Dunne**
- **David Gilbert**
- **Susan Hadley**
- **Teena Kohli**
- **Kenneth Lawrence**
- **Evan Loh**
- **Paul McGovern**
- **Federico Perez**
- **Debra Poutsiaka**
- **George H. Talbot**
- **Our patients and their families**

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Questions, Comments?

- @hboucher3
- hboucher@tuftsmedicalcenter.org
- Helen.boucher@tufts.edu

Tufts

Dr. Helen Boucher
Chief, Division of Geographic Medicine and Infectious Diseases;
Chair, Physician of Tufts Medical Center
Tufts Medical Center

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10

Antibacterial Drugs II: Key Points and Questions that Could Be On The Exam

Dr. Helen Boucher

10 – Antibacterial Drugs II: Key Points & Questions that Could Be On The Exam

Speaker: Helen Boucher, MD

Antibacterial Drugs II: Key Points and Questions that Could Be On The Exam

Helen Boucher, MD, FACP, FIDSA
Professor of Medicine
Tufts University School of Medicine

Disclosures of Financial Relationships with Relevant Commercial Interests

- Editor
  - ID Clinics of North America
  - Antimicrobial Agents and Chemotherapy
  - Sanford Guide
- 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

In *Staphylococcus aureus*, the protein encoded by the mecA gene is which of the following:

A	Leukocidin
B	PBP 2a
C	Oxacillinase
D	IL28 TT
E	ESBL

3

Question 2

Which of the following would be the best choice, among the drugs listed, to treat MSSA bacteremia

A) Doripenem
B) Imipenem
C) Ceftriaxone
D) Cefazolin
E) Aztreonam

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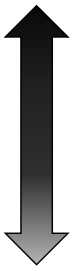
β-lactam Spectrum

- **Penicillins**
- **Semi-synthetic penicillins**
- **1st gen cephalosporins**
- **2nd gen cephalosporins**
- **3rd gen cephalosporins**
- **4th gen cephalosporins**
- **Carbapenems**
- **Monobactams**



Gram-positive

Gram-negative

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Question 3

Which of the following has microbiologic and clinical activity against *Enterococci faecalis*

A) Cefazolin
B) Ceftriaxone
C) Imipenem
D) Aztreonam
E) Piperacillin-tazobactam

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10 – Antibacterial Drugs II: Key Points & Questions that Could Be On The Exam

Speaker: Helen Boucher, MD

Important Resistant Gram+ Organisms

- Enterococcus
  - Resistant: All cephalosporins and monobactams
- MSSA
  - Resistant: All penicillin and monobactams
  - Ceftriaxone does NOT work well
- MRSA
  - Resistant: All beta-lactams except ceftaroline

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IV and Oral MRSA Drugs

IV
- Vancomycin
- Daptomycin
- Linezolid/Tedizolid
- Ceftaroline
- Telavancin
- Minocycline
- Clindamycin
- Dalbavancin/Oritavancin
- Delafloxacin

Oral
- Linezolid/Tedizolid
- TMP-SMX
- Doxy/minocycline
- Clindamycin
- Delafloxacin

Combination Therapy
- See Chambers lecture

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Drug Regimens Active Against VRE (faecium)* Resistant to Vanco and Ampicillin

- Linezolid (FDA approved)
- Daptomycin plus probably one of following
  - Ampicillin or ceftaroline or ceftriaxone
- Ampicillin if amp MIC <=32 mcg/ml
- Ampicillin-sulbactam
  - if resistance due to beta lactamase production
- Not Quinupristin/dalfopristin-FDA approval withdrawn for VRE
- For cystitis (not pyelonephritis)
  - Nitrofurantoin
  - Fosfamycin

**E faecalis* resistant to vanco are often susceptible to ampicillin

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Question 4

What is the mechanism of action for vancomycin resistance for *Staphylococcus aureus*

A) Mec A

B) Efflux pump

C) Change in vancomycin binding site on peptidoglycan

D) Porin

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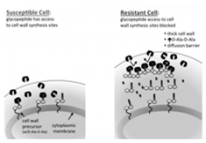
Vancomycin Resistance

- VISA
  - Thick walls, generous binding sites…
- Vancomycin resistance
  - Not in Streptococcus
  - RARE in Staphylococcus
  - Common in Enterococcus
    - Rare in *E. faecalis* (4% in 2014)
    - Common in *E. faecium* (71% in 2014)
    - Mechanism
      - Change in vancomycin binding site on peptidoglycan



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Question 5

Eosinophilic pneumonia is a complication of which of the following:

A) Ceftaroline

B) Delafloxacin

C) Doripenem

D) Daptomycin

E) Linezolid

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Question 6

Drug interference with clotting tests are most often a complication of which of the following

A) Vancomycin

B) Linezolid

C) Dalbavancin

D) Oritavancin

E) Tedizolid

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Question 7

- How common is vancomycin resistant *S. aureus* (VRSA) in the United States
- A) 20% isolates
- B) 10% isolates
- C) <5% isolates
- D) < 50 total isolates
- E) Zero

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Question 8

- Which of the following glycopeptides has the best activity against *C. difficile*
- A) Dalbavancin
- B) Oritavancin
- C) Telavancin
- D) Vancomycin
- E) Teicoplanin

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Question 9

Which of the following would be a bad choice to treat a urinary tract infection empirically

A) Ciprofloxacin

B) Levofloxacin

C) Moxifloxacin

D) Delafloxacin

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Question 10

A 55 year old man 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 **Cefepime**
D **Imipenem-cilastatin-relebactam**
E **Eravacycline**

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Question 11

Which of the following drugs can cause hyperkalemia

A) Linezolid

B) Delafloxacin

C) Trimethoprim

D) Daptomycin

E) Eravacycline

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TMP-SMX Adverse Effects

- **Anaphylaxis**
- **Skin rashes**
- **Bone marrow toxicity**
- **Hemolysis (G6PD def)**
- **Hepatitis**
- **Gastrointestinal effects**
- **"Nephrotoxicity"**
- **Fever**
- **Drug-drug interactions**
- **Hyperkalemia**

TMP COMPETES FOR TUBULAR SECRETION

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Good Luck!!

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Questions, Comments?

- @hboucher3
- hboucher@tuftsmedicalcenter.org
- Helen.boucher@tufts.edu

Dr. Helen Boucher
Chief, Division of Geographic Medicine and Infectious Diseases;
Chair, Physician of Tufts Medical Center
Tufts Medical Center

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11

Antifungal Drugs

Dr. John Bennett

11 – Antifungal Drugs

Speaker: John Bennett, MD

Antifungal Drugs

John E. Bennett, MD
Bethesda, Maryland

Disclosures of Financial Relationships with Relevant Commercial Interests

- **None**

Disclosures of Off-Label Use

- **Will be cited as discussed**

Plan of the talk

- 1. review of antifungals
  - Key points are underlined
- 2. questions on antifungals with answers
- 3. Key points

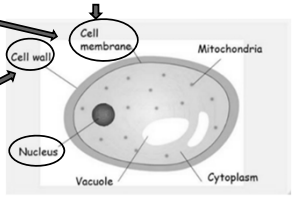
Antifungal drugs

Amphotericin makes cell membrane leak

Azoles stops sterol synthesis for the cell membrane

Echinocandins block cell wall synthesis (glucan fibers)

Flucytosine blocks DNA synthesis in nucleus



DRUG RESISTANCE IN FUNGI: BLOCK TARGET ENZYME

1. ASPERGILLUS AND CANDIDA: AZOLE RESISTANCE IN CYP51A

- gene CYP51A ← modified CYP51A =drug resistance

Lanosterol → C14-demethylase → ergosterol in cell membrane

Azole

2. CANDIDA : ECHINOCANDIN RESISTANCE IN FKS1, FKS2

genes FKS1 and FKS2 ← modified gene=drug resistance

Substrates → glucan synthase → glucan fibers in cell wall

Echinocandin

Antifungal resistant species

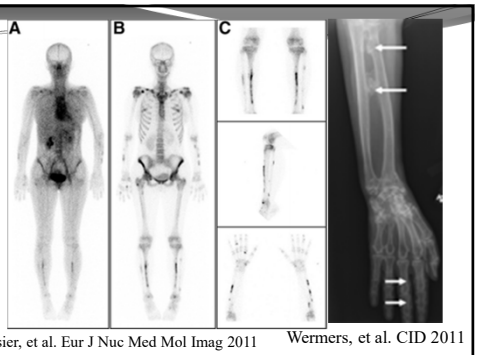
- Amphotericin B resistant: Scedosporium apiospermum (Pseudallescheria boydii), Aspergillus terreus, Variable in Candida lusitaniae, C. auris +/-
- Fluconazole resistant: All moulds, Candida krusei, Candida auris, Candida haemulonii, some Candida glabrata
- Voriconazole resistant: mucormycosis, some cryptic Aspergillus species higher MIC's: (lentulus, ustus, calidoustus)
- Posaconazole resistance: like vori but more mucormycosis activity
- Echinocandin resistance: Cryptococcus, Trichosporon, Histoplasma, Blastomyces, Coccidioides, moulds other than Aspergillus.

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. Teratogenic.
- Isavuconazonium 372mg=isavuconazole 200 mg
- Load with 200 mg q8h X6 then 200 mg qd, IV or PO
- No dose change for renal or moderate liver failure.

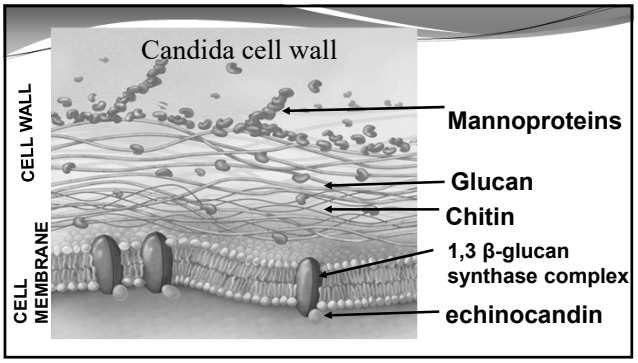
Posaconazole

- 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

FLUCONAZOLE

- FEW SIDE EFFECTS ,WIDE DOSAGE RANGE. DRY SKIN, ALOPECIA
- FOUND IN URINE, CSF. ACCUMULATES IN AZOTEMIA.
- DRUG-DRUG INTERACTIONS. TERATOGENIC
- CANDIDIASIS, COCCIDIOIDAL MENINGITIS, PROPHYLAXIS IN HSCT,
- VERY LOW BIRTHWEIGHT INFANTS, RINGWORM, OTHERS
- NO MOLD ACTIVITY

Echinocandins



Caspofungin, Micafungin, Anidulafungin

- All Candida (including C. auris and C. parapsilosis) 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

- Treatment candidemia)
- Caspofungin, micafungin, anidulafungin effective

- Isavuconazole "not noninferior" to caspofungin in candidemia (don't use)

- Prophylaxis for candidiasis: trials in micafungin (neutropenia), fluconazole (HSCT), posaconazole (HSCT)

Caspofungin and Micafungin in invasive aspergillosis

- IDSA Guidelines: "Primary therapy with an echinocandin is **NOT** recommended.

- Prophylaxis for aspergillosis: micafungin best studied, most often used, not FDA approved

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 known HIV, poorly compliant with ARV, last CD4 20/mcl, presents with low grade fever and headache. Blood culture is growing a yeast, not yet identified. Starting micafungin would be a poor choice if the isolate is which of the following:

a. A. Candida parapsilosis
b. B. Cryptococcus gattii
c. C. Candida auris
d. D. Candida krusei
e. E. Candida glabrata

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 prolonged neutropenia or acute graft-vs-host disease .

Question #5 Continued

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?

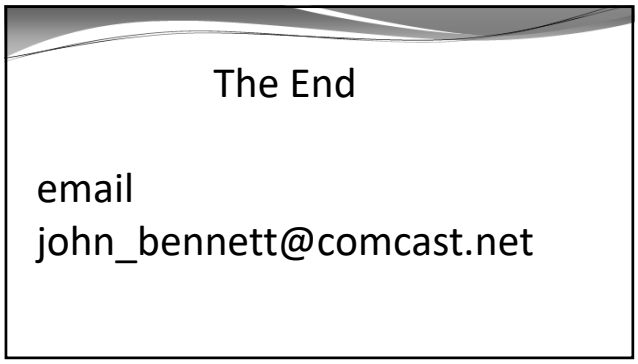
A. flucytosine
B. phenytoin
C. glipizide
D. cyclophosphamide
E. cytomegalovirus

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



12

Core Concepts: Antiviral Drugs

Dr. Andrew Pavia

12 - Core Concepts: Antiviral Drugs

Speaker: Andrew Pavia, MD

Core Concepts: Antiviral Drugs

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

- **Antimicrobial Therapy Inc, WebMD, Merck and Company**

What you need to know

- Common basic mechanism e.g. target and drug type
  - Target: Polymerases (including reverse transcriptase
    - Types: nucleoside/nucleotide analogs, NNRTI's
  - Target: Entry
  - Target: Uncoating
  - Target: Integration
  - Target: Budding or release
- Clinically important resistance mechanisms

Herpes Viruses

Herpes Viruses

- Selective pressure contributes to the development of resistance
- Risk of resistance related to
  - Selective antiviral drug pressure (therapy/prophylaxis)
  - Viral load
    - (higher VL, such as in severely immunocompromised hosts, more likely for resistance to develop)

Herpes Virus Resistance Testing

- Susceptibility testing is available for some herpes viruses at certain commercial and reference labs
  - Phenotypic testing
    - Plaque reduction assay in cell culture (especially for HSV)
  - Genotypic testing
    - PCR and sequencing of target genes with report of mutations associated with resistance
    - Examples: Sequences of UL97 phosphotransferase gene and UL 54 DNA polymerase gene for CMV

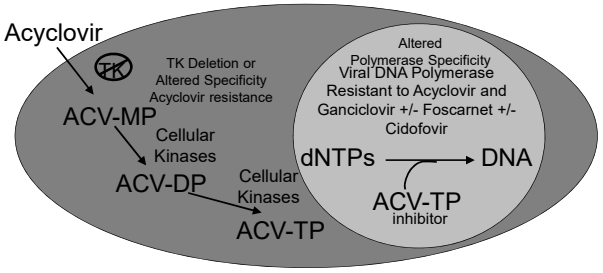
12 - Core Concepts: Antiviral Drugs

Speaker: Andrew Pavia, MD

Acyclovir and Valacyclovir

- Acyclic guanosine analogs
- Therapeutic uses:
  - HSV-1, HSV-2, VZV but NOT CMV or EBV
- Resistance occurs almost exclusively in immunosuppressed hosts (especially HSCT recipients and advanced HIV)
  - More common with HSV than VZV
  - When acyclovir resistant HSV or VZV disease is successfully treated, if recurrent disease occurs, the recurrent isolate is characteristically wild type, i.e. acyclovir sensitive
  - Secondary resistance (due to drug pressure) is more common than primary (the acquired virus is resistant)
  - Acyclovir resistance also confers resistance to valacyclovir (and famciclovir which is not available in US)
  - Mechanisms of resistance
    - Thymidine kinase deficient viral mutants (absent TK)
      - Acyclovir and ganciclovir resistant viruses remain sensitive to foscarnet, cidofovir
    - Thymidine kinase alterations
      - Same as above
    - DNA Polymerase mutations (UL 54 mutation)
      - Acyclovir resistant: may also be resistant to ganciclovir or foscarent or cidofovir

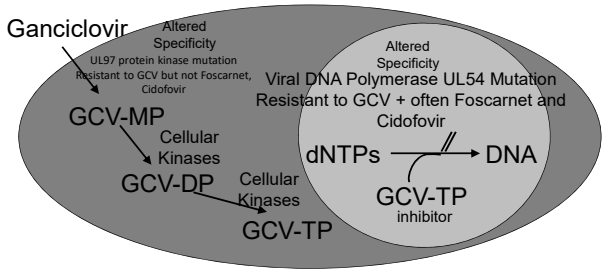
Acyclovir Mechanism of Action
Mechanism of Resistance Within Virus



Ganciclovir and Valganciclovir

- Guanosine analog
  - Active against CMV, HSV-1, HSV-2, VZV
- Requires initial phosphorylation by CMV UL97 ser/thr kinase
- Triphosphate inhibits viral DNA polymerase
- Resistance usually due to drug pressure (secondary resistance) rather than primary (transmitted virus is resistant)
  - UL 97-only resistant to ganciclovir
    - Usually appear first
    - Sensitive to foscarnet, cidofovir
  - UL 54 (polymerase)-resistant to ganciclovir and often to foscarnet and /or cidofovir

Mechanism of Action of Ganciclovir
Mechanism of Resistance Within Virus



Foscarnet

- Activity
  - Binds to DNA polymerase
  - Active against HSV, VZV, CMV
- Resistance
  - DNA Polymerase mutations
  - (UL54 and others, but not UL 97)

Cidofovir

- Mechanism of action
  - Acyclic phosphonate nucleotide analog
  - Inhibitor of phosphorylation by viral DNA Polymerase
- Activity
  - HSV-1, HSV-2, CMV
  - pox viruses, adenovirus, polyoma virus, papillomavirus
- Use with caution
  - Significant renal toxicity
  - Unclear efficacy for adenovirus, polyoma viruses
- Resistance
  - Viral DNA polymerase mutations (not UL 97)

Letermovir

- Mechanism of action
  - Inhibitor of viral terminase subunit pUL56, a component of the terminase complex involved in DNA cleavage and packaging
- Activity
  - CMV
  - NOT HSV, VZV
- Use for prophylaxis approved
  - Little data on treatment
- Drug Interactions
  - Cytochrome p450 3A inhibitor: increases cyclosporine, tacrolimus, sirolimus and decreases voriconazole
- Toxicity
  - Not myelosuppressive
- Resistance
  - Not likely testable: UL56 gene of terminase complex

Hepatitis B

Therapy for Hepatitis B

- Lamivudine
  - Active against both HIV and HBV
  - Resistance:
    - most common: YMDD motif in viral DNA polymerase, (similar to M184V in HIV)
    - most often in patients chronically treated with lamivudine monotherapy
- Tenofovir
  - Activity: HIV and HBV
  - Nothing testable about mechanism of resistance
- Telbivudine
  - Active against HBV only – DNA polymerase inhibitor
  - Nothing testable about mechanism of resistance
  - Not active against HIV
- Adefovir, Entecavir
  - Active against HBV and has some anti HIV activity
  - Nothing testable about mechanism of resistance

HBV Therapy

Resistance Concerns if Patient Has HBV/HIV Coinfection

- Because emtricitabine (FTC), lamivudine (3TC), and tenofovir (TDF) have activity against both HIV and HBV, if HBV or HIV treatment is needed, ART should be initiated with the combination of TDF + FTC or TDF + 3TC as the nucleoside reverse transcriptase inhibitor (NRTI) backbone of a fully suppressive antiretroviral (ARV) regimen.
- TAF has activity against HBV similar to TDF but not likely to be tested
- If HBV treatment is needed and TDF cannot safely be used, the alternative recommended HBV therapy is entecavir in addition to a fully suppressive ARV regimen
- Entecavir has activity against HIV; its use for HBV treatment without ART in patients with dual infection may result in the selection of the M184V mutation that confers HIV resistance to 3TC and FTC. Therefore, entecavir must be used in addition to a fully suppressive ARV regimen when used in HIV/HBV-coinfected patients
- If ART needs to be modified due to HIV virologic failure and the patient has adequate HBV suppression, the ARV drugs active against HBV should be continued for HBV treatment in combination with other suitable ARV agents to achieve HIV suppression

Influenza

Influenza Therapy

- Adamantanes (Rimantidine, Amantadine)
  - Not recommended because resistance is widespread and stable
  - Activity
    - Influenza A only
  - Mechanisms of action
    - M2 protein
- Neuraminidase Inhibitors (Oseltamivir, Zanamivir, Peramivir)
  - Activity
    - Influenza A and B
  - Mechanisms of action
    - Inhibits release of new virions from surface of infected cell
  - Resistance:
    - H274Y mutation is most common (oseltamivir only, not zanamavir) which occurs mostly in Influenza A, confers partial resistance to peramivir
    - Occasionally emerges in HSCT patients on prolonged treatment or with prophylaxis

Influenza Therapy

- Baloxavir Single dose active against Influenza A and B
  - Mechanisms of action
    - Inhibits replication of viral RNA by interfering with polymerase complex via Cap-Dependent Endonuclease
  - Resistance
    - Several mutations (don't memorize) predominantly changes to I38X (Thr, Phe or Met)
    - Treatment emergent resistance in 5% to as high as 20% in children
    - Resistance more common in H3N2 than H1N1 and rare in influenza B
    - Do date, only limited transmission of resistant variants

Summary of Influenza Resistance 2020-2021 Much is Non Testable Since It Changes With Time!

- Neuraminidase Inhibitor Resistance
  (Oseltamivir, Zanamavir, Peramivir)
  - Seasonal H3N2 = sensitive
  - 2009/Pandemic H1N1 = sensitive (Current H1N1 are closely related)
  - Influenza B – sensitive but higher IC50
  - Seasonal H1N1 2008 = resistant (These strains have not circulated since 2009)
- Adamantine Resistance
  (Rimantidine)
  - Essentially all circulating viruses resistant
- Baloxavir
  - 2 isolates with resistance detected in nationwide surveillance in Japan

SARS-CoV-2

SARS-CoV-2

- Remdesivir
  - Mechanism
    - Acts as nucleoside analog
    - Inhibits RNA-dependent RNA polymerase
  - Resistance
    - Resistant mutant selected for by serial passage in vitro, but none detected in clinical samples (with very limited data)
  - Not testable yet
- Molnupiravir
  - Mechanism
    - Acts as nucleoside analog
    - Causes "catastrophic errors" in replication

Good Luck on the Exam!
andy.pavia@hsc.utah.edu
twitter: @AndrewPaviaMD

13

Nontuberculous Mycobacteria in Normal and Abnormal Hosts

Dr. Kevin Winthrop

13 - Nontuberculous Mycobacteria in Normal and Abnormal Hosts

Speaker: Kevin Winthrop, MD

Nontuberculous Mycobacteria in Normal and Abnormal Hosts

Kevin L. Winthrop, MD, MPH
Professor, Divisions of Infectious Diseases
Public Health and Preventive Medicine
Oregon Health & Science University

Disclosures of Financial Relationships with Relevant Commercial Interests

- Research Grant: Insmed
- Consultant: Insmed, Spero, Red Hills, Paratek

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

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

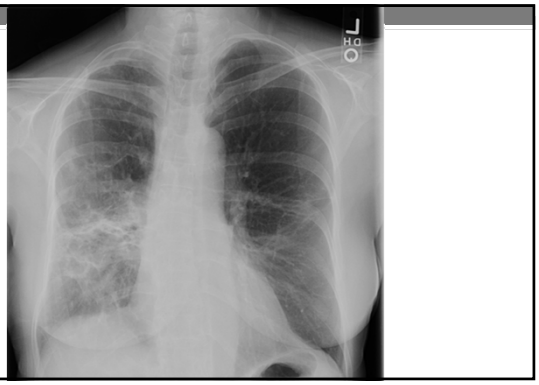
Pulmonary NTM

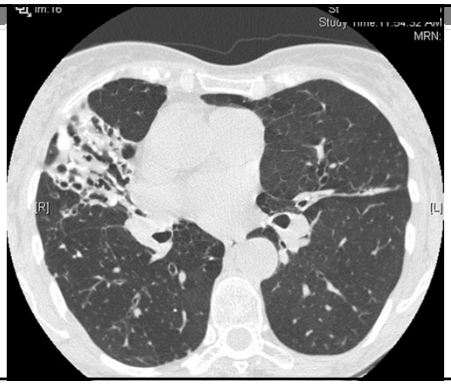
- MAC is most common etiology (60-90%)
- M. kansasii and M. abscessus
  - *M. kansasii* primarily in the South
  - Recent *M. abscessus* increase in CF
- Other organisms of importance
  - *M. xenopi* (northern US/ Canada, Europe)
  - *M. malmoense* (Europe)

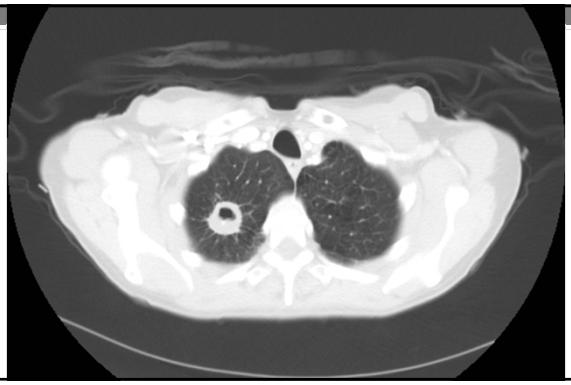
Two Types of MAC Pulmonary Diseases

- 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

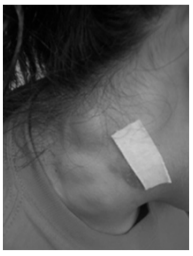
EXTRAPULMONARY NTM

1. Immunocompetent settings
2. Immunocompromised settings

Immunocompetent settings

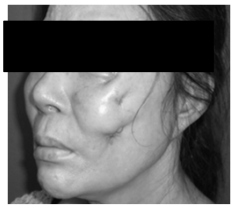
- Nail salon, trauma, surgical or injection procedures, fishtank, hot tubs
- Rapid or slow growing NTM
- Incubation period
  - Infection usually occurs 2-8 weeks after contact with contaminated water source

Children under 5 years NTM > TB



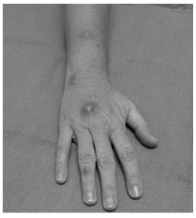
- Usually MAC
  - Males > females, age 1-2 years old
- Surgical resection alone is best therapy
- Adjunctive ABX rarely needed

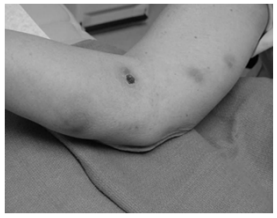
Post- plastic surgery



- Usually Rapid Grower:
  - *M. chelonae*
- Remove foreign-bodies
- Therapy as per in-vitro susceptibility
- Length 4-6 months

M. marinum---fish tank granuloma



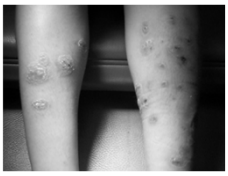


Treatment: multiple drugs

- 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

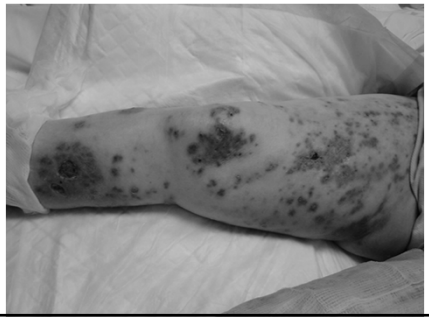
* For evidence quality, see Table 1.
† Rifabutin dose may need to be modified based on drug–drug interactions (*see* text).
‡ Preventive therapy indicated for persons with < 50 CD4+ cells/μl; may stop if > 100 cells/μl.

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

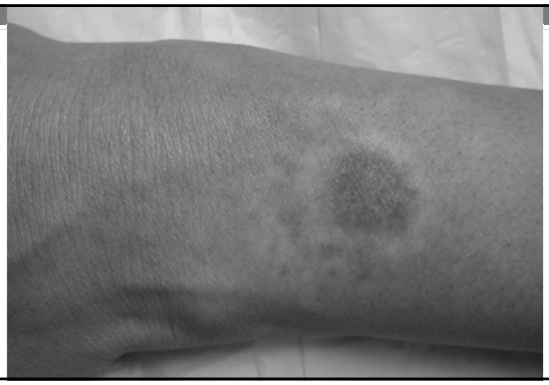
- Slow growing. M. avium complex.
- Requires molecular identification
- Over 150 cases from open heart surgery: prosthetic valve, vascular graft, LVAD, heart transplant
- Aerosol from contaminated heater-cooler units used in operating room for cardiac by-pass.
- Time to diagnosis 1.7-3.6 years post-op, with cases reported up to 6 years postoperatively.
- Mycobacterial blood cultures
- Treatment: ???

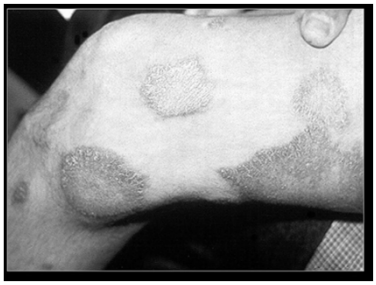
Hansen's Disease (Leprosy)

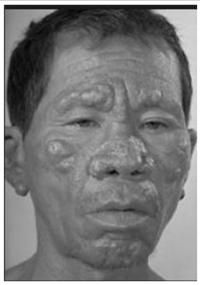
- Rare in US (40-50 cases per year)
  - Armadillos and gulf region
  - Rest imported
- Most humans resistant
  - Household contacts at risk (low risk)
  - Nasopharyngeal transmission?
- *M. leprae* does not grow in culture

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

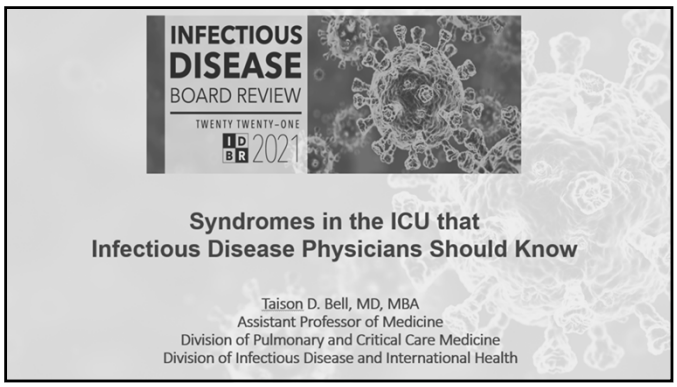
14

Syndromes in the ICU that ID Physicians Should Know

Dr. Taison D. Bell

14 – Syndromes in the ICU that ID Physicians Should Know

Speaker: Taison Bell, MD



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	General internal medicine
Systemic inflammatory response syndrome (SIRS) and sepsis	Malignancies
Ventilator-associated pneumonias	Hemophagocytic lymphohistiocytosis (Hemophagocytic syndrome)
Noninfectious pneumonias (eosinophilic and acute respiratory distress syndrome [ARDS])	Noninfectious inflammatory disorders (e.g., vasculitis, lupus, inflammatory bowel disease)
Bacterial pneumonias	Dermatologic disorders
Viral pneumonias	Hematologic disorders
Hyperthermia and hypothermia	Noninfectious central nervous system disease
Near-drowning and *Scedosporium* and *Pseudallescheria* infection	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 was started two weeks prior to admission

Her clinical syndrome is most consistent with:

A. Sepsis

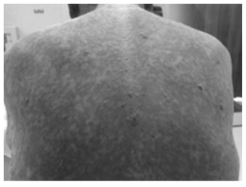
B. Stevens–Johnson syndrome (SJS)/toxic epidermal necrolysis (TEN)

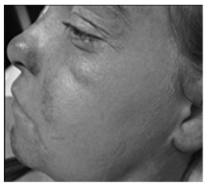
C. DRESS (drug-induced hypersensitivity syndrome)

D. Erythema Multiforme

E. Neuroleptic Malignant Syndrome (NMS)

Morbilliform Rash with Facial Edema and Eosinophilia





14 – Syndromes in the ICU that ID Physicians Should Know

Speaker: Taison Bell, MD

Exanthematous drug eruptions

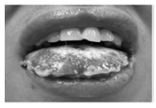
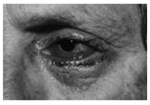
- T-cell-mediated, delayed type IV hypersensitivity reaction
- Diffuse maculopapular rash (morbilliform)
- Highest incidence with aromatic antiseizure medications: carbamazepine, phenytoin, and lamotrigine (1:100)

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

Stevens Johnson Syndrome and Toxic Epidermal Necrolysis

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

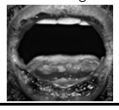
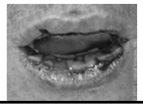
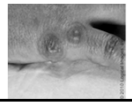
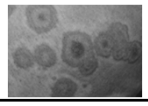
Stevens Johnson and Toxic Epidermonecrolysis

- "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

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

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

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

14 – Syndromes in the ICU that ID Physicians Should Know

Speaker: Taison Bell, MD

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)

www.nmsis.org, 1-888-667-8367

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. Started on 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

14 – Syndromes in the ICU that ID Physicians Should Know

Speaker: Taison Bell, MD

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 CENTERS FOR MEDICARE & MEDICAID SERVICES

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

Surviving Sepsis Campaign: Other Things

CMS CENTERS FOR MEDICARE & MEDICAID SERVICES

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

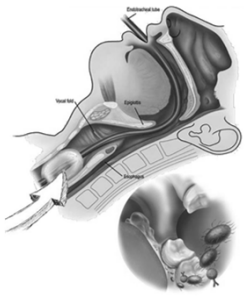
14 – Syndromes in the ICU that ID Physicians Should Know

Speaker: Taison Bell, MD

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

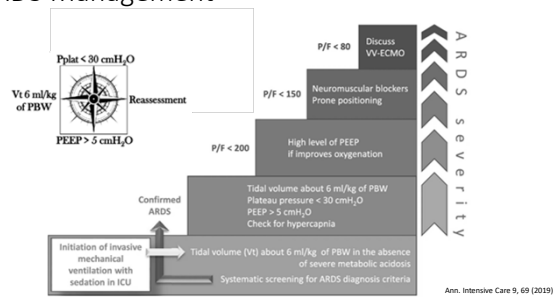
Question

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

ARDS Management



Ann. Intensive Care 9, 69 (2019)

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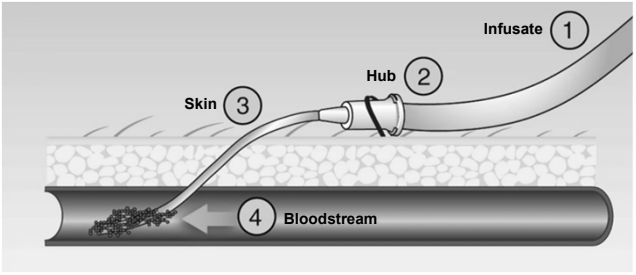


Antiseptic Techniques: Catheter Insertion

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

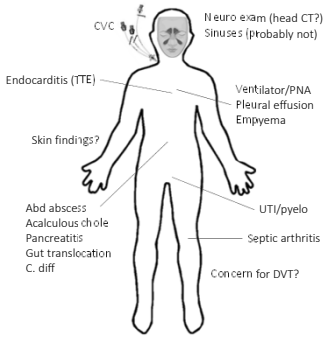
- Prophylactic Antibiotics
  - Not indicated unless water grossly contaminated
  - Steroids not indicated
- Etiologic Agents
  - Water borne organisms common
    - Pseudomonas, Proteus, Aeromonas
- Therapy for Pneumonia
  - Directed at identified pathogens

14 – Syndromes in the ICU that ID Physicians Should Know

Speaker: Taison Bell, MD

Approach

- Run med list
- Consider AI
- Pyrexic syndromes



Thank You

- Good luck!
- Please give feedback
- Contact
  - taison.bell@virginia.edu
  - Twitter: @TaisonBell

15

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

Dr. Rajesh Gandhi

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

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

Disclosures of Financial Relationships with Relevant Commercial Interests

Scientific advisory boards:
Merck (> 1 year ago)
Gilead (> 2 years ago)

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

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.

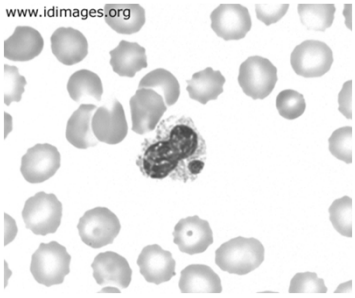
PMH: None.

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

Contributed by Anne Kasmar, M.D.

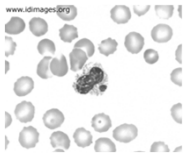
PE: She appeared well. T 103.5, BP 104/50, HR 122, RR 18, O_2 sat 97% on RA. She had no rash or adenopathy. Remainder of exam was normal.

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



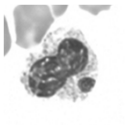
Differential Diagnosis

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.

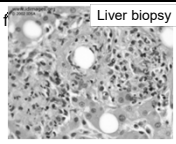


- Diagnosis confirmed with PCR testing.
- She was treated with doxycycline; symptoms completely resolved.

Case 2

- Man in his 20s presented with nine days of vomiting, diarrhea, fever, headaches.
- He lived on farm with goats, chickens, guinea pigs, turkeys, cats, dogs.
- He appeared acutely ill. T104.4° F. Exam otherwise normal.
- AST 111, ALT 79, Alk. Phos 146.

Liver biopsy



A. Coxiella
B. Cryptococcus
C. Histoplasma
D. Cyclospora
E. Bartonella

Contributed by Paul M. Jost, MD

Case 3

63 yo M with history of renal transplant developed multiple erythematous, raised, pruritic lesions on his thighs over the course of several weeks.

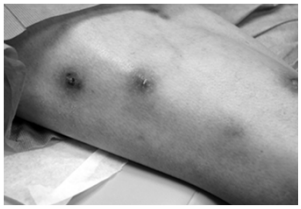
PMH: ESRD due to post-streptococcal glomerulonephritis, s/p cadaveric renal transplant in 1982; HCV infection.

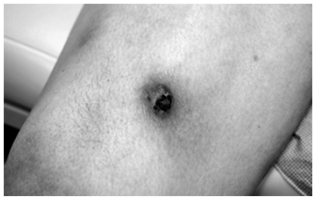
Meds: prednisone 15 mg qd; azathioprine 150 mg qd

SH: Patient had a healthy cat at home. He lived in rural Maryland near farm animals and frequently saw deer in his yard. Avid gardener but recalled no recent puncture wounds. Several tick bites in the past year. Travel history: Mexico 2 yrs ago.

Contributed by Raj Gandhi, M.D.

PE: T: 36.8. Multiple erythematous nodules on both lower extremities. Lesions were tender and non-fluctuant, some with a central necrotic area. There was no discharge. The remainder of his exam was normal.





Studies:

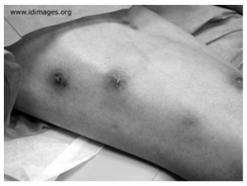
WBC 3.3; Hematocrit 26%; Platelets 118,000; BUN 59 mg/dL, Creatinine 2.1 mg/dL; Bilirubin (total/direct) 2.1/1.3; AST 70; Alkaline Phosphatase 321.

CXR: normal

Blood Cultures: no growth

Differential Diagnosis

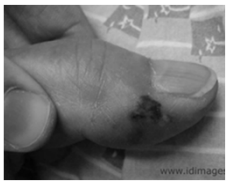
1. Cryoglobulinemic vasculitis related to HCV infection
2. Nocardiosis
3. Nontuberculous mycobacteria
4. Cutaneous aspergillus
5. Botryomycosis



Diagnosis and Follow-up

- Patient underwent skin biopsy of a lesion on his lower extremity.
- Microscopic examination: abscess containing many polymorphonuclear leukocytes, scattered multinucleated giant cells.
- Special stains revealed acid-fast bacilli.
- Culture grew *Mycobacterium chelonae*.

Case 4



- 72 yo M with bioprosthetic aortic valve presents with fever, dyspnea, anorexia.
- Lives in Boston; no recent travel.
- T: 101˚ Non-tender lesion on thumb.

A. Herpetic whitlow
B. Herpes zoster
C. Tache noir (Rickettsial infection)
D. Fusariosis
E. Endocarditis

Case 5

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.

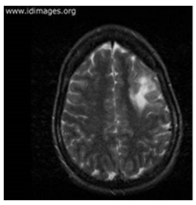
On exam, she was afebrile. She had oral thrush. She had difficulty naming objects and right-sided weakness.

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

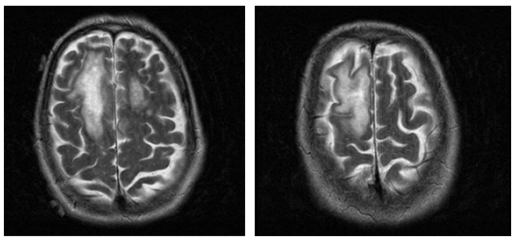


MRI: Abnormal T2 signal involving white matter, left fronto-parietal region. No enhancement, edema, mass effect

Progressive multifocal leukoencephalopathy

- CSF JC virus positive
- Demyelinating disease of central nervous system caused by reactivation of JC virus, a polyoma virus
- Immunocompromised hosts (heme malignancy; HIV, natalizumab, rituxamab)
- Rapidly progressive focal neurologic deficits, usually due to cerebral white matter disease.
- Rx: reversal of immunodeficiency. In people with HIV: antiretroviral therapy

PML



Contributed by Vince Marconi, M.D.

Case 6

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.

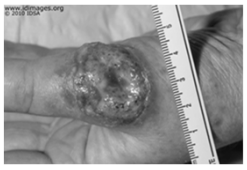
Reported seeing several kinds of insects and receiving several bites. No known animal exposures or tick bites.

Contributed by Rojelio Mejia, MD

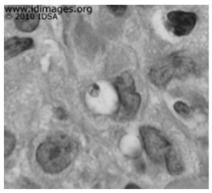
Differential Diagnosis

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



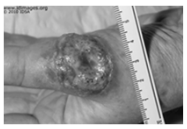
Skin biopsy showed amastigote, with kinetoplast in a vacuole. Culture of tissue from skin biopsy in Schneider's Media revealed promastigotes. PCR of tissue: *Leishmania guyanensis*.



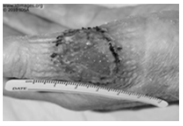
Skin biopsy, H and E stain

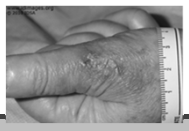
Culture of skin biopsy tissue in Schneider's medium

Treated with liposomal amphotericin



One week after treatment

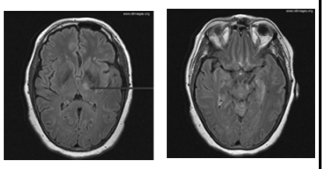




Follow-up at 3 months

Case 7

- 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

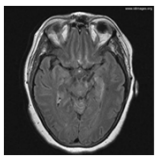


MRI: T2 hyperintensity left thalamus and substantia nigra; leptomeningeal enhancement

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



Case 8

HPI: 25 yo male with 2 days of fever and rash. Rash was predominantly on hands.

PMH: None. **Medications:** none

SH: Lived in New England. One female sexual partner. Denied travel or animal exposures.

PE: Oral and hand lesions, as shown. Otherwise, normal exam.

Contributed by Johanna Daily, M.D.

Differential Diagnosis

A. Syphilis
B. Acute HIV-1 infection
C. RMSF
D. Erythema multiforme
E. Erythema migrans

Diagnostic Procedures/Results

- Culture of oral ulcer: HSV-1.
- Diagnosis: HSV-1-associated erythema multiforme.

- Detailed history revealed he had previous episode one year before, at which time he had first developed an oral ulcer.
- Treated with acyclovir, with complete resolution of his symptoms.
- Subsequently has had recurrent episodes

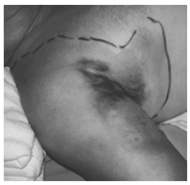
Case 9

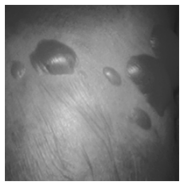
- 60 yo M presented to ED with a few hours of severe pain in right upper extremity. There was no history of trauma. Exam was normal with no obvious skin changes. He was discharged home.
- Over the next few hours, he developed progressive swelling of right upper extremity.
- Exam: right upper extremity 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





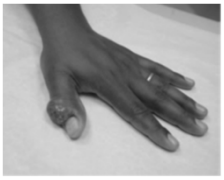
Case 10:
If you get this one . . . !

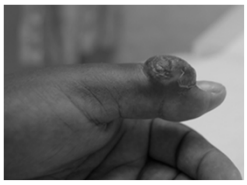
30 yo man of Ethiopian descent cut his left thumb with a knife while slaughtering a lamb as part of Easter festivities. He washed the wound with water and applied lemon juice and alcohol. One week later, he developed swelling and tenderness and a fluctuant lesion at the site.

Two weeks after the injury, he underwent incision and drainage; cultures grew *Staph. aureus* (oxacillin sensitive). Treated with cephalexin but did not improve.

Contributors: Drs. Isaac Bogoch, Rajesh Gandhi

Afebrile. 2 x 2 x 2 cm firm lesion on his thumb, without discoloration, purulent discharge, fluctuance, or bleeding.

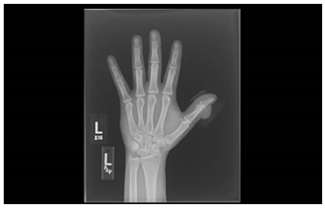




Creatinine and LFTs normal. Glucose 158.

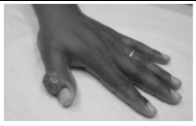
WBC 4.2 (normal differential).

X-ray: fungating soft tissue lesion on dorsal aspect of distal thumb; no underlying bone or joint abnormality



Question

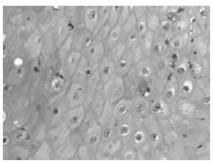
A. Botryomycosis due to *S. aureus*
B. Nocardia
C. Brucella
D. Orf
E. Salmonella



Contributors: Dr. Isaac Bogoch, Rajesh Gandhi

Follow-up

- Lesion removed surgically.
- Pathology: hyperkeratosis, epidermal necrosis, dermal infiltrate of mixed inflammatory cells; surface keritonocytes with eosinophilic inclusions
- PCR testing at CDC + for orf virus DNA



Appearance consistent with ecythma contagiousum

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

16

Skin and Soft Tissue Infections

Dr. Helen Boucher

16 – Skin and Soft Tissue Infections

Speaker: Helen Boucher, MD

Skin and Soft Tissue Infections

Helen Boucher, MD, FACP, FIDSA
Professor of Medicine
Tufts University School of Medicine

Disclosures of Financial Relationships with Relevant Commercial Interests

- Editor
  - ID Clinics of North America
  - Antimicrobial Agents and Chemotherapy
  - Sanford Guide
- 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)

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- **Voting Member, Presidential Advisory Council on Combating Antibiotic Resistant Bacteria (PACCARB)**

3

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 %**

4

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)**

5

Six pathogens that can cause infection after cat bites?

1. ***Pasteurella species***
2. **Anaerobic bacteria: e.g., *Fusobacteria***
3. ***Bartonella henselae (Cat Scratch disease)***
4. **Rabies virus**
5. ***S. aureus***
6. ***Streptococcal species***

6

Question #2

A 50 year old female alcoholic suffered a provoked dog bite.

- **Bite was cleansed, tetanus toxoid given, and the dog placed under observation**
- **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**

7

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***

8

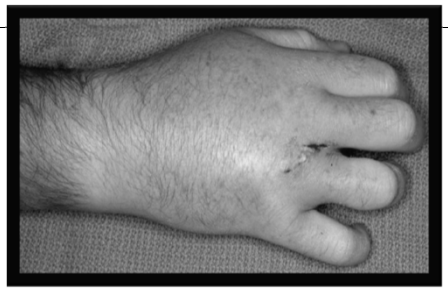
Question #3

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?***

9



10

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?***

11

Question #5 (Extra Credit)

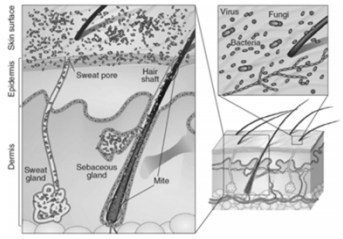
Medicinal leeches are applied to a non-healing leg ulcer.

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***

12

The Skin: Local Invasion by Structure



https://www.id.theclinics.com/article/S0891-5520(20)30090-8/pdf

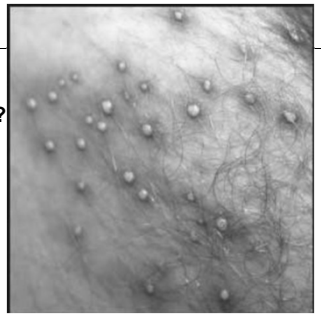
13

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

14

What is this?



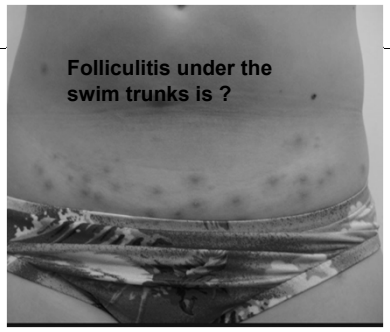
15

Superficial Folliculitis

- Purulence (sometimes mixed with blood) where hair follicles exit skin
- 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**

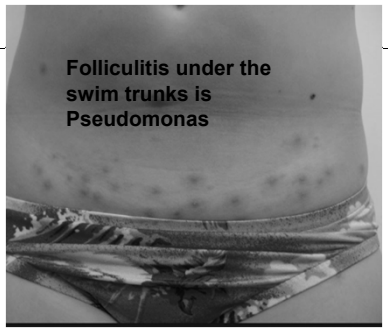
16

Folliculitis under the swim trunks is ?



17

Folliculitis under the swim trunks is Pseudomonas



18

Microbial Etiology?

19

Streptococcal Infection of the Epidermis
Name of the Clinical Syndrome?

Infection of outer layers of epidermis with production of "honey-crust" scales

Prevalent in warm, humid environments – esp. in children.

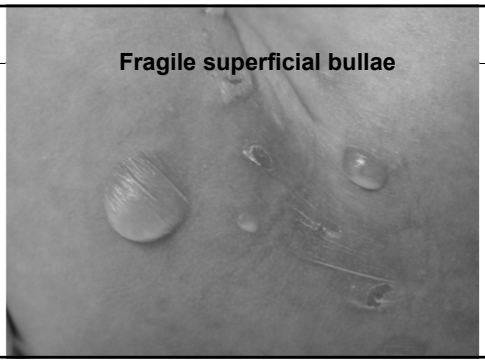
Microbial etiology

- **Streptococci: Grps A, B, C, G**

Name?

- **Streptococcal impetigo**

20



21

Fragile Bullae in Epidermis

Diagnosis?

- **Bullous impetigo**

Etiology?

- ***S. aureus***

22

Impetigo ("to attack")

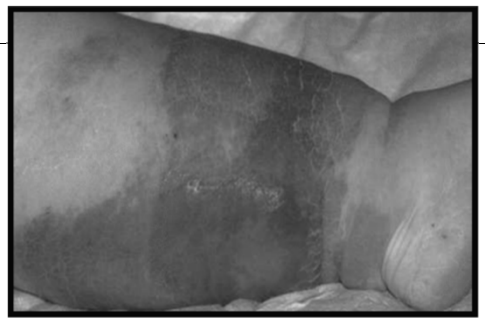
- **Bullous impetigo: *S. aureus***
- **Non-bullous impetigo: *S. pyogenes, group A***
- **So, empiric therapy aimed at *S. aureus* as could be MRSA**
- **Topical: topical antibiotic ointment (TAO), mupirocin, retapamulin**
- **Oral rarely needed**
  - **e.g, Clindamycin, doxycycline**

23

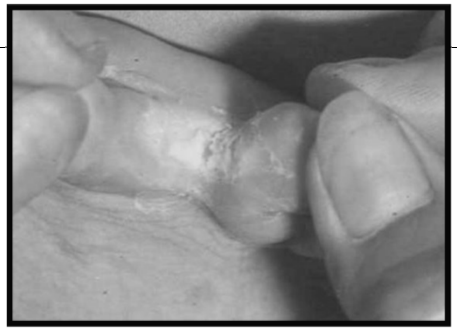
Complications of *S.pyogenes, S. dysgalactiae (Gps C&G)* impetigo

- **Post-streptococcal glomerulonephritis due to nephritogenic strains**
- **Rheumatic fever has "never" occurred after streptococcal impetigo**

24



25



26

Acute onset of painful, rapidly spreading red plaque of inflammation involving epidermis, dermis, and subcutaneous fat

NO PURULENCE

Diagnosis?

27

Acute onset of painful, rapidly spreading red plaque of inflammation involving epidermis, dermis, and subcutaneous fat

NO PURULENCE

Diagnosis:

Erysipelas: Non-purulent cellulitis

28

Acute onset of painful, rapidly spreading red plaque of inflammation involving epidermis, dermis, and subcutaneous fat.

NO PURULENCE

Diagnosis:

- **Erysipelas: Non-purulent cellulitis**

Etiology?

29

Acute onset of painful, rapidly spreading red plaque of inflammation involving epidermis, dermis, and subcutaneous fat. NO PURULENCE

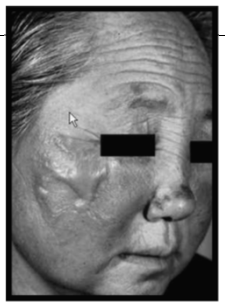
Diagnosis?

- **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***

30



31

Erysipelas ("Red Skin")

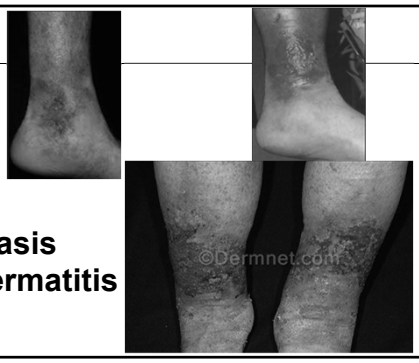
- Acute onset of painful skin, rapid progression +/- lymphangiitis
- Inflamed skin elevated, red, and demarcated
- Etiology: Streptococci--Gps. A,B,C, & G (*S.pyogenes, S. agalactiae, S.dysgalactiae subsp. equisimilis)*
- Predisposition:
  - Lymphatic disruption, venous stasis

32

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

33



Stasis Dermatitis

34

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

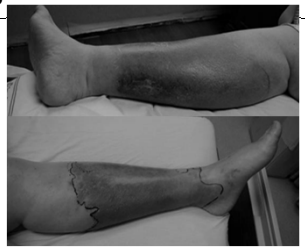
35

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

36

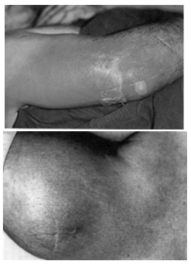
Cellulitis

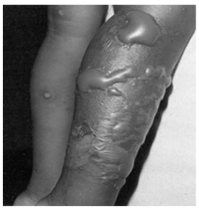


- Without localization or preceding macro or micro trauma: usually Beta strep. (usually GAS), extremities > face, elsewhere
- With localization (cut, pustule, etc.) or preceding trauma: *S. aureus*

37

Severe Cellulitis





Microbiology: Streptococci (grp A>B,C,G); less often *S. aureus*; rarely GNR

38

Recurrent Cellulitis

- Frequently non-group A streptococci (esp. B,G)
- Relapse > recurrence
- Prophylaxis:
  - benzathine penicillin IM
  - oral penicillin; other systemic antibiotics
  - decolonization (nasal, elsewhere)

39

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

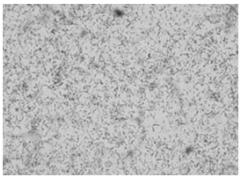
40

Erysipelothrix (Gram + rod)

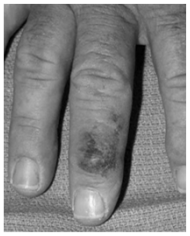
- On finger after cut/abrasion exposure to infected animal (swine) or fish
- Subacute erysipelas (erysipeloid)
- Severe throbbing pain
- Diagnosis: Culture of deep dermis (aspirate or biopsy)
- Treatment: Penicillin, cephalosporins, clindamycin, fluoroquinolone

41

Erysipelothrix rhusiopathiae Infection



Gram stain of the organism (G+ rod) identified on culture



Resolving cellulitis caused by *Erysipelothrix rhusiopathiae*

42

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 40C, diffuse erythema of the skin. Oxygen sat. 88% RA**
- **WBC 3000 with 25% polys and 50% band forms. Platelet count is 60,000**

(Continued)
43

Question #6 Continued

Which one of the following is the most likely complication of the erysipelas?

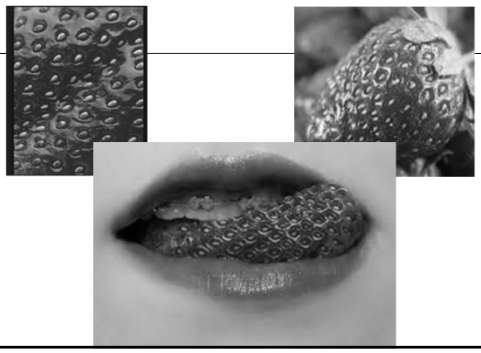
A. **Bacteremic shock due *to S. pyogenes*?**
B. **Toxic shock due to *S. pyogenes*?**
C. **Bacteremic shock due to *S. aureus*?**
D. **Toxic shock due to *S. aureus*?**

44

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**

45



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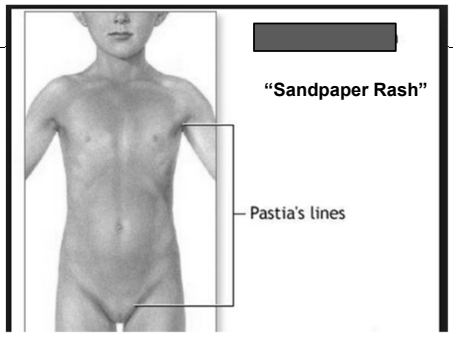

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The most likely diagnosis ?

- **Infectious mononucleosis**
- **Coxsackie hand, foot and mouth disease**
- **Scarlet fever**
- ***Arcanobacterium hemolyticum***

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The most likely diagnosis ?

- Infectious mononucleosis
- Coxsackie hand, foot and mouth disease
- Scarlet fever
- *Arcanobacterium hemolyticum*

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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

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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?

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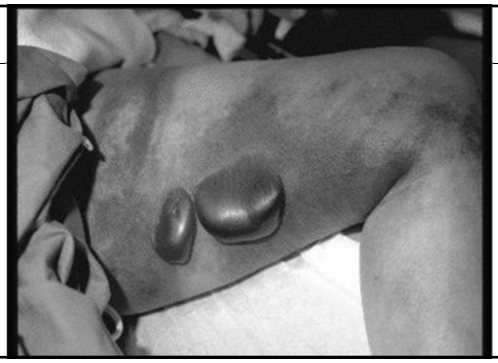

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Erysipelas with loss of pain, hemorrhagic bullae, rapid progression..

Necrotizing fasciitis is 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

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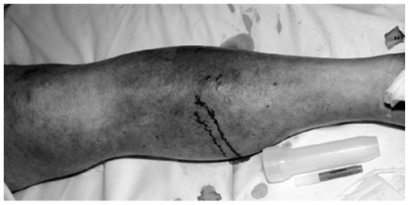
Necrotizing Fasciitis: at the bedside



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

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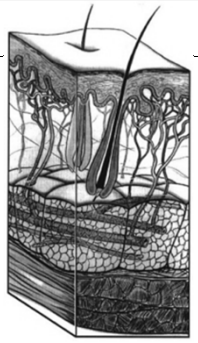
Treatment of necrotizing fasciitis

- Think of it
- Surgical debridement: sometimes several times so as to achieve source control
- Appropriate antimicrobial therapy

55



Anatomy	Syndrome
Epidermis Skin	Erysipelas Impetigo Folliculitis
Dermis	Ecthyma Furunculosis Carbunculosis
	All of this is Cellulitis
Superficial fascia Subcutaneous tissue Subcutaneous fat, Nerves, arteries, veins	Necrotizing fasciitis
Deep fascia	
Muscle	Myonecrosis (clostridial and non-clostridial)

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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

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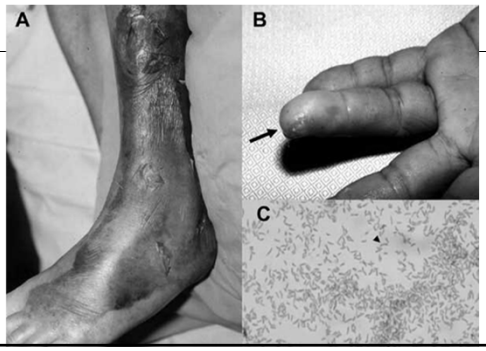

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Organisms Whose Growth is Stimulated by Excess Iron

- *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"

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Thank You!

- David Gilbert

- Our patients and their families

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Questions, Comments?

- @hboucher3
- hboucher@tuftsmedicalcenter.org
- Helen.boucher@tufts.edu

Tufts

Dr. Helen Boucher
Chief, Division of Geographic Medicine and Infectious Diseases;
Chair, Physician of Tufts Medical Center
Tufts Medical Center

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Sunday, August 22, 2021

AM Moderator: Pavia
PM Moderator: Masur

#	Start		End	Presentation	Speaker
17	9:30 AM	-	10:00 AM	**Daily Question Preview Day 2**	*Andrew Pavia, MD (Moderator)*
18	10:00 AM	-	11:00 AM	**Clinical Immunology and Host Defense**	*Steven Holland, MD*
19	11:00 AM	-	11:45 AM	**Respiratory Viral Infections Including Influenza, Immunocompetent, and Immunocompromised Patients**	*Andrew Pavia, MD*
	11:45 AM	-	12:15 PM	***BREAK with FACULTY CHAT***	
20	12:15 PM	-	1:00 PM	**Board Review Day 2**	*Drs. Pavia (Moderator), Aronoff, Chambers, Nelson and Trautner*
21	1:00 PM	-	1:45 PM	**Bone and Joint Infections**	*Sandra Nelson, MD*
22	1:45 PM	-	2:30 PM	**Photo Opportunity II: More Photos and Questions to Test Your Board Preparation**	*John Bennett, MD*
	2:30 PM	-	3:00 PM	***BREAK with FACULTY CHAT***	
23	3:00 PM	-	4:00 PM	**Endocarditis of Native and Prosthetic Devices, and Infections of Pacers and Ventricular Assist Devices**	*Henry Chambers, MD*
24	4:00 PM	-	4:45 PM	**Zoonoses**	*David Aronoff, MD*
25	4:45 PM	-	5:00 PM	**Penicillin Allergies**	*Sandra Nelson, MD*
	5:00 PM	-	5:30 PM	***BREAK with FACULTY CHAT***	
26	5:30 PM	-	6:15 PM	**Staphylococcal Disease**	*Henry Chambers, MD*
27	6:15 PM	-	6:45 PM	**Helicobacter and Clostridioides Difficile**	*David Aronoff, MD*
28	6:45 PM	-	7:30 PM	**HIV-Associated Opportunistic Infections I**	*Henry Masur, MD*
	7:30 PM	-	8:00 PM	***END OF THE DAY FACULTY CHAT***	

17

Daily Question Preview *2*

Dr. Andrew Pavia (Moderator)

17 – Daily Question Preview: Day 2

Moderator: Andrew Pavia, MD

Daily Question Preview: Day 2

Moderator: Andrew Pavia, MD

PREVIEW QUESTION

2.1 **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.

PREVIEW QUESTION

2.1 **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

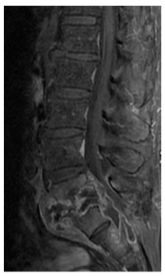
C) Zanamivir is clearly preferred because of low systemic absorption

D) Oseltamivir should be started as soon as possible

PREVIEW QUESTION

2.2 **57-year-old male presented with 3 months 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**



PREVIEW QUESTION

2.2 **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

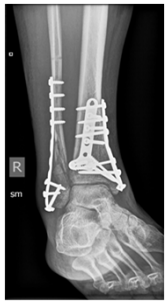
PREVIEW QUESTION

2.3 **44-year-old healthy woman suffered a right ankle closed pilon fracture and underwent open reduction and internal fixation (ORIF)**

Chronically discharging wound despite courses of cephalexin and trimethoprim-sulfamethoxazole

Two months after ORIF, superficial wound culture grows methicillin-susceptible Staph aureus

Plain films: Hardware intact; fracture not yet consolidated



17 – Daily Question Preview: Day 2

Moderator: Andrew Pavia, MD

PREVIEW QUESTION

2.3 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

PREVIEW QUESTION

2.4 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.

PREVIEW QUESTION

2.4 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

PREVIEW QUESTION

2.5 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.

PREVIEW QUESTION

2.5 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

PREVIEW QUESTION

2.6 19-year-old 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.

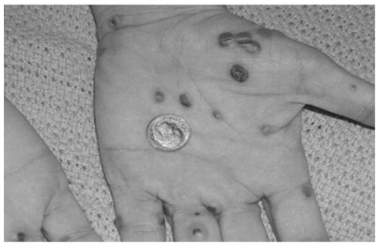
She reported her new pet prairie dog was also ill (lethargy, wasting, not eating)

17 – Daily Question Preview: Day 2

Moderator: Andrew Pavia, MD

PREVIEW QUESTION

2.6



Sejvar JJ, *JID* 2004:190

PREVIEW QUESTION

2.6 **What is the most likely infection?**

A) Erysipelothrix rhusiopathiae

B) Smallpox

C) Gambian cutaneous ulcerans

D) Monkeypox

E) Yaws (Treponema pallidum pertenue)

PREVIEW QUESTION

2.7 **25-year-old male 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: T37oC, 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. cephalexin 250 mg qid. One week later: mass unchanged. Culture neg. Syphilis FTA & HIV neg.

PREVIEW QUESTION

2.7 **Most likely dx:**

A) Bartonella henselae

B) Treponema pallidum

C) Haemophilus ducreyi

D) Francisella tularensis

E) Klebsiella (Calymmatobacterium) granulomatis

PREVIEW QUESTION

2.8 **28-year-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**

PREVIEW QUESTION

2.8 **Most likely diagnosis:**

A) Malaria

B) Dengue

C) Ehrlichiosis

D) Leptospirosis

E) Zika

17 – Daily Question Preview: Day 2

Moderator: Andrew Pavia, MD

PREVIEW QUESTION

2.9 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.

PREVIEW QUESTION

2.9 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

PREVIEW QUESTION

2.10 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.

PREVIEW QUESTION

2.10 What do you do counsel?

A) Administer clindamycin

B) Administer cefazolin

C) Administer cefazolin after intraoperative test dose

D) Administer ceftriaxone

E) Administer vancomycin

PREVIEW QUESTION

2.11 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.

PREVIEW QUESTION

2.11 Which one of the following would you recommend?

A) Bone biopsy with culture as the blood isolate is likely a contaminant

B) Request speciation of the blood isolate

C) PET-CT to look for another focus of infection for biopsy

D) Fungal serologies, PPD

17 – Daily Question Preview: Day 2

Moderator: Andrew Pavia, MD

PREVIEW QUESTION

2.12 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).

PREVIEW QUESTION

2.12 Which one of the alternative agents would you recommend?

A) Penicillin

B) Cefazolin

C) Vancomycin

D) Daptomycin

PREVIEW QUESTION

2.13 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).

PREVIEW QUESTION

2.13 Which one of the following would you recommend?

A) Ceftaroline

B) Dalbavancin

C) Telavancin

D) Vancomycin

E) Linezolid

PREVIEW QUESTION

2.14 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

PREVIEW QUESTION

2.15 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

17 – Daily Question Preview: Day 2

Moderator: Andrew Pavia, MD

PREVIEW QUESTION

2.16 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

PREVIEW QUESTION

2.17 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

PREVIEW QUESTION

2.17 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

PREVIEW QUESTION

2.18 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.

PREVIEW QUESTION

2.18 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

18

Clinical Immunology and Host Defense

Dr. Steven Holland

18 - Clinical Immunology and Host Defense

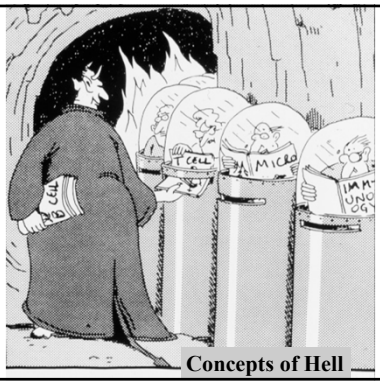
Speaker: Steven Holland, MD

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

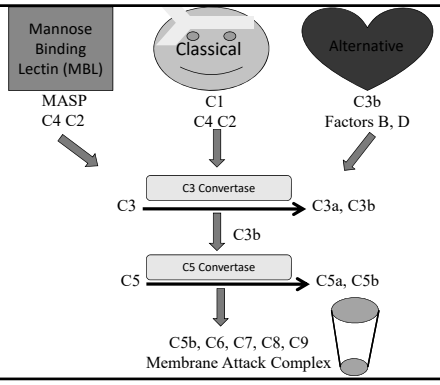
Patients with impaired inflammation:
- may be unable to tell you they are sick (feel fine)
- are often sicker than they look
- often have more extensive disease than is apparent
- may require longer treatment than normals
- may have unusual infections

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?

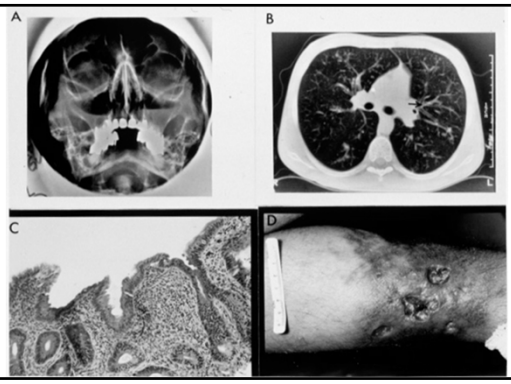
J Clin Immunol 2020 May;40(4):576-591

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.

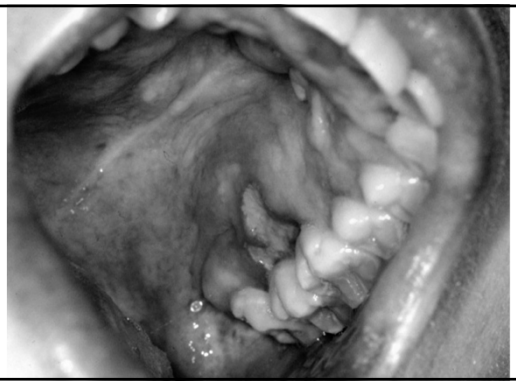
Recurrent digital and oral ulcers occurring every month or so for the last 4 months.

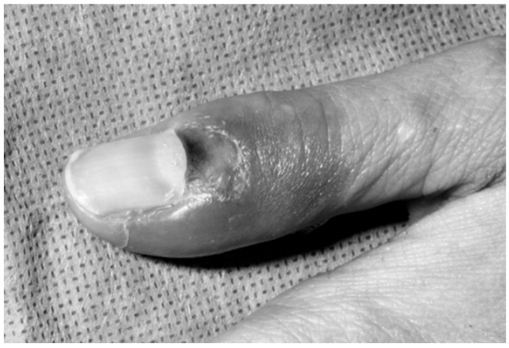
One CBC showed an ANC of 100, but on repeat several days later was normal.

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 (ELANE) 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)

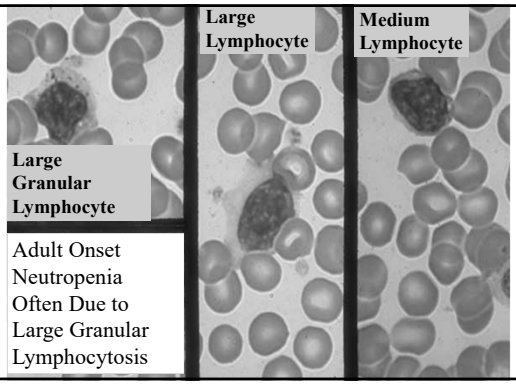
Dx- clonal CD3+/8+/57+ lymphs (LGL)

(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

Hematol Malig Rep. 2020 Apr;15(2):103-112.



Myeloperoxidase (MPO) deficiency (AR)

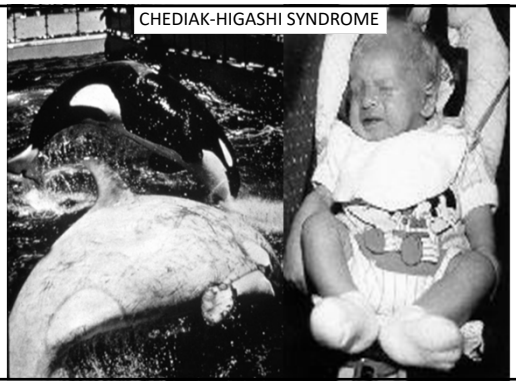
most common neutrophil disorder (1/2000)

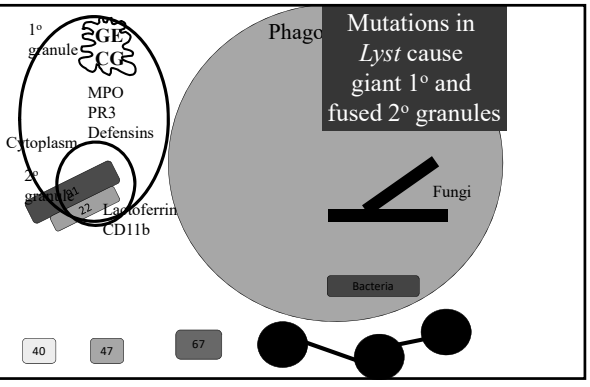
- not a pathologic condition *per se*
- failure of H_2O_2 -----MPO-----> HOCl
- compensated by increased H_2O_2 production
- appears to need another condition to potentiate, such as diabetes mellitus

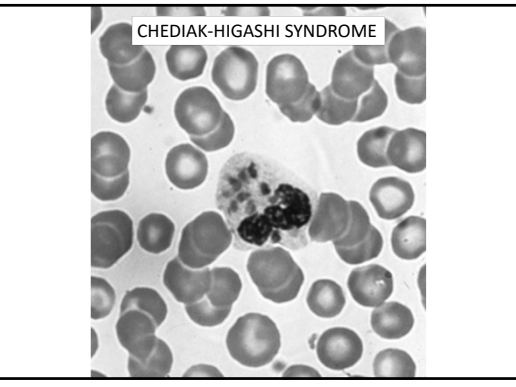
Dx- absence of peroxidase positive granules due to mutations in *MPO* gene

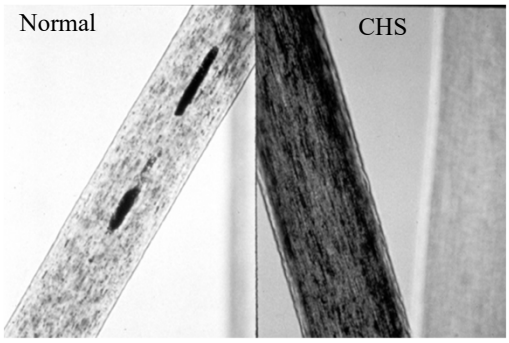
Rx- treat invasive infections (*Candida*), no specific therapy

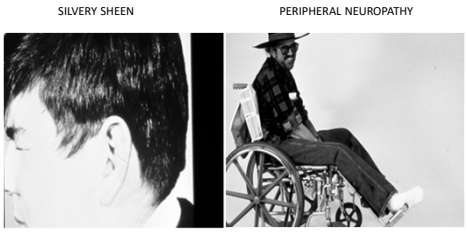
J Leukoc Biol. 2013 Feb;93(2):185











Chediak-Higashi Syndrome (AR)

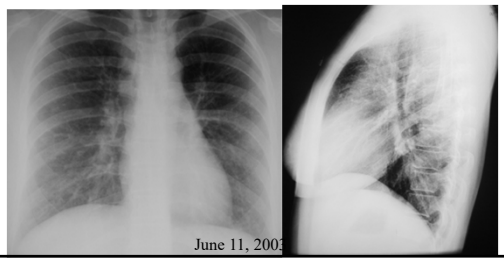
recurrent cutaneous, sino-pulmonary infections
  GNR, staph, strep, no fungi
  mild neutropenia (intramedullary destruction)
partial oculocutaneous albinism,
mental retardation, neuropathy (late),
lymphoma or HLH-like "accelerated phase" (late)

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

Drug Discov Today Dis Models. 2020 Summer;31:31-36

23 yo woman; athletic coach

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



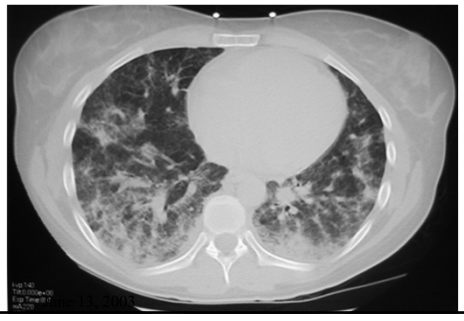
ER presentation

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

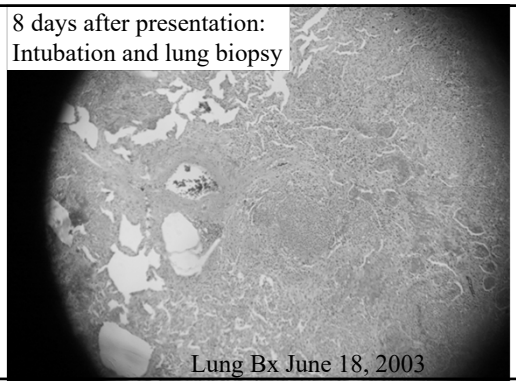
2 days later, hypoxia and fever



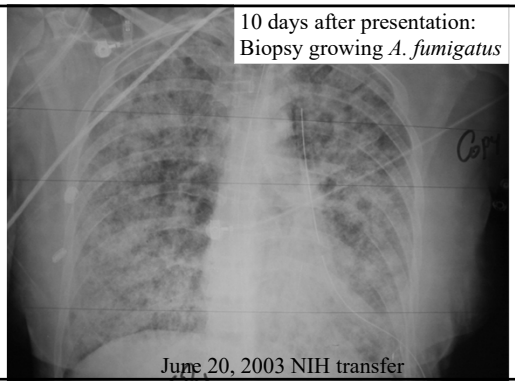
Hospital Course

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



Lung Bx June 18, 2003



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

June 20, 2003 NIH transfer

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

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

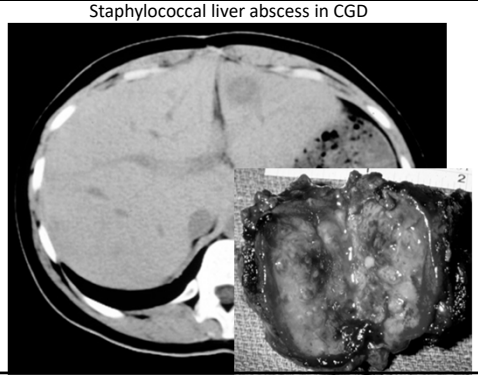
Infections in CGD

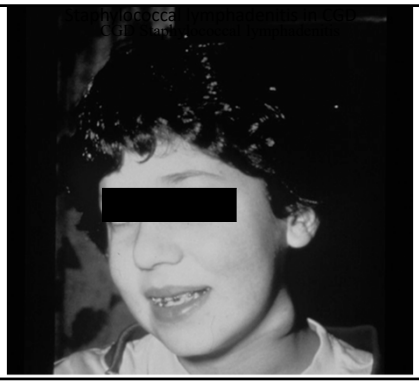
S. aureus	(liver, lymph nodes, osteo)
S. marsescens	(skin, lung, lymph nodes)
B. cepacia	(pneumonia, bacteremia)
Nocardia spp.	(pneumonia, brain, liver)
Aspergillus spp.	(lung, esp. miliary, spine)
Salmonella	(enteric, bacteremia)
BCG	(local/regional infections)

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.

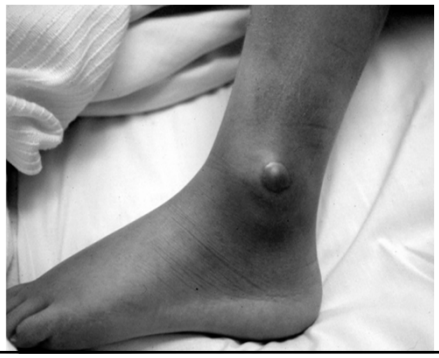
Pediatric Health Med Ther 2020 Jul 22;11:257-268

Staphylococcal liver abscess in CGD

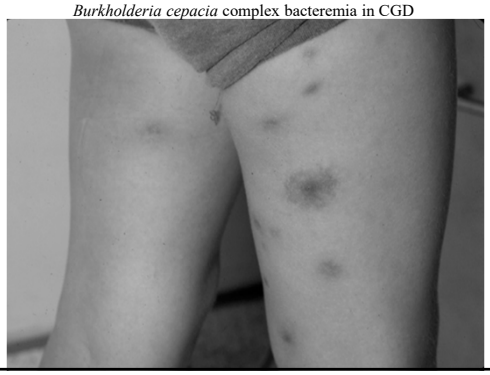




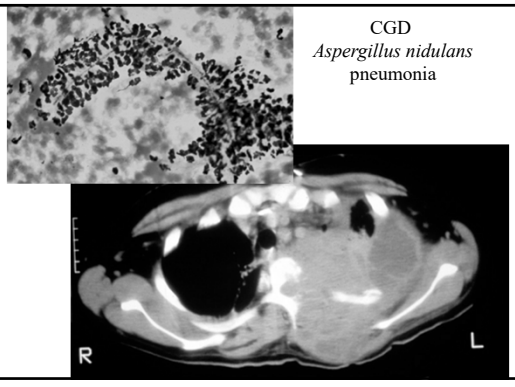
Staph aureus osteomyelitis in CGD



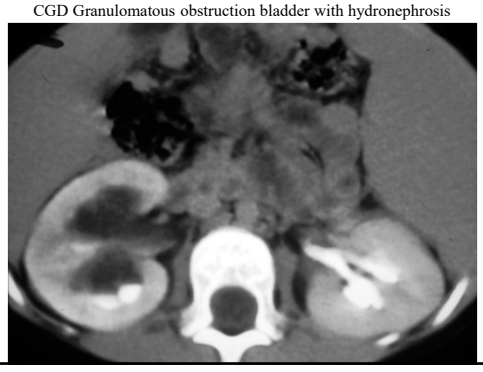
Burkholderia cepacia complex bacteremia in CGD



CGD
Aspergillus nidulans
pneumonia

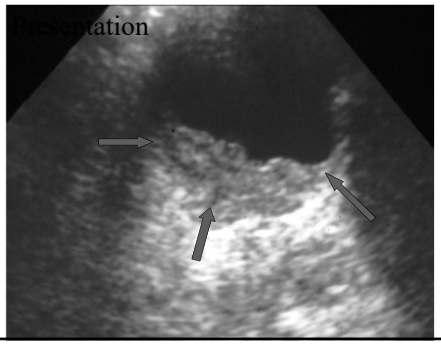


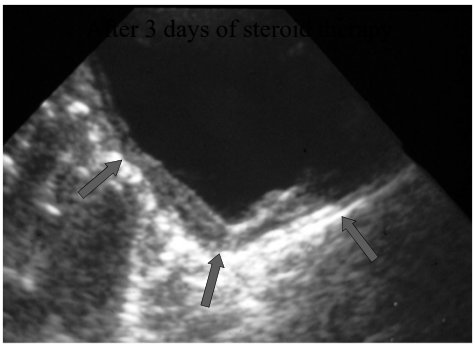
CGD Granulomatous obstruction bladder with hydronephrosis



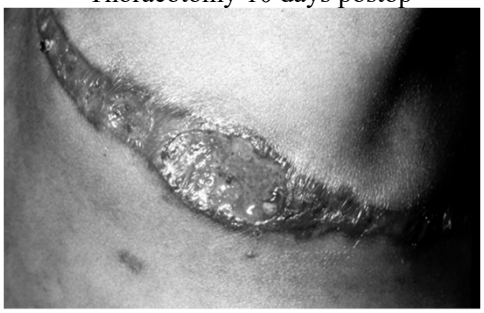
CGD Granulomatous cystitis

Presentation

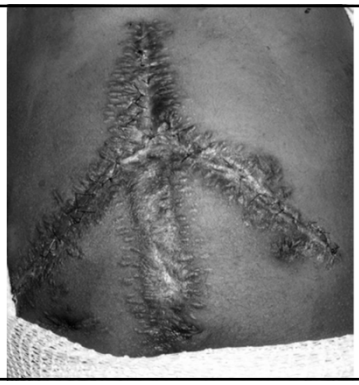




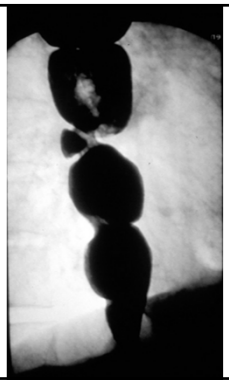
Thoracotomy 10 days postop



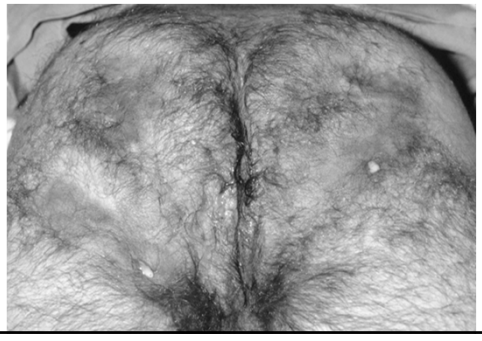
CGD granulomatous wound dehiscence



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

CGD Genetics

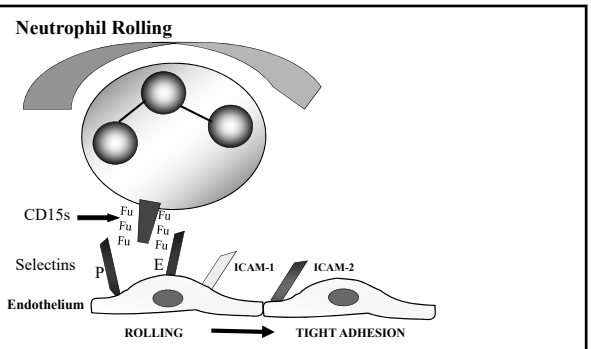
X-linked, chr. Xp21 (70% of cases)
- carrier females are mosaic (Lyonization)
- 1/2 of offspring of carrier Mom will receive the gene
  - about 1/3 of carriers are sporadic, from sperm
- X-linked male: all daughters carriers, no sons affected

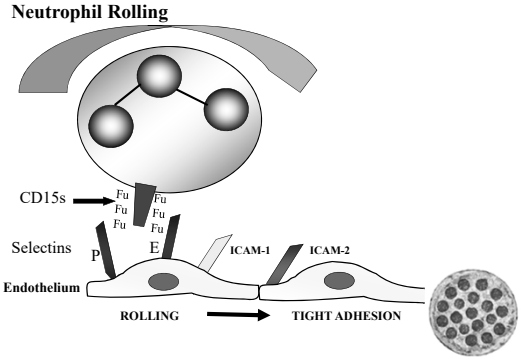
autosomal recessive (30% of cases)
- 1/2000 carry the gene for the most common AR form
  - bad luck happens

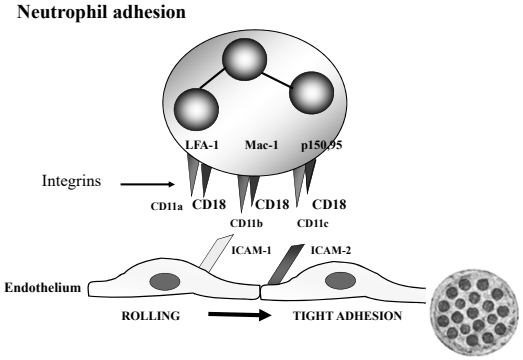
CGD Management and Treatment

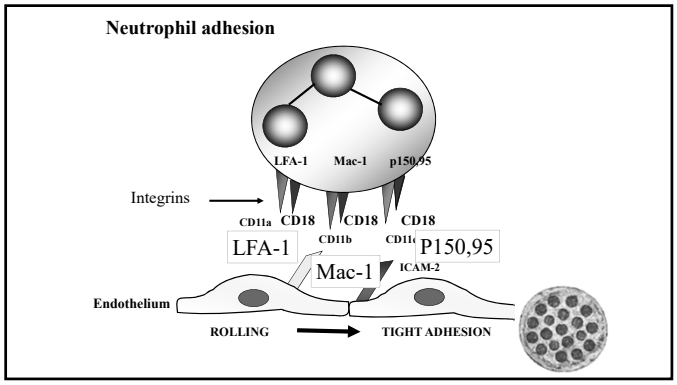
90% overall long-term survival
follow ESR, radiographs
prophylactic antibiotics and antifungals
TMP/SMX, itraconazole
prophylactic interferon gamma
50 µg/m2 subcutaneously three times weekly
aggressive search for and treatment of infections
BMT
(gene therapy)

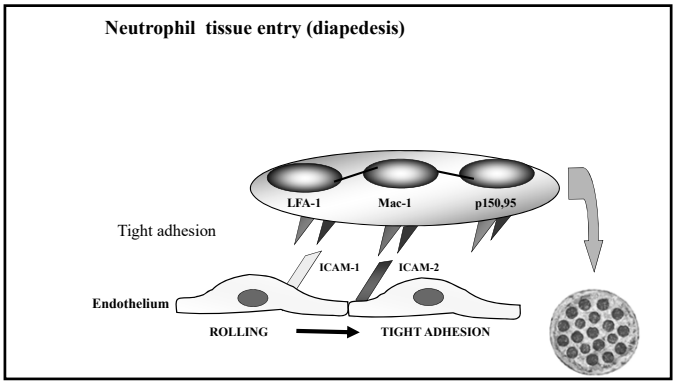
Hematol Oncol Clin North Am. 2013 Feb;27(1):89-99

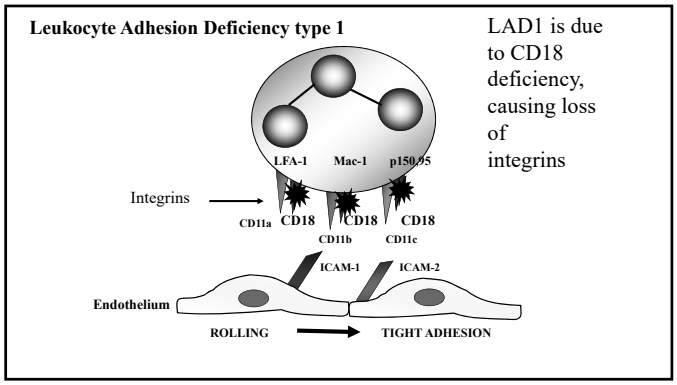












LAD1 is due to CD18 deficiency, causing loss of integrins

Leukocyte Adhesion Deficiency Type 1 (AR)

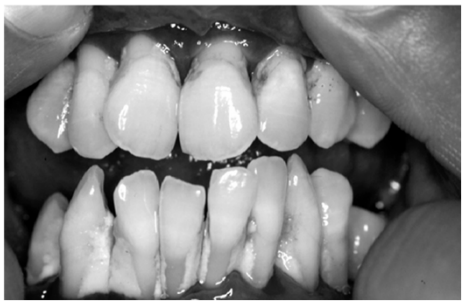
Recurrent necrotizing infections: skin, perineum, lung, gut

Enteric GNR, GPC, NOT fungi or *Candida*

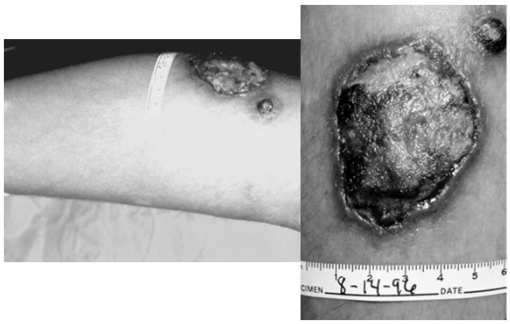
baseline leukocytosis, further WBC increase to infection

rare, consanguinity common

Almost universal tooth loss in LAD1 by adulthood



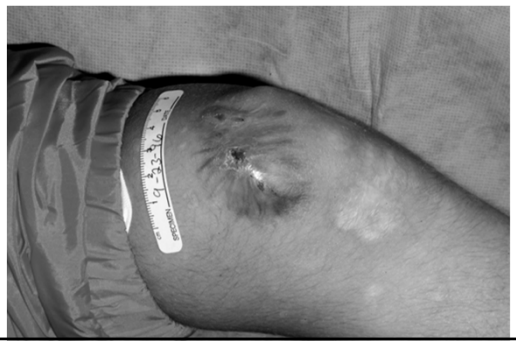
Impaired wound healing in LAD1

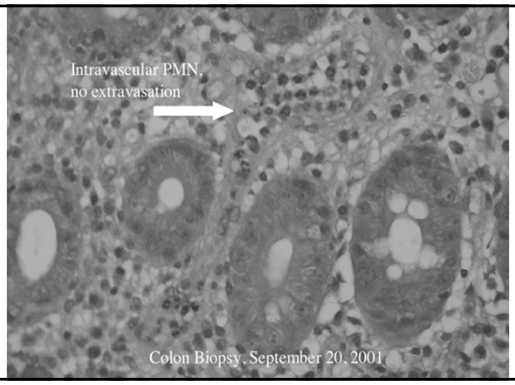


Leukocyte Adhesion Deficiency I

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

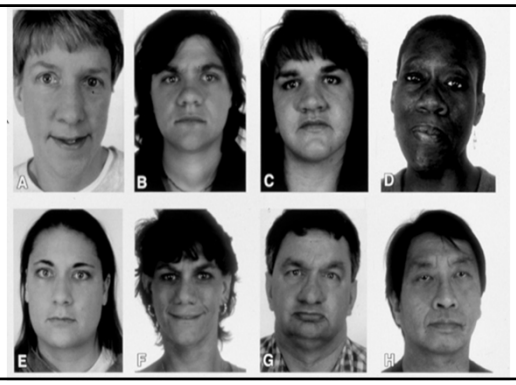
Referred from her internist for recurrent boils with *S. aureus*

IgE of 12,376 IU.

"Bronchitis and sinusitis at least once a year"

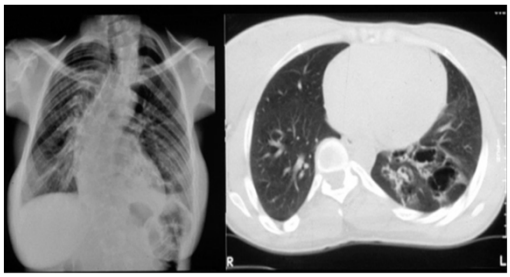
Persistent eczema requiring topical steroids.

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

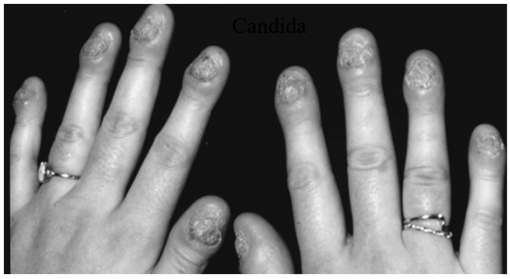
Secondary pathogens:

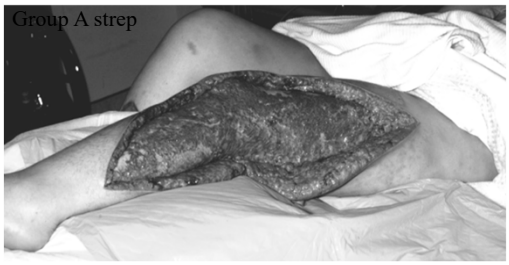
Pseudomonas aeruginosa

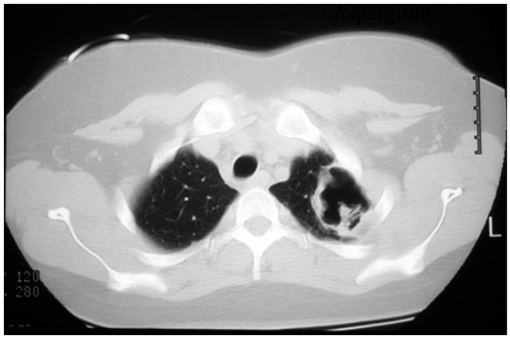
Aspergillus fumigatus

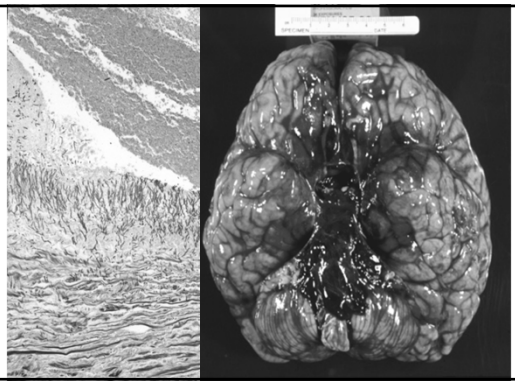
Others:

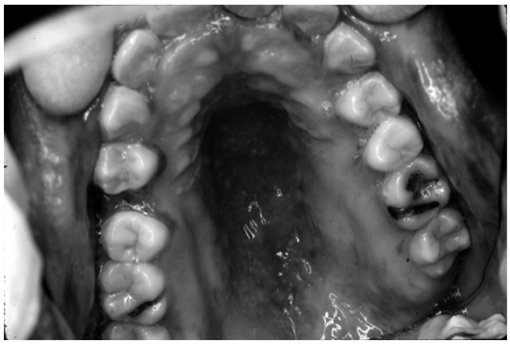
Pneumocystis jiroveci, M. avium complex

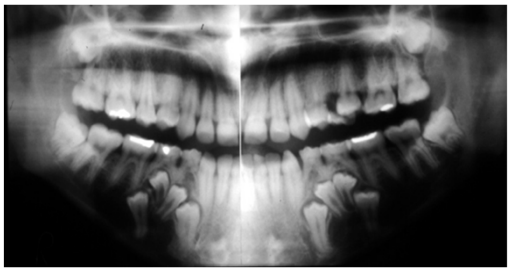








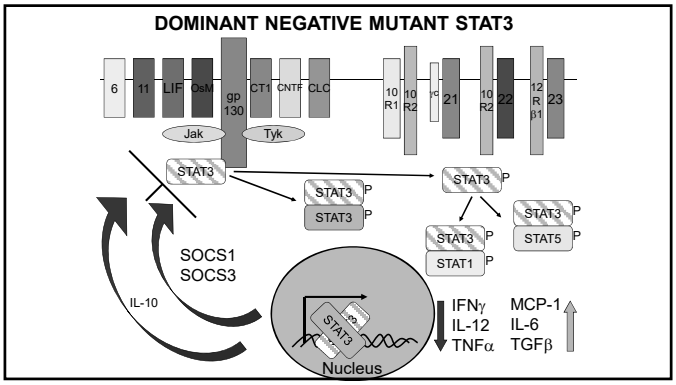




HIE Laboratory Findings

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

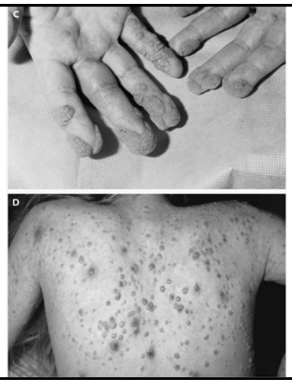
Candida, Cryptococcus, Histoplasma

HPV, HSV, molluscum

Squamous cell carcinomas, lymphoma

J Clin Immunol 2021 May 1. doi: 10.1007/s10875-021-01051-1.

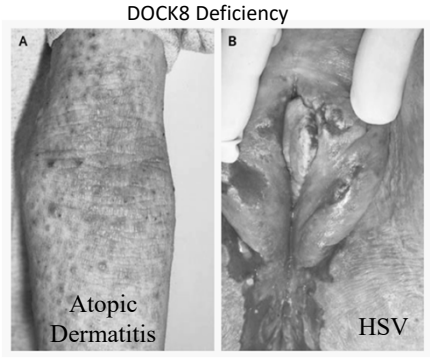
DOCK8 Deficiency



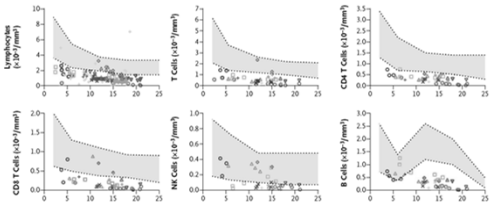
HPV

Molluscum contagiosum

DOCK8 Deficiency



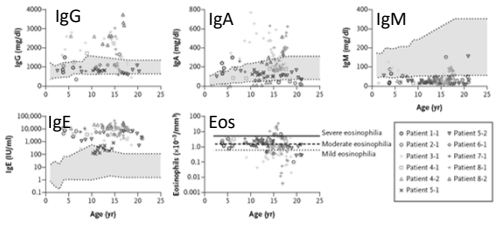
DOCK8: Lymphopenia is common and somewhat progressive



Age in years

NEJM 361:2046, 2009

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 <u>not</u> 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.*

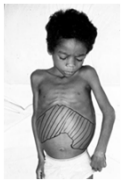
PMH recurrent salmonellosis as a child.

Sibling had tuberculosis but is now cured.

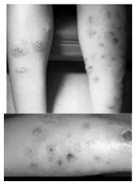
CD4+ number is normal, HIV -

Clinical Spectrum of NTM Infections

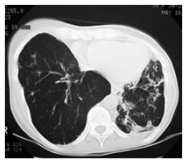
Disseminated
Severe, Young
IFNγ/IL-12 defects
NEMO, STAT1



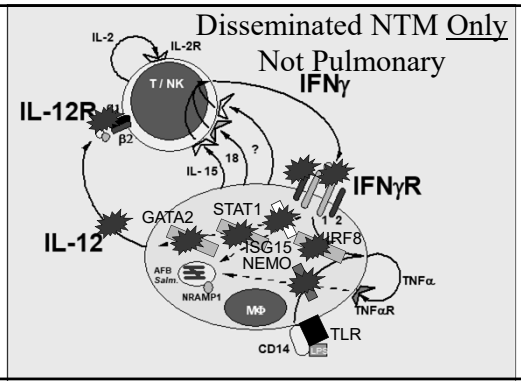
Skin
Exposure
Inoculation

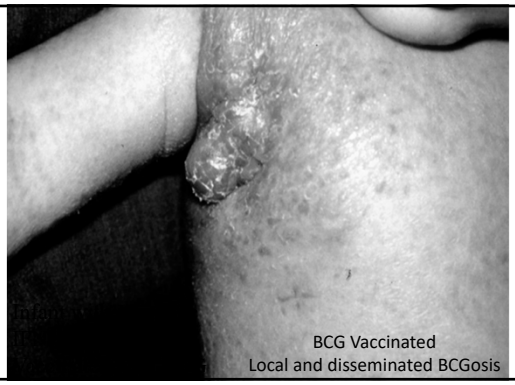


Pulmonary
Chronic, Older
Bronchiectasis
Cystic fibrosis (CF)
Ciliary dyskinesia (PCD)

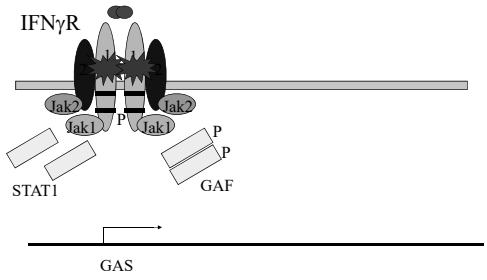


Disseminated NTM Only Not Pulmonary

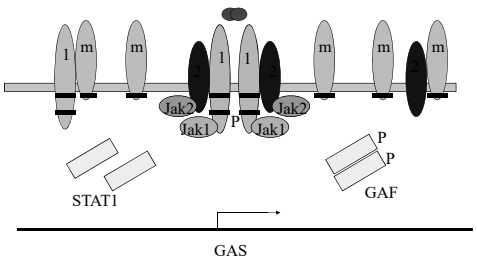




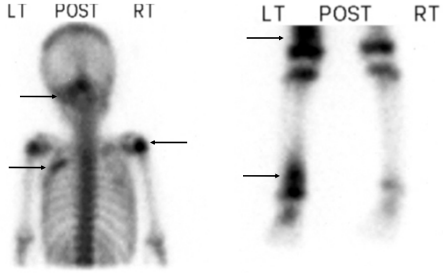
Autosomal Recessive IFNGR1 (both alleles)



Autosomal Dominant IFNGR1 (one allele)



Mycobacterial Osteomyelitis in Dominant IFNγR1 Deficiency



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

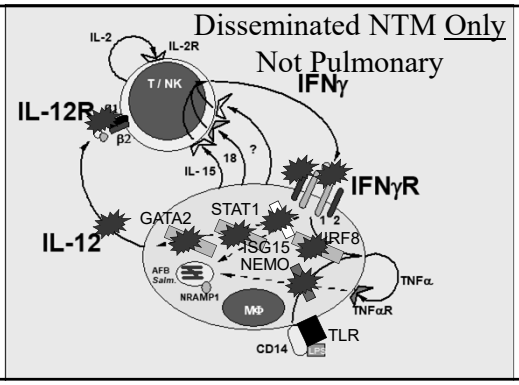
Interferon γ Receptor Deficiencies

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)

N Engl J Med. 2017 Sep 14;377(11):1077-1091.

Disseminated NTM Only Not Pulmonary

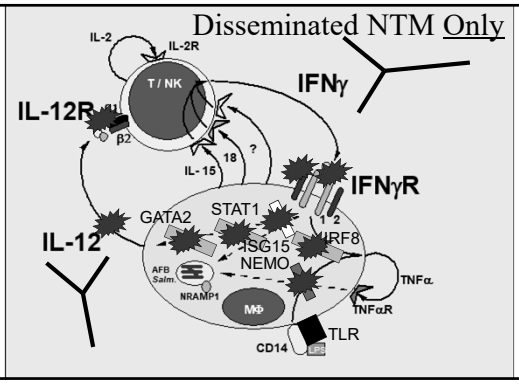


IL-12βR1 Deficiency

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

Disseminated NTM Only



Anti-IFNγ autoantibody syndrome

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

Dx- autoantibody detection
Rx- antimycobacterials, possibly rituximab

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:

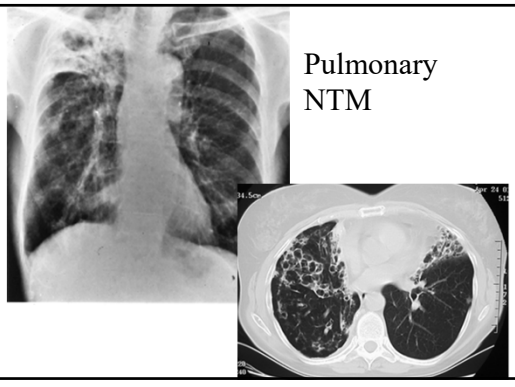
a) Show high TNFα from stimulated cells
b) Show high IL-12 from stimulated cells
c) Show high IFNγR1 on cell surfaces
d) Show high TNFαR on cell surfaces
e) Show low IFNγR1 on cell surfaces

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

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

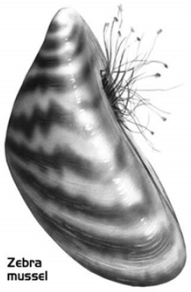
It is the SOS

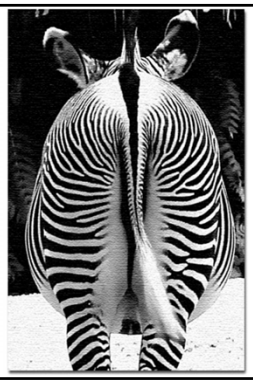
History

Physical

Imaging

Laboratories
(talk to the lab yourself!!!)





19

Respiratory Viral Infections including Influenza, Immunocompetent, and Immunocompromised Patients

Dr. Andrew Pavia

19 - Respiratory Viral Infections including Influenza, Immunocompetent, and Immunocompromised Patients

Speaker: Andrew T. Pavia, MD

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

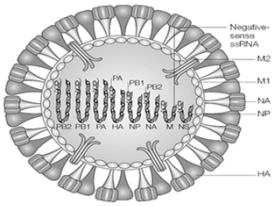
- **Antimicrobial Therapy Inc, WebMD, Merck and Company**

What you need to know for the boards

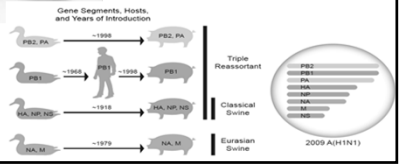
- Minimal virology
- Epidemiology including H7N9
- Diagnosis
- Complications
- Treatment
- Vaccines

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



Epidemic Shift
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

19 - 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, cough, 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 diagnosis would be:

A. H1N1 influenza
B. H3N2 influenza
C. Leptospirosis
D. H7N9 influenza
E. Blastomycosis

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

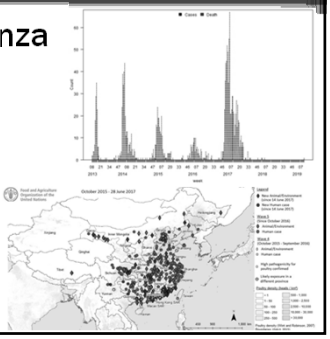
Influenza A viruses infecting humans

- 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
- H10N3: First human case 2021

* 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
- Largely disappeared after avian vaccine



19 - 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

http://www.cdc.gov/flu/professionals/infectioncontrol/healthcaresettings.htm

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

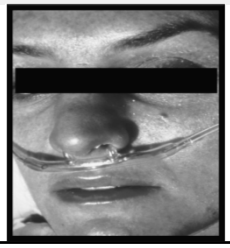
On exam she was slow to respond and had diffuse rales and mild abdominal tenderness that was non focal.

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

19 - Respiratory Viral Infections including Influenza, Immunocompetent, and Immunocompromised Patients

Speaker: Andrew T. Pavia, MD

Influenza associated hemorrhagic pneumonitis

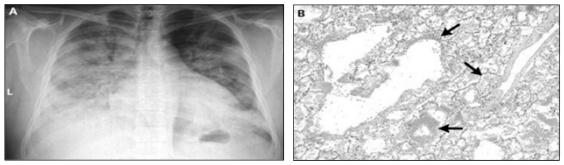


Photo: Perez-Padilla. *NEJM* 009; 361 (7): 680

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 and troponin 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
Guillian 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

19 - 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

19 - Respiratory Viral Infections including Influenza, Immunocompetent, and Immunocompromised Patients

Speaker: Andrew T. Pavia, MD

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

- Recommended medications: oseltamivir and zanamivir, baloxavir
- 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

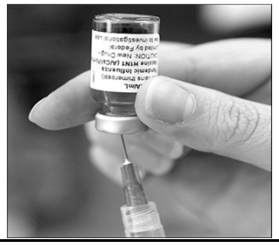
Antiviral Prophylaxis

- 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

Vaccines



19 - Respiratory Viral Infections including Influenza, Immunocompetent, and Immunocompromised Patients

Speaker: Andrew T. Pavia, MD

ACIP Recommendations for Influenza vaccination 2021-2022

- 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.

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

Other important respiratory viruses Adenovirus, RSV, hMPV, parainfluenza, coronaviruses, hantaviruses (and more)

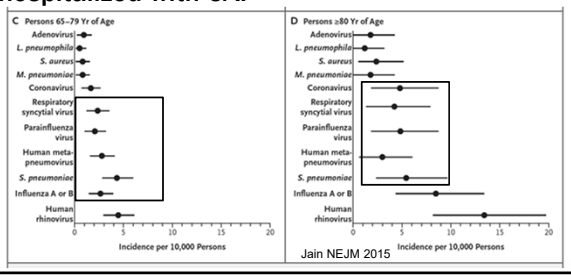
19 - Respiratory Viral Infections including Influenza, Immunocompetent, and Immunocompromised Patients

Speaker: Andrew T. Pavia, MD

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

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
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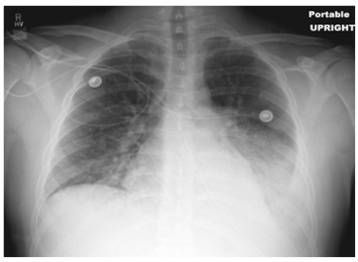


Case

An 25 yo school teacher presents in March in Portland OR with several days of fever, cough, chest pain, tachypnea, hypoxia and conjunctivitis with this CXR.

No travel, hiking, animals

WBC 3.0, platelets 160, CRP 2.5, AST 75

19 - Respiratory Viral Infections including Influenza, Immunocompetent, and Immunocompromised Patients

Speaker: Andrew T. Pavia, MD

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

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 75 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.
- Rapid Covid test negative. CXR shows bilateral perihilar infiltrates but no consolidation 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

19 - Respiratory Viral Infections including Influenza, Immunocompetent, and Immunocompromised Patients

Speaker: Andrew T. Pavia, MD

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

- 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; Late fall to spring (usually December- April)
- As common as influenza among hospitalized persons > 65

Falsey NEJM 2005, Widmer 2012

RSV, hMPV in older adults

- RSV, hMPV, Parainfluenza viruses are common as cause of CAP in elderly
- COPD and heart disease are risk factors
- Exposure to children probably a risk factor
- Nosocomial transmission has been documented in hospitals and ECF
- Testing and use of appropriate precautions may be important

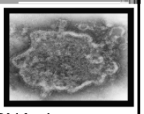
RSV

- 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

19 - Respiratory Viral Infections including Influenza, Immunocompetent, and Immunocompromised Patients

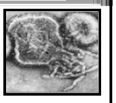
Speaker: Andrew T. Pavia, MD

Human Metapneumovirus



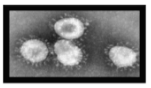
- "Discovered' in the last decades
- Nonsegmented, single stranded, negative sense RNA virus: Paramyxoviridae family, Pneumovirinae subfamily
- Causes URI, bronchiolitis, pneumonia similar to RSV
- Winter/Spring in temperate climates
- In younger adults, URI common with sore throat, hoarseness, wheezing, 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

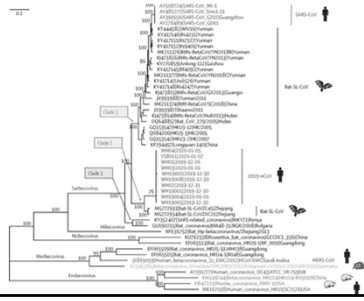


- HuCoV 229e, HuCoV OC43
  - "Older" associated predominantly with URI
- HuCoV HKU1, HuCoV NL63
  - Recently described using molecular techniques. Associated with URI and some pediatric and adult pneumonia
- May be detected on newer multiplex platforms (Luminex, FilmArray). Do not cross react with SARS-CoV-2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

MERS coronavirus

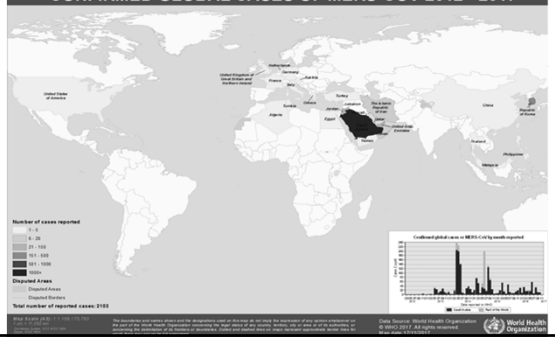
- Discovered April 2012
- > 600 cases in or with contact with Gulf area, predominantly Saudi Arabia
- Transmission documented in health care settings and families but to date, super spreaders suspected in Korea
- Mortality 56% with small number of asymptomatic
- Closest relative is a bat virus
- Camels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

Phylogenetic relationships among members of the subfamily Coronavirinae



Lancet Feb 2020: 395

CONFIRMED GLOBAL CASES OF MERS-COV 2012 - 2017



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)

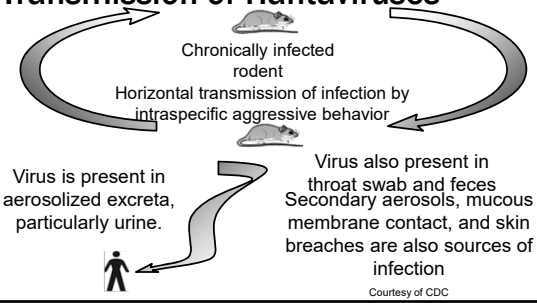
Which of the following is the most likely cause of his illness?

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

Transmission of Hantaviruses



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

19 - Respiratory Viral Infections including Influenza, Immunocompetent, and Immunocompromised Patients

Speaker: Andrew T. Pavia, MD

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

20

Board Review Session 2

Drs. Pavia (Moderator), Aronoff, Chambers, Nelson and Trautner

20 – Board Review Day 2

Speaker: Drs. Pavia (Moderator), Aronoff, Chambers, Nelson, and Trautner

Board Review: Day 2

Moderator: Dr. Pavia
Faculty: Drs. Aronoff, Chambers, Nelson, and Trautner

BOARD REVIEW DAY 2

#16 **A 68-year-old woman underwent left hip arthroplasty 16 months ago for osteoarthritis. She had no perioperative complications and reported resolution of hip pain within 2 months of surgery. However, she has had slowly increasing pain over the last six months and her ability to walk longer distances has been compromised.**

Her hip examination is normal.

ESR is 28 mm/h and CRP is 9.5 mg/L.

BOARD REVIEW DAY 2

#16 **On plain films, the hardware is in good position without periprosthetic lucency. Three phase bone scintigraphy reveals diffuse uptake on early and delayed phases.**

Percutaneous synovial fluid sampling demonstrated 1895 nucleated white blood cells with 64% neutrophils.

Culture recovered a single colony of coagulase-negative Staphylococcus.

Lateral flow alpha defensin is positive.

BOARD REVIEW DAY 2

#16 **Of the available tests, which is most consistent with infection?**

A) Triple phase bone scan

B) Erythrocyte sedimentation rate (ESR)

C) Synovial fluid nucleated cell count

D) Synovial fluid culture

E) Synovial fluid alpha-defensin

BOARD REVIEW DAY 2

#17 **An 85-year-old woman with vascular dementia, history of stroke, and atrial fibrillation requiring anticoagulation is hospitalized for failure to thrive with a 30 lb weight loss over 3 months.**

She was previously ambulatory after her stroke but since has become bedbound, and her daughter has had difficulty providing care for her.

BOARD REVIEW DAY 2

#17 **On examination she is cachectic.**

She has a low-grade temperature and mild tachycardia (heart rate 112 bpm) with a normal blood pressure.

There is a large unstageable sacral ulcer with superficial tissue necrosis and malodor.

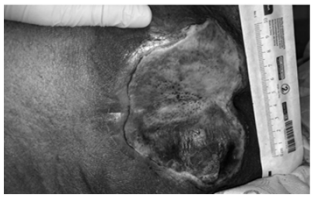
There is mild surrounding erythema and the skin is tender, but there is no fluctuance or crepitus. Movement is painful.

20 – Board Review Day 2

Speaker: Drs. Pavia (Moderator), Aronoff, Chambers, Nelson, and Trautner

BOARD REVIEW DAY 2

#17



Her creatinine is 0.28 mg/dL. Albumin is 2.1 g/dL. WBC is 16.3 x 103/µL. Hgb is 9 g/dL. ESR is 71 mm/Hr. CRP is 94.7 mg/L.

Plain films of the pelvis are normal.

She is started on piperacillin-tazobactam.

BOARD REVIEW DAY 2

#17 **In addition to offloading and nutritional optimization, what is the next best management option for her infected sacral ulcer?**

A) Local wound care with antimicrobial dressing

B) Place PICC line for six weeks of IV antimicrobial therapy

C) Assess for osteomyelitis with MRI

D) Surgical debridement and placement of negative pressure wound dressing (vacuum-assisted closure)

E) Diverting colostomy to minimize ongoing fecal contamination

BOARD REVIEW DAY 2

#18 **A 52 y/o woman was admitted with a 4 x 5 cm abscess of the right buttock which she says started as a tender bump about a week ago.**

She has had subjective fevers beginning the day prior to admission. Vital signs on admission were a temperature of 38.5oC, pulse 100, respiratory rate 16, blood pressure 125/80. Except for the buttock abscess the physical examination was unremarkable including no cardiac murmur, no rash or other skin findings.

Admission chest x-ray was normal.

Complete blood count was normal except for a white blood cell count of 10,500 per mL with 85% neutrophils.

Metabolic panel, serum creatinine, hepatic enzymes, coagulation tests, and urinalysis were all normal.

BOARD REVIEW DAY 2

#18 **The abscess was drained and empiric vancomycin was administered on hospital day 1. She has had no further fevers since drainage of the abscess and feels much improved.**

Culture of the abscess fluid grew a methicillin-susceptible strain of Staphylococcus aureus (MSSA) and did one of two blood cultures from admission.

Follow-up blood cultures obtained hospital day 2 and day 3 are negative and transthoracic echocardiogram is negative.

On hospital day 5 you are asked to make recommendations for antimicrobial therapy.

BOARD REVIEW DAY 2

#18 **Which is your recommendation?**

A) No further antimicrobial therapy is needed, since source control has been established

B) Continue vancomycin to complete a 7-day course

C) Continue vancomycin to complete a 14-day course

D) Switch to cefazolin to complete a 7-day course

E) Switch to cefazolin to complete a 14-day course

BOARD REVIEW DAY 2

#19 **A 72-year-old man with 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.**

His temperature is 38.9oC, pulse regular at 110 beats per minute, and blood pressure 145/95 mm Hg.

His lungs are clear; a 3/6 systolic ejection murmur is heard at the right upper sternal boarder.

20 – Board Review Day 2

Speaker: Drs. Pavia (Moderator), Aronoff, Chambers, Nelson, and Trautner

BOARD REVIEW DAY 2

#19 **Laboratory tests are notable for hemoglobin 12 g/dl, white blood cell count 13,500 per mm3 (80% polymorphonuclear cells), serum glucose 340 mg/dl, serum creatinine 1.7 mg/dl, and urinalysis with 3+ protein, 20-50 white cells per high power field, and 4+ glucose.**

Two blood cultures and a urine culture are positive for gentamicin-resistant Enterococcus faecalis.

BOARD REVIEW DAY 2

#19 **What antimicrobial regimen would you recommend for this patient?**

A) Daptomycin

B) Ampicillin

C) Ampicillin + ceftriaxone

D) Vancomycin + streptomycin

E) Ampicillin + streptomycin

BOARD REVIEW DAY 2

#20 **A 27-year-old man with a history of injection drug use and a prior episode of tricuspid valve endocarditis caused by methicillin-resistant Staphylococcus aureus (MRSA) is admitted with one week of fevers.**

A 3/6 systolic murmur is heard at lower left sternal border. Chest x-ray shows multiple peripheral infiltrates bilaterally.

He says that during treatment of the prior endocarditis he had a bad reaction to vancomycin with fevers, a rash all over his body and swelling of his face.

BOARD REVIEW DAY 2

#20 **What antimicrobial regimen would you recommend for this patient?**

A) Dalbavancin

B) Daptomycin

C) Linezolid

D) Telavancin

E) Vancomycin

BOARD REVIEW DAY 2

#21 **A 36-year-old female is 2 years post-cadaveric renal transplantation for renal failure due to chronic glomerulonephritis.**

She now presents with fever of five days duration. She had some nausea but no urinary, respiratory, or abdominal symptoms.

She presented to an outside hospital three days previously where a chest x-ray, urinalysis and blood culture were negative.

She was given levofloxacin but remained febrile with malaise.

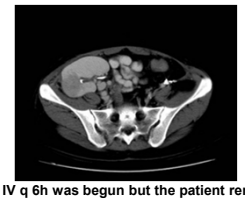
BOARD REVIEW DAY 2

#21 **Current medications included mycophenolate, sirolimus and prednisone 20 mg.**

- **Examination found a fever of 39.2˚C grade 1 systolic ejection murmur over the left sternal border, and a non-tender transplanted kidney in the right lower quadrant. Renal ultrasound of the transplanted kidney was normal.**
- **Urine culture grew 100,000 colonies of E. faecalis, susceptible to ampicillin.**
- **Urinalysis found 100 WBC per hpf, nitrate and protein negative.**
- **WBC was 10,700. Creatinine 1.3 mg/dl**

BOARD REVIEW DAY 2

#21 Abdominal CT with contrast showed a lobe of the kidney which did not perfuse well with contrast and was swollen (Fig). There is no evidence of abscess formation.



Ampicillin 2 gm IV q 6h was begun but the patient remained febrile the next 24 hours.

BOARD REVIEW DAY 2

#21 Which of the following is the most appropriate management?

A) CT-guided biopsy of the affected kidney

B) Add gentamicin

C) Wedge resection of affected area of kidney

D) Check urine for "decoy" cells of BK virus

E) Continue ampicillin at same dose

BOARD REVIEW DAY 2

#22 A 17-year-old man from Arizona presents with leg pain. He was in his usual state of good health until 8 months ago when he developed localized pain in his left leg just below the knee.

He denied any antecedent trauma. He also denied any skin lesions, erythema, fevers, chills, sweats, weight loss, or fatigue.

He is a competitive swimmer but he gave up the sport about four months earlier as a result of his leg pain. He denies tobacco, alcohol, or illicit drug use. He has never left Arizona.

He is sexually active with a single female partner.

BOARD REVIEW DAY 2

#22 On examination, his vital signs are normal. The left leg appears normal on visual inspection. Deep palpation below the left knee over his tibia elicits mild discomfort.

The knee joint is normal. Muscle strength and sensation are normal.

A radiograph of his lower extremity demonstrates a lytic lesion in the proximal tibial metaphysis surrounded by a sclerotic rim (see radiograph below).

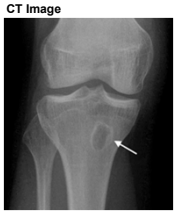
MRI demonstrates the "penumbra sign" on T1 weighted imaging (see MRI and bone film below).

Chest x-ray and chest CT are normal.

BOARD REVIEW DAY 2

#22

CT Image



MR Images

Moser et al, Imaging, Volume 93, Issue 5, May 2012, Pages 351-9

BOARD REVIEW DAY 2

#22 Which of the following is most likely to be isolated from a biopsy of this lesion?

A) Histoplasma capsulatum

B) Mycobacterium marinum

C) Pseudomonas aeruginosa

D) Staphylococcus aureus

E) Streptococcus pyogenes

BOARD REVIEW DAY 2

#23 **The hypervirulent strain of C. difficile designated North American Pulse Field 1 (NAP1), 027 by PCR ribotyping, and BI by restriction endonuclease analysis (REA) is characterized by which of the following?**

A) Patient mortality in excess of 50% within 30 days

B) Recurrent *C. difficile* infection rates of over 35%

C) High level toxin A and B production

D) Vancomycin resistance

E) Fidaxomicin resistance

BOARD REVIEW DAY 2

#24 **A 45-year-old male is diagnosed with Helicobacter pylori infection by endoscopy and antral gastric biopsy performed for weight loss and abdominal pain.**

There is a family history of gastric cancer.

He is treated for 14 days with omeprazole, clarithromycin, and amoxicillin.

BOARD REVIEW DAY 2

#24 **What would be best option to evaluate this patient regarding Helicobacter infection/disease after completing antibiotic therapy?**

A) No further testing is necessary for one year

B) Perform the stool Helicobacter pylori antigen test 8 weeks after treatment

C) Perform the urea breath test 3 weeks after treatment

D) Repeat endoscopy, biopsy, and rapid urease test (RUT) 6 weeks after treatment

BOARD REVIEW DAY 2

#25 **A 72 y/o retired fireman who has a history of chronic obstructive lung disease is seen in the emergency department because of 96 hours of cough, chills, sore throat, and body aches.**

He lives in an assisted care facility where he has his own room but takes meals in a congregate dining room.

He reports that a number of other residents and servers in the dining room have been coughing.

In the emergency room a rapid test for influenza is positive.

He is hypoxemic and admitted to the intensive care unit.

BOARD REVIEW DAY 2

#25 **Regarding treatment for influenza, he should receive:**

A) No specific anti-viral because the patient has been ill for substantially more than 48 hours

B) Zanamivir

C) Zanamivir and Oseltamivir

D) Oseltamivir

E) Rimantadine

BOARD REVIEW DAY 2

#26 **A 65-year-old man 6 weeks post right total knee arthroplasty presents with pain and swelling of the right knee that started two weeks ago.**

He has no fever.

Physical examination shows a well-healed wound, surrounded by erythema and some bogginess over the right knee.

BOARD REVIEW DAY 2

#26 **Which of the following is the next best step?**

A) Measurement of C-reactive protein

B) Knee aspiration for alpha defensin testing

C) Knee aspiration for cell count and differential and bacterial culture

D) Knee aspiration for 16S ribosomal RNA gene PCR and sequencing

BOARD REVIEW DAY 2

#27 **A 36-year-old male with HIV infection and ocular syphilis has a history of penicillin allergy.**

He reports a serious rash that occurred when he was treated with penicillin for a dental infection.

He was told never to take penicillin again and is confident that he has not taken penicillin or any related drug since.

BOARD REVIEW DAY 2

#27 **Which feature of the rash would exclude the use of penicillin for his ocular syphilis?**

A) Immediate onset of rash within 24 hours

B) Need for antihistamine therapy

C) Associated fever with the rash

D) Blistering or mucous membrane involvement

E) Prolonged time (7 days) to resolution of rash

BOARD REVIEW DAY 2

#28 **A 22-year-old female has had frequent episodes of lower urinary tract infections.**

She has frequent intercourse with a single partner, who always uses condoms with spermicide.

BOARD REVIEW DAY 2

#28 **Which one of the following actions would be most likely to decrease the frequency of her infections?**

A) Have her partner discontinue spermicide use with condoms

B) Vaginal douching after intercourse

C) Discontinue wearing of pantyhose

D) Urinate after intercourse

E) Drink cranberry juice for prophylaxis

BOARD REVIEW DAY 2

#29 **A 22-year-old previously healthy male from El Paso, Texas, who presented to the Emergency Room with a 3-month history of lower back pain elicited after lifting weights at the gym.**

He also reported intermittent fevers and chills as well as a 20-pound unintentional weight loss.

He denied any recent travel and worked as a correctional officer.

On physical exam he had normal vital signs, no spinal or paraspinal tenderness, and no neurologic deficits.

20 – Board Review Day 2

Speaker: Drs. Pavia (Moderator), Aronoff, Chambers, Nelson, and Trautner

BOARD REVIEW DAY 2

#29 An MRI was notable for findings concerning for discitis/osteomyelitis of L5/S1 with abscess formation, so the patient was admitted and subsequent interventional radiology-guided biopsies were performed twice, and cultures and pathology were negative for bacteria, fungi, and acid-fast bacilli.

He was discharged on vancomycin, ceftriaxone, and doxycycline for the treatment of osteomyelitis of unknown origin.

On follow-up it was discovered that he regularly consumed fresh cheese from Mexico (queso fresco) and occasionally ate sushi from a local restaurant. He had remained symptomatic with fevers.

BOARD REVIEW DAY 2

#29 Which of the following infections does this likely represent?

A) *Francisella tularensis*

B) *Nocardia brasiliensis*

C) *Brucella melitensis*

D) *Actinomyces israelii*

E) *Shigella boydii*

BOARD REVIEW DAY 2

#30 A 42-year-old man is referred for asymptomatic elevation of his liver function tests.

He underwent a living-related donor kidney transplantation 14 months earlier secondary to end-stage renal disease from uncontrolled hypertension (CMV D-/R-).

Six months after his transplant, his physicians noted an asymptomatic increase in aminotransferases, with aspartate aminotransferase (AST) 8 times the upper limit of normal (ULN), alanine aminotransferase (ALT) 6 x ULN, and gamma glutamyl transferase (GGT) 5 x ULN.

His total bilirubin was mildly elevated and his alkaline phosphatase was normal.

BOARD REVIEW DAY 2

#30 The following were serologies were negative:

- Hepatitis A virus
- Hepatitis B virus (HBV) surface antigen
- hepatitis C virus (HCV)
- human immunodeficiency virus (HIV)- 1,2
- Epstein-Barr virus VCA IgM
- herpes simplex virus 1 and 2 IgG
- cytomegalovirus IgG

Also negative or normal were:

- HBV DNA and HCV RNA were undetectable.
- Liver autoimmunity panel was negative.
- Abdominal ultrasound was normal.

BOARD REVIEW DAY 2

#30 He denied alcohol consumption. He recently returned from living the past year in Germany and is an avid consumer of sausage.

His immunosuppressive regimen included tacrolimus, mycophenolate mofetil, and prednisolone.

His liver function tests have continued to be elevated over the past 9 months despite changes in his immunosuppressive regimen and antihypertensive medications.

His physical examination was unremarkable.

His BMI was 20 kg/m2. No scleral icterus was noted and no stigmata of cirrhosis were noted.

A liver biopsy demonstrated lobular hepatitis without fibrosis.

BOARD REVIEW DAY 2

#30 Which of the following entities is most likely responsible for his hepatitis?

A) Coxiella burnetii

B) Hepatitis D

C) Hepatitis E

D) Leptospira interrogans

E) Non-alcoholic hepatosteatosis

21

Bone, Joint and Musculoskeletal Infections

Dr. Sandra Nelson

21 – Bone and Joint Infections
Speaker: Sandra Nelson, MD

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:

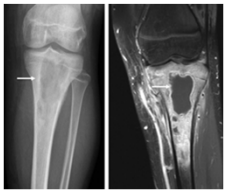
- Hematogenous Osteomyelitis
  - Metaphyseal long bone (more common in children)
  - Vertebral spine (Spondylodiscitis)
  - Usually monomicrobial
- Contiguous Osteomyelitis
  - Trauma / osteofixation
  - Diabetic foot ulceration
  - Infections in decubitus ulcer
  - Often polymicrobial

Osteomyelitis: Unifying Principles

- MRI and CT are the best radiographic studies
  - Bone scan has high 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 in setting of retained hardware

Brodie's Abscess (Subacute hematogenous osteomyelitis)

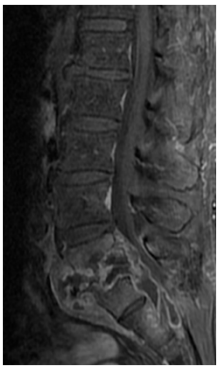
- More common in children and young adults
- Bacteria deposit in medullary canal of metaphyseal bone, become surrounded by rim of sclerotic bone → intraosseous abscess
- "Penumbra sign" on MRI
  - Granulation tissue lining abscess cavity inside bone gives appearance of double line
- *Staph aureus* most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



Simpfendorfer Infect Dis Clin N Am 2017;31:299

Case #1

- 57-year-old male presented with 3 months 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



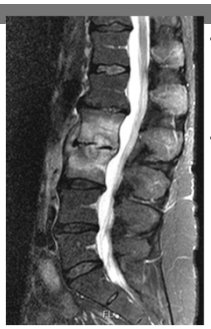
Case #1: Vote

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

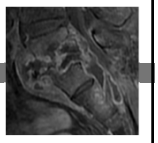
Pyogenic Vertebral Osteomyelitis: diagnosis

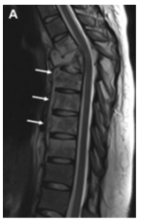


- Plain films and CT useful in subacute to chronic infection
  - Loss of disc height, endplate sclerosis
  - Can look similar to degenerative disease
- MRI best imaging test in early infection
  - Disc hyperintensity and loss of disc height
  - Marrow edema
  - Contrast enhancement
  - Erosive changes involving endplates
  - Infection: almost always involves two contiguous vertebral bodies

MASSACHUSETTS GENERAL HOSPITAL HARVARD MEDICAL SCHOOL 9

Pott's Disease



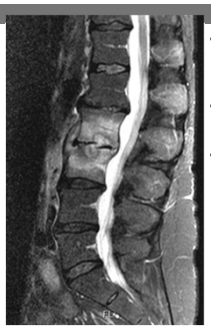


- Clinically:
  - More indolent than pyogenic osteomyelitis
  - Constitutional symptoms common
  - Anterior collapse may lead to gibbus deformity
- Radiographic:
  - Thoracic>lumbar with anterior involvement
  - Relative sparing of the disc space until later
  - Multi-level disease, large paraspinal 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

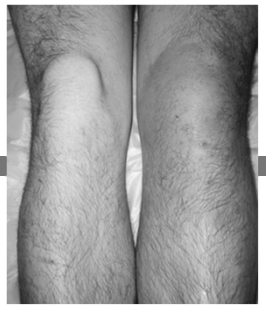
Pyogenic Vertebral Osteomyelitis: diagnosis



- 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)
  - 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 (higher yield)

MASSACHUSETTS GENERAL HOSPITAL Reference: 2015 IDSA Guidelines HARVARD MEDICAL SCHOOL 11

Septic Arthritis



MASSACHUSETTS GENERAL HOSPITAL HARVARD MEDICAL SCHOOL 12

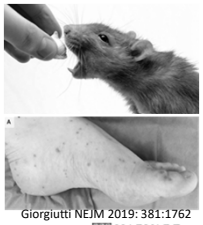
Septic Arthritis: Clinical Pearls

- 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 13

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

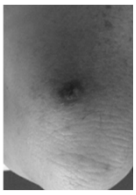


Giorgiutti NEJM 2019: 381:1762

MASSACHUSETTS GENERAL HOSPITAL HARVARD MEDICAL SCHOOL 14

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



MASSACHUSETTS GENERAL HOSPITAL 15

Viral arthritides

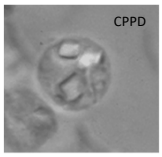
- Symmetric polyarthritis, often involving small joints, often associated with fever and rash
- Diagnose serologically (+IgM or 4 fold rise in IgG titer)

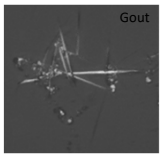
Most common viruses to cause arthritis	Clinical and Epidemiologic Clues
Rubella	Non-immune (non US born). See cervical lymphadenopathy, fever, rash.
Parvovirus B19	More common in women. History of exposure to young children, often a teacher or parent. Hands most common; can be severe.
Hepatitis B Virus	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

16

Crystalline arthritis: clinical pearls

- Acute gout flare mimics septic arthritis
  - Fever common
  - Monoarthritis and polyarthritis forms
  - Clues: rapid onset (hours), history of prior 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

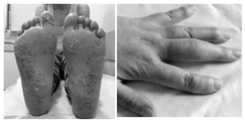




MASSACHUSETTS GENERAL HOSPITAL Images: Taljanovic RadioGraphics 2015;35:2026 HARVARD MEDICAL SCHOOL 17

Masquerading as Infection…

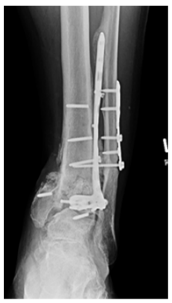
- Other noninfectious causes of arthritis:
  - Reactive arthritis
    - Following enteric or genitourinary infection
    - Asymmetric mono or oligo-arthritis affecting knees/ankles
    - Associated features: enthesitis (tendon insertion), dactylitis (sausage digits), mucosal lesions, urethritis, conjunctivitis/uveitis,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



Coelho BMJ Case Reports 2017-222475

MASSACHUSETTS GENERAL HOSPITAL HARVARD MEDICAL SCHOOL 18

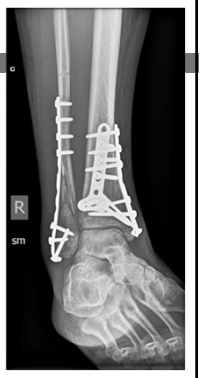
Osteofixation Infections



MASSACHUSETTS GENERAL HOSPITAL HARVARD MEDICAL SCHOOL 19

Case #2

- 44 year old healthy woman suffered a right ankle closed pilon fracture and underwent open reduction and internal fixation (ORIF)
- Chronically discharging wound despite courses of cephalexin and trimethoprim-sulfamethoxazole
- Two months after ORIF, superficial wound culture grows methicillin-susceptible *Staph aureus*
- Plain films: Hardware intact; fracture not yet consolidated



MASSACHUSETTS GENERAL HOSPITAL HARVARD MEDICAL SCHOOL 20

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 21

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 23

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 Virulent organisms	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 Consider rifampin if Staph species Consider suppression until fracture consolidates, especially if *Staph aureus*	Pathogen-directed therapy Duration not well studied

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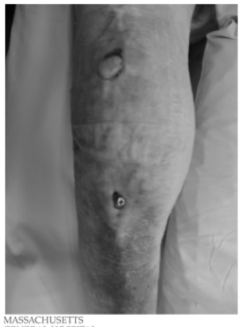
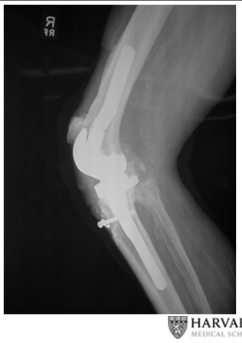
Prosthetic Joint Infection





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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 (anytime after arthroplasty)
  - Acute onset fever, joint pain, swelling in previously well joint replacement
  - Hematogenous seeding, virulent organisms (*Staph aureus, Streptococcus)*

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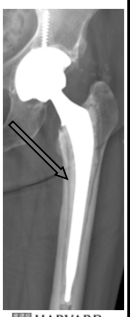
Prosthetic Joint Infection: Diagnostic pearls

- Diagnosis of acute PJI usually straightforward
- Multiple diagnostic algorithms have been developed for chronic PJI. Diagnosis of chronic PJI confirmed if:
  - Sinus tract to the joint
  - Two synovial fluid or tissue cultures positive with the same organism

	Early PJI and Late hematogenous	Delayed (chronic) PJI
ESR/CRP	High	May be normal or moderately elevated
Plain films	May be normal; effusion	May be normal or show periprosthetic lucency
Synovial fluid	WBC > 10,000/µL % pmns > 90	WBC > 3000/µL % pmns > 70



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Case #3

- A 57-year-old woman underwent total hip arthroplasty
  - She never achieved a pain-free state after surgery
- Eighteen months postoperatively, she was diagnosed with delayed periprosthetic infection due to *Enterococcus faecalis*
  - Sensitive to ampicillin, vancomycin, linezolid, daptomycin, gentamicin
- Her orthopedist plans a two-stage exchange procedure utilizing a temporary spacer comprised of polymethylmethacrylate (PMMA)

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Case #3: Vote

You are asked to provide recommendations about systemic and local antimicrobial therapy for the spacer. She has no antimicrobial allergies. You advise:

A. Ampicillin in the cement; systemic vancomycin
B. Ampicillin in the cement; systemic ampicillin
C. Gentamicin in the cement; systemic ampicillin
D. Tobramycin in the cement; systemic daptomycin
E. Ceftriaxone in the cement; systemic linezolid

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PJI Management

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

* 2012 IDSA Guidelines

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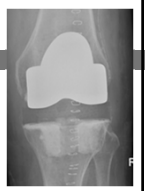
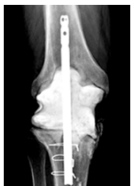
Antimicrobial Cement (PMMA)

- Mechanical function "spacer":
  - Joint stability, allows mobility, prevents contractures, facilitates reoperation
- Antimicrobial considerations
  - Known or suspected organisms
  - Thermal stability (avoid most β-lactams)
  - Osteocyte toxicity (avoid quinolones)
  - Vancomycin and aminoglycosides most common
  - Toxicity and allergy reported but rare
- Elution: high levels within the first few days
  - Local tissue concentration exceeds systemic delivery
  - May elute for months or longer





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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.

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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

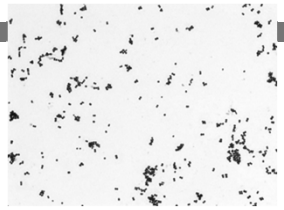
MASSACHUSETTS GENERAL HOSPITAL HARVARD MEDICAL SCHOOL 34

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;
  - Do not screen for asymptomatic bacteriuria
- Dental prophylaxis: no more!
- *Staph aureus* decolonization reduces surgical site infection

MASSACHUSETTS GENERAL HOSPITAL HARVARD MEDICAL SCHOOL 36

Microbiology of Musculoskeletal Infections



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Case #5

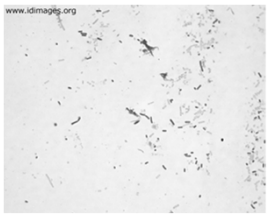
- 56-year-old man presents to ED with a one-week history of atraumatic right knee pain and swelling and low-grade fevers. Weight bearing is now uncomfortable.
- PMHx: poorly controlled diabetes
- One month ago he travelled to the Dominican Republic
  - Swam in pools, fished in the ocean
  - No illnesses while traveling
- He last saw a dentist six months ago; no tooth pain
- No history of injection drug use

- Exam: moderate effusion; pain with passive range of motion
- ESR 68 CRP 17 mg/dL
- Synovial fluid: 45,000 WBCs (82% neutrophils)
  - Negative gram stain

MASSACHUSETTS GENERAL HOSPITAL HARVARD MEDICAL SCHOOL 38

Case #5: Vote

Culture growth at 3 days incubation



What is the most likely organism?

A. Serratia marcescens
B. Salmonella heidelberg
C. Staphylococcus aureus
D. Kingella kingae
E. Pasteurella multocida

MASSACHUSETTS GENERAL HOSPITAL HARVARD MEDICAL SCHOOL 35

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 41

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 42

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

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Thank you!

MASSACHUSETTS GENERAL HOSPITAL HARVARD MEDICAL SCHOOL 44

22

Photo Opportunity II: More Photos and Questions to Test Your Board Preparation

Dr. John Bennett

22 – Photo Opportunity II: More Photos & Questions to Test Your Board Preparation

Speaker: John Bennett, MD

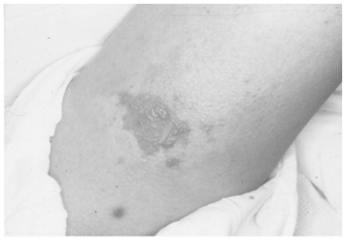
Photo Opportunity: More Photos and Questions to Test Your Board Preparation

John E. Bennett, MD
Bethesda, Maryland

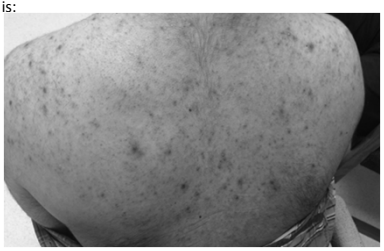
Disclosures of Financial Relationships with Relevant Commercial Interests

- **None**

- Which of the following would be the most likely cause of this rapidly expanding skin lesion in this patient with acute myelogenous leukemia, profound neutropenia and fever:
- A. Nocardia asteroides
- B. Streptococcus pyogenes
- C. Borrelia burgdorferi
- D. Pseudomonas aeruginosa
- D. Streptococcus anginosus

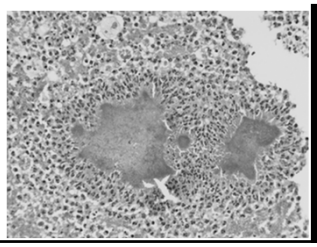


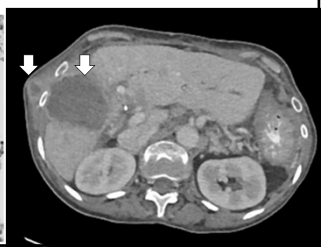
- 24 yr old male arrived in Washington, DC from Afghanistan 15 days ago for a World Bank conference, stayed and ate in hotel . Four days ago developed fever, cough, headache, anorexia, and sore throat. Three days ago was seen in ER, given azithromycin. One day ago developed nonpruritic rash on face, then torso. Today has temp 101.6F, maculopapular rash on face and trunk, small lymph nodes in neck and axilla, throat mild erythema, conjunctiva injected. Dry cough. WBC 4,200 with normal differential. Lives and works in Kabul. No sick relatives. Unsure about immunizations. No meds.Most likely cause of rash is:
- A. Dengue
- B. Scarlet fever
- C. Typhoid
- D. Measles
- E. Chickenpox



57 yr old female from Greece presented with fever, a tender red lump on the right flank and had the CT shown and liver biopsy H&E stain. The source of this infection is most likely which of the following:

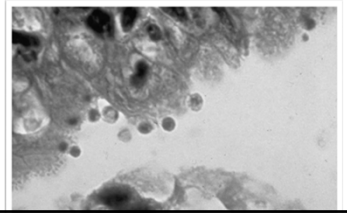
A. Sheep dog in Greece
B. Her colonic flora
C. Unpasteurized Greek cheese
D. Fecal contamination of food
E. Cholangitis





What is the most likely source of the 4-6 micron parasite emerging from the surface of the intestinal epithelium into the stool of an AIDS patient with profuse, watery diarrhea?

A. Water
B. Poorly cooked hamburger
C. Cole slaw
D. Raspberries
E. Raw oysters

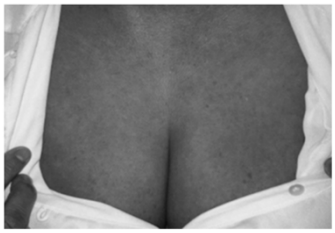


22 – Photo Opportunity II: More Photos & Questions to Test Your Board Preparation

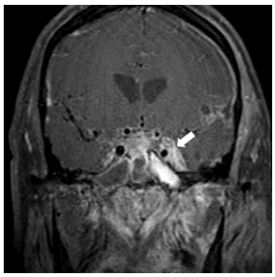
Speaker: John Bennett, MD

This 51 yr old woman presented with fever and rash two days after returning from Panama. She was born in Panama but lived in the USA for 30 years. Recently, she spent three weeks back in Panama , living with a cousin and visiting friends and family in Panama City. Everyone was well. She did not leave the city or eat anything unusual. The household where she stayed had a hamster and a dog but she didn't didn't do any care of rhe pets. She felt fine until two days after returning , when she developed fever, a bad headache and muscles aches. The next day she noted a fine, nonpruritic rash across her upper body. She came to the emergency room that day where her temperature was 102F, there was a fine petechial rash on her arms and upper chest and two small tender occipital lymph nodes. Routine lab work was normal except for a WBC of 1,600, normal differential, no atypical lymphocytes and a normal platelet count of 168,00-. She probably got this infections from which of the following:

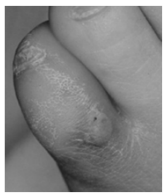
A . Food
B. Mosquito
C. Tick
D. Dog flea
E. Hamster urine



This patient with a cavernous sinus thrombosis would be expected to have which finding:
A. Bell's palsy
B. Loss of smell
C. Deaf left ear
D. Ocular palsy
E. Blind left eye

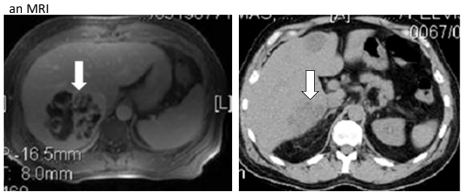


A 38-year-old marine sergeant reported to sick bay a week after shore leave with the acute onset of fever, malaise and five pustular skin lesions including the one shown here.
He is acutely ill but his vital signs (other than temperature) are normal. He had pain on flexion and slight swelling in the right wrist; his wrist flexor tendons are quite tender. His left ankle was tender the day before but is now asymptomatic.
While on shore leave in a port city in Mexico he had sex with a commercial sex worker, consumed a lot of alcohol and passed out in an alley infested with rats and mice . The most likely organism to grow from his blood culture in 2-3 days is which of the following:



A. Spirochete
B. Gram negative bacillus
C. Gram negative coccus
D. Gram positive bacillus
E. Endemic mycosis

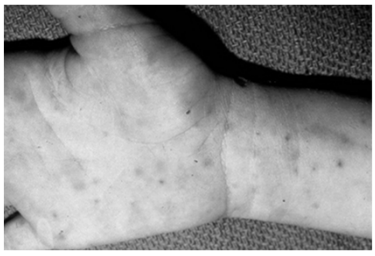
A CT is shown from a previously healthy 51-year-old white male from Maryland who just returned from his first overseas trip, a three week cruise that began in the southern tip of Africa and ended in the Mediterranean Sea with ports of call all along the West and North African coast, Italy, and Greece.He often ate on shore to sample the local cuisine. His wife, who remained well, ate only on board. He had only been home a week when he had the onset of fever. Workup was normal except for a slight fever (38.3C) and mild leukocytosis (16000 leukocytes) without eosinophilia.
His liver is enlarged and tender. The following are noncontrast CT views and an MRI



Which of the following is the most likely cause of his liver lesion?

A.Enteric bacteria
B. Echinococcus multilocularis
C. Fasciola hepatica
D. Cysticercosis
E. Paragonimus westermani

This 16-year-old girl from a dairy farm near Frederick, Maryland had the sudden onset in July of fever, severe headache, nausea, vomiting and muscle aches. On the fourth day, she developed the rash shown here on her wrists, palms, ankles, and soles.

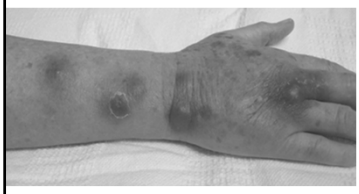


She should immediately receive
A.ceftriaxone
B. Ampicillin
C. Levofloxacin
D. Doxycycline
E. Meropenem

22 – Photo Opportunity II: More Photos & Questions to Test Your Board Preparation

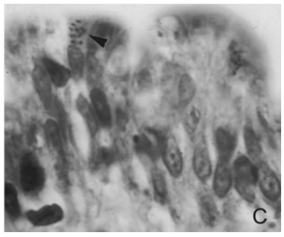
Speaker: John Bennett, MD

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.. What is the best way to culture this organism?



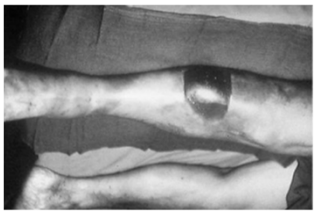
A. Addition of ferric citrate to mycobacterial agar
B. Use of fresh chocolate agar
C. Sabouraud's agar without antibiotics
D. Incubation on mycobacterial agar at 30°C
E. NNN medium

A 38-year-old man who refused therapy for his far advanced HIV was admitted for inanition, weakness, profound weight loss and chronic diarrhea.



WHAT IS THE MOST LIKELY ORGANISM?
A. Cyclospora cayetanensis
B. Microsporidium africanus
C. Enterocytozoon bieneusi
D. Cryptosporidium parvum
E. Rhodococcus equi

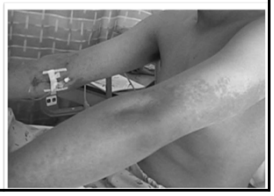
This 69-year-old male long-term alcoholic went into shock 3 days after eating raw oysters.
Examination in the emergency room revealed a dramatically abnormal lower extremity. What is the most likely source?



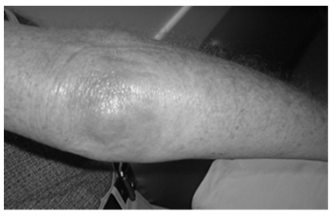
A.Streptococcus
B.Staphylococcus
C.Vibrio
D. Clostridium
E. Aeromonas

A 19-year-old college student presented to the student health service with a sore throat and fever of three days' duration. He had not previously sought medical care because it was "dead week," studying for final examinations. He has not felt great, but he has been able to study and function fairly normally. Today, the rash shown in the photo appeared. It was nonpruritic. Except for a temperature of 101°F, some tonsillar exudates bilaterally and the rash, his examination was normal. A rapid strep test was negative so a throat culture was obtained and treatment withheld. The next day the culture was reported as having no beta-hemolytic streptococci.

What organism is most likely?
A.Gram negative coccus
B. Gram positive bacillus
C. Gram negative bacillus.
D. Weakly acid fast bacillus

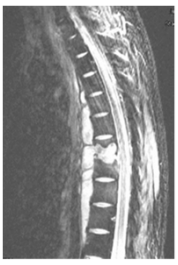


This 40-year-old dentist presented with pain and swelling in his elbow of three days duration. He had full range of motion in the elbow despite discomfort on motion. He was afebrile. He has never had such episodes before, and is in good health, having recently finished a marathon. What is the diagnosis?



A. Olecranon bursitis
B. Streptococcal cellulitis (erysipelas)
C. Septic arthritis
D. Tophaceous gout

A. This 25-year-old college student who lived in India until immigrating to the United States at age 18 years and has not returned in the intervening 7 years. He lives with his sister, who is healthy, He works part time in a parking lot. He presented with progressive thoracic back pain of three weeks' duration. Transcutaneous aspiration of the vertebral mass was negative on Gram stain and routine culture. Chest xray was normal. The most likely portal of entry for this infection is
A. Lung
B. Gastrointestinal tract
C. Skin
D.Urinary tract

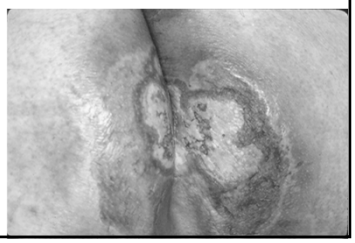


22 – Photo Opportunity II: More Photos & Questions to Test Your Board Preparation

Speaker: John Bennett, MD

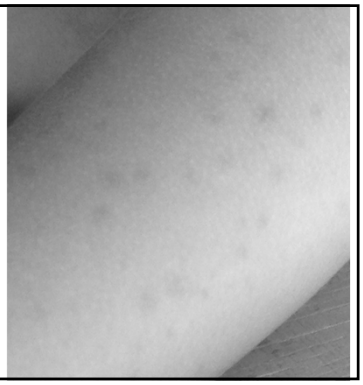
60 yr old obese woman with CLL and poorly controlled diabetes mellitus was admitted a week ago and started on high dose prednisone and rituximab. She complained of pain in her buttocks and was found to be afebrile but to have the lesion shown in her gluteal cleft. Her absolute neutrophil count was 600/cu mm, blood glucose 189 mg/dl. The most likely cause is which of the following:

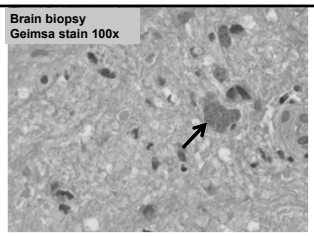
A varicella zoster virus
B. Herpes simplex virus
C. Candida albicans
D. Rhizopus arrhizus
E. Pseudomonas aeruginosa

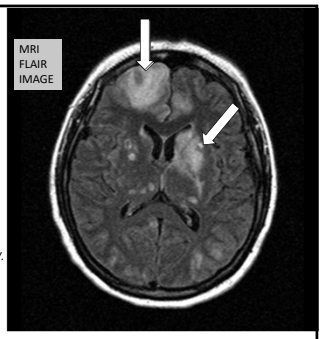


This 35 yr old woman became ill while vacationing in a resort in the Seychelles (Indian Ocean) with headache, fever, "aching all over" and a nonpruritic rash, which she captured by a cell phone photo of her arm. The fever and rash went away over a week so she flew home. The arthralgia never went away completely and now the pain in hand, feet, wrists and ankles are so severe she has not been able to return to her office job. Routine laboratory work is normal. The most likely cause is:

A. Chikungunya
B. Zika
C. Parvovirus (Erythrovirus)
D. Dengue
E. Scrub typhus







32 YR OLD HOMELESS MAN WITH ADVANCED HIV [CD4 10 , VL 1.2 MILLION) HISTORY OF DRUG ABUSE, FOUND DOWN IN ALLEY. POSSIBLE SOURCE OF THIS INFECTION IS :

A. RAT BITE
B. LOUSE
C. HUMAN FECES
D. POOR COOKED CHICKEN
E. POORLY COOKED BEEF

23

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

Dr. Henry Chambers

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

Speaker: Henry Chambers, MD

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

- Equity: Moderna
- Data Monitoring Committee: Merck
- Consultant: Janssen

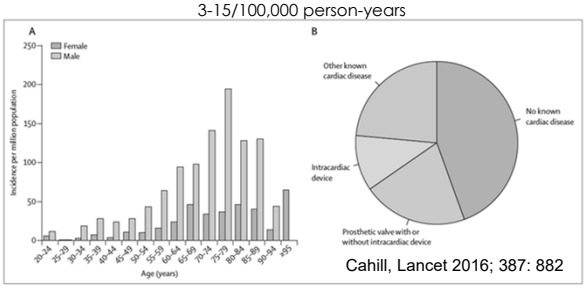
Topics for Discussion

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

Diagnosis of Endocarditis

Epidemiology

3-15/100,000 person-years



Cahill, Lancet 2016; 387: 882

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

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

Speaker: Henry Chambers, MD

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

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	Two major criteria	Three minor criteria
OR	OR	OR
Evidence of a vegetation or intracardiac abscess, confirmed by histology showing active endocarditis	Five minor criteria OR One major plus three minor criteria	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	Vegetation, defined as an oscillating intracardiac mass on a valve or supporting structure	New
OR	OR	OR
Persistently positive blood cultures (two > 12h apart, all of 3 or majority of ≥ 4)	Abscess	(worsening old murmur does not count)
OR	OR	
Single positive blood culture for Coxiella burnetii or phase I IgG antibody titer >1:800	New partial dehiscence of a prosthetic valve	

**Staphylococcus aureus*, viridans group 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 ≥38.0°C (100.4°F)
- 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

Modified Duke Criteria for Diagnosis of Endocarditis

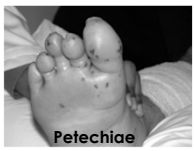
Definite pathologic diagnosis	**Definite Clinical Diagnosis**	**Possible Clinical Diagnosis**
Organisms on histology or culture of vegetation, intracardiac abscess or peripheral embolus	Two major criteria	Three minor criteria
OR	OR	OR
Evidence of a vegetation or intracardiac abscess, confirmed by histology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

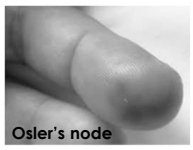
Sensitivity: 70% (definite), 95% definite + possible
Specficity: 95%

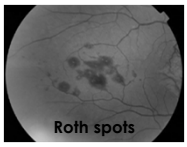
23 – Endocarditis of Native and Prosthetic Devices, and Infections of Pacers and Ventricular Assist Devices

Speaker: Henry Chambers, MD

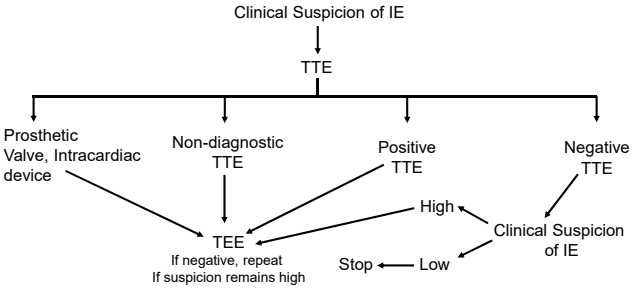
Microvascular/Immunologic Phenomena







Role of Echocardiograpy



European Heart Journal (2015) 36, 3075–3123

Harmonic TTE vs TEE for Diagnosis of IE

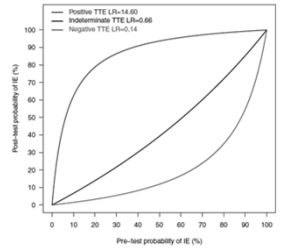


Figure 3 Utility of harmonic TTE in patients without prosthetic valves.

- Conclusively negative harmonic TTE useful to r/o native valve IE
- TTE less sensitive than TEE for detecting prosthetic IE vegetations, dehiscence, abscess
- Indeterminant TTE not useful to r/o endocarditis
- TTE insensitive for abscess, IE of implantable cardiac device
- Specificity of TTE is ~95%

Bai, J Am Soc Echocardiogr 2017; 30:639-646.e8

High Risk Factors for Proceeding to TEE

- 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

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

23 – 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 Staph. 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)

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

Speaker: Henry Chambers, MD

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

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

Speaker: Henry Chambers, MD

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

Culture-Negative Scenarios

- **Coxiella burnetii (Q fever)**: Direct or indirect animal contact, hepatosplenomegaly, abnormal or prosthetic valve. **Rx:** Doxycycline + hydroxychloroquine x 18 mo.
- **Bartonella quintana**: Homeless, indolent, valve normal or abnormal, louse vector. **Rx:** 6 wks doxycycline plus two wks gentamicin or plus 6 wks rifampin, then doxy for another 6 wk (resected valve) to 3 mo (no valve surgery).
- **Tropheryma whippeli:** Indolent, protracted course with arthralgias, diarrhea, malabsorption, weight loss, CNS involvement . **Rx:** Doxycycline + hydroxychloroquine x 12 mo, then more doxy…

32

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 and Device-Related Endocarditis

Diagnosis of PVE

- Duke criteria and TEE less sensitive for PVE compared to native valve endocarditis
- PET-CT (^{18}F-fluorodeoxyglucose positron emission tomography/computed tomography) plus Duke criteria*
  - Increased sensitivity: 84% vs. 57%
  - Reduced specificity: 71% vs 96%
- Multislice/Cardiac CT angiography similar to TEE in sensitivity and specificity, but added anatomic detail, useful if TEE non-diagnostic

*J Am Coll Cardiol Img 2020;13:2605
Clin Infect Dis 2021; 72:1687; Journal of Cardiology 2019; 73:126

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

Adapted from Karcher and Chu, UpToDate, 2020

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

Speaker: Henry Chambers, MD

Mycobacterium chimaera PVE

- Culture-negative endocarditis
- Indolent, may occurs years after cardiac surgery
- Due to contamination of heater-cooler units (Sorin Stockert 3T; LiveNova PLC, London, UK) connected to cardiac bypass machines

Antimicrobial 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 (optional 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

Transcatheter Aortic Valve Replacement

- Enterococci > S. aureus/CoNS > streptococci
- Risk of PVE for TAVR similar to surgical aortic valve replacement (SAVR)
- Sensitivity of TEE probably less in TAVR compared with SAVR
- Higher early and 1-year mortality with TAVR than SAVR, likely due to patient selection
- Antimicrobial therapy as for PVE

Clin Infect Dis 2021; 72:1687; PlosOne 2020;15: e0225077; Clin Microbiol Infect 2020;26:999

Cardiac Implantable Device Infections

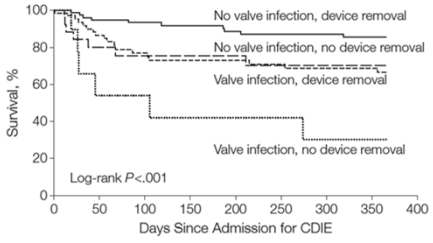
(permanent pacemakers, defibrillators)

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

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%
- PET-CT may detect localized infection if work-up is inconclusive

Survival with and without Device Removal

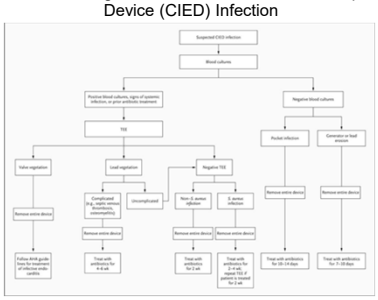


Athan, JAMA. 2012; 307:1727-1735

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

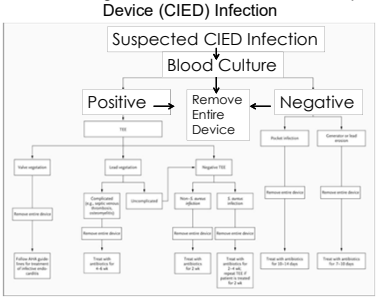
Speaker: Henry Chambers, MD

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



Baddour LM et al. N Engl J Med 2012;367:842-849

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



Baddour LM et al. N Engl J Med 2012;367:842-849

AHA Guidelines for Management of Cardiac Implantable Device Infections

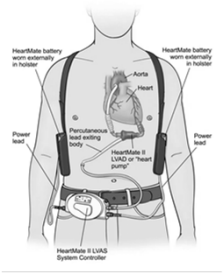
- Blood cultures before antibiotics
  - If positive, then TEE
- Gram stain, culture of pocket tissue, lead tips
- Device removal for all infections and occult staphylococcal bacteremia (conside for bacteremia with other endocarditis-causing organisms)
- Therapy (antibiotic based on susceptibility)
 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

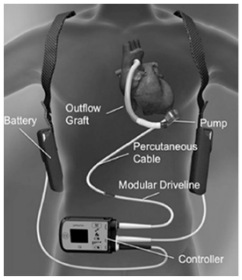
Circulation 2010;121:458-77

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

Infection of Ventricular Assist Devices





Types of VAD Infections

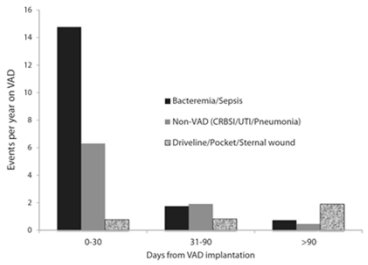
- VAD-specific infections
  - Pump pocket/cannula infections
  - Pocket infections
  - Driveline exit site infections (superficial or deep)
- VAD-related infections
  - Bloodstream infections (VAD-related, IV catheter/non-VAD related)
  - Endocarditis (pump or cannula, native valve)
  - Mediastinitis, sternal wound infections
- Non-VAD infections

Clinical Transplantation 2019;33:e13552.

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

Speaker: Henry Chambers, MD

Timing and Types of Infections After VAD Implantation



Clinical Transplantation 2019;33:e13552.

Microbiology of VAD-Specific Infections

- S. aureus/coag-negative staphylococci
- Pseudomonas aeruginosa
- Enteric Gram-negatives
- Enterococci
- Candida

Clinical Transplantation 2019;33:e13552.

Antimicrobial Therapy

- Initial empirical coverage for MRSA and Pseudomonas aeruginosa
- Pathogen-directed therapy when possible
- Chronic suppressive therapy to prevent relapse

Clinical Transplantation 2019;33:e13552;
Open Forum Infect Dis. 2020 Nov 16;8(1):ofaa532

Antimicrobial Therapy

Infection type	Initial therapy	Chronic suppressive therapy (oral or IV)
BSI, non-L-VAD	IV, 2 wk	Probably not needed
BSI, L-VAD-related	IV, 6 wk	Expected
Mediastinitis	IV, 4-8 wk	Expected
Superficial driveline	Oral or IV, 2 wk	OK to stop, but may relapse
Deep driveline	IV, 2-8 wk depending on source control, BSI present	Expected
Pump pocket	IV, 4-8 wk, source control/device exchange	Expected unless device removed
Pump/cannula	IV, ≥ 6 wk, device exchange	Expected unless device removed

Clinical Transplantation 2019;33:e13552;
Open Forum Infect Dis. 2020 Nov 16;8(1):ofaa532

Other Management Issues

Surgical Management of NVE

- 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

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

Speaker: Henry Chambers, MD

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

Thanks

24

Zoonoses

Dr. David Aronoff

24 – Zoonoses
Speaker: David Aronoff, MD

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 I. 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
- *Erysipelothrix 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

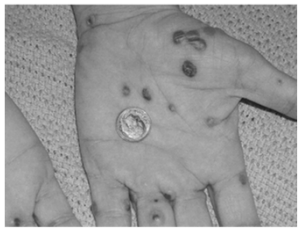
Question #1

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 male 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. cephalexin 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*

Suppurative inguinal lymph nodes (continued)

- *Staphylococcus aureus*. Gram stain of pus & culture positive. Distal lesion may be present.
- Lymphogranuloma venereum (LGV)-
  - Sexually transmitted
  - *Chlamydia trachomatis* L1-L3: genital lesion usually inapparent
  - "Stellate abscesses" on bx
  - (+) Nucleic acid amplification test on urine or wound

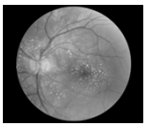
Cat Scratch Disease

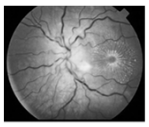
- *B. henselae* causes most cases
- >13,000 cases in the USA per year[1]
- Clinical findings:
  - 80% <21 yrs old, acute suppurative lymphadenitis proximal to bite, scratch, lick of young cat
  - Cats have chronic bacteremia but seem healthy
- Cat fleas may transmit between cats & occasionally to humans

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

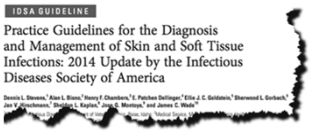
Cat Scratch Disease

Rx: 10% drain spontaneously

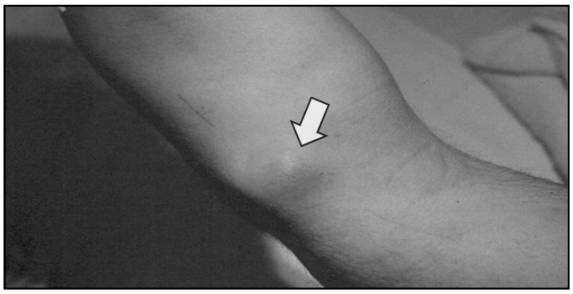
If not, node aspiration improves pain & helps exclude *Staph. aureus*

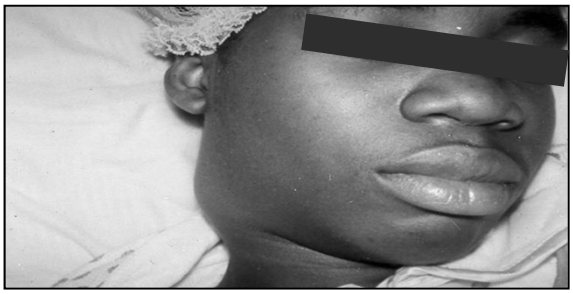
Treatment = AZITHROMYCIN (a bit better than no Rx)

(TMP/SMX alternative)



Shorbatli LA, *et al. Int J Clin Pharm.* (2018)





Warthin Starry silver stain

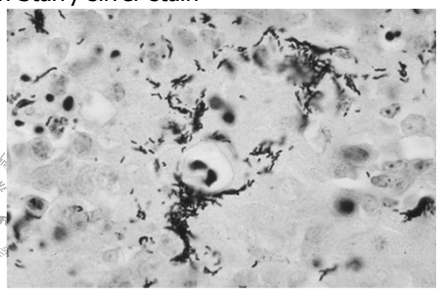
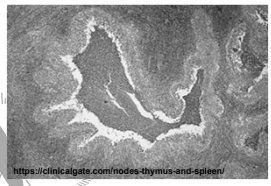


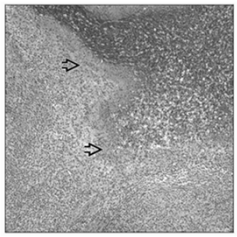
Photo by Andrew Margileth, MD., from http://emedicine.medscape.com/article/214100-workup#c8

Cat Scratch Lymphadenopathy
Stellate abscesses, necrotizing granulomas
Necrotic area with neutrophils surrounded by **palisading histiocytes**



https://clinicalgate.com/nodes-thymus-and-spleen/

Lymph nodes showing central abscess formation surrounded by palisaded histiocytes



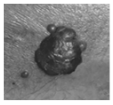
https://basicmedicalkey.com/cat-scratch-disease/

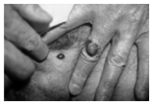
Major Syndromes due to *Bartonella* species

- *Bartonella*: **Slow growing** weakly Gram (-) rod
- *B. henselae*- cat scratch disease, peliosis
- *B. bacilliformis*- the **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 persons experiencing **homelessness**, trench fever
  - **Endocarditis**

Major Syndromes due to *Bartonella* species

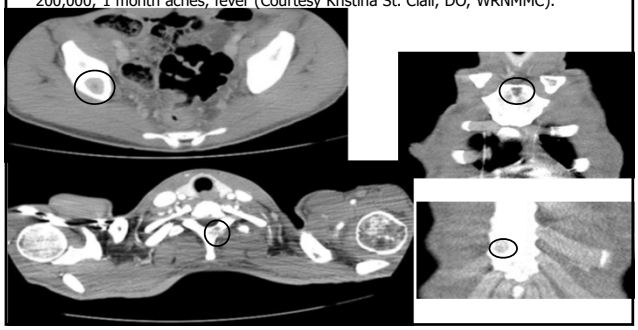
- HIV-associated (CD4<<100)
  - **Bacillary angiomatosis** (cutaneous)
    - Caused by either *B. henselae* or *B. quintana*
    - Lesions bleed easily
    - Biopsy: vascular proliferation, plump endothelial cells, bacilli
    - DDx = Kaposi sarcoma
  - Bacillary **peliosis** (*B. henselae*)
  - Osteomyelitis (lytic; *B. quintana*)
  - Chronic bacteremia/endocarditis





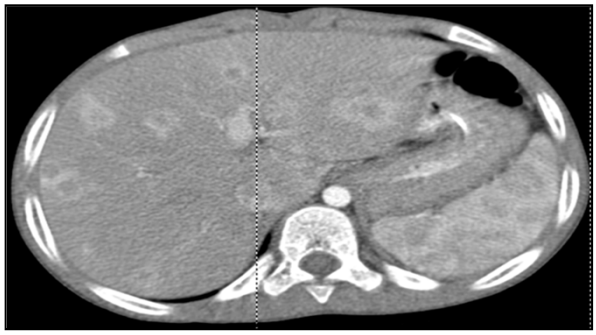
Images from http://mddk.com/bacillary-angiomatosis.html

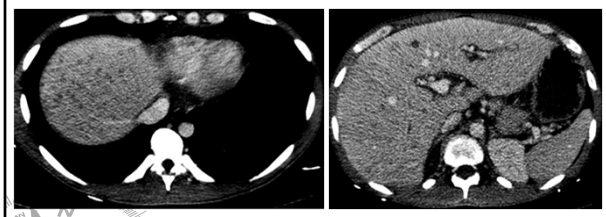
Bartonella osteomyelitis: 30 yr old man with HIV, CD 4=3, viral load 200,000, 1 month aches, fever (Courtesy Kristina St. Clair, DO, WRNMMC).



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.

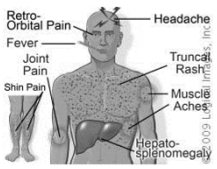
Case courtesy of Dr. Sam Bailin (Vanderbilt)

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, **homelessness** +/- alcoholics

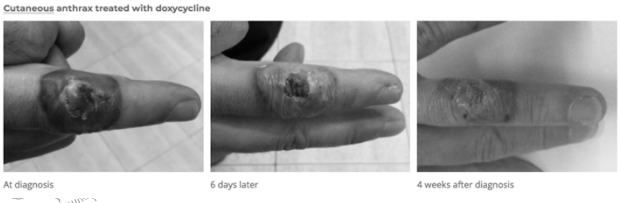


Brouqui P, *et al. NEJM* (1999)

Bartonella endocarditis

- <5% of all bacterial endocarditis
- Consider *B. quintana* or *B. henselae* in **homelessness** & 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

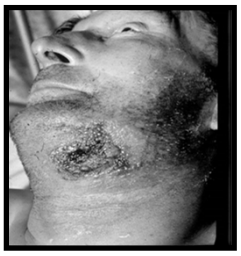
ANTHRAX



Images from https://www.dermnetnz.org/topics/anthrax

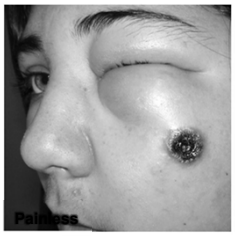
ANTHRAX

- 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

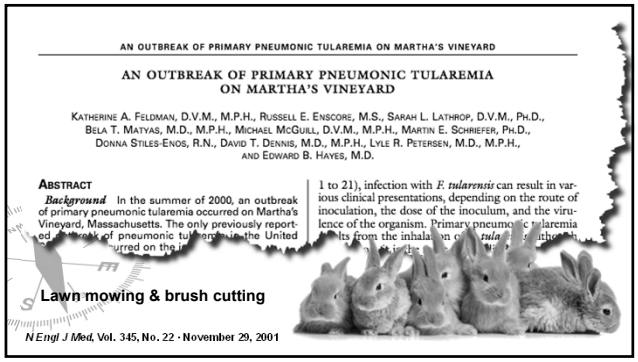
Edema
Vesicles
Necrotic ulcer



https://www.nejm.org/doi/full/10.1056/NEJMicm0802093

TULAREMIA

- 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 reported outbreak of pneumonic tularemia in the United

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

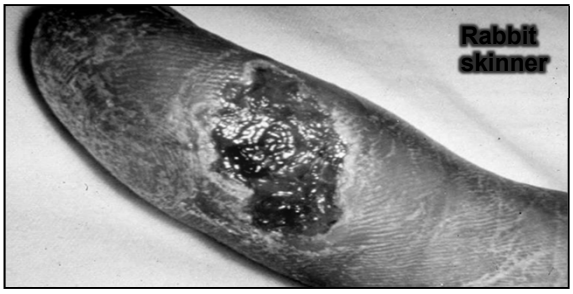
Lawn mowing & brush cutting

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)



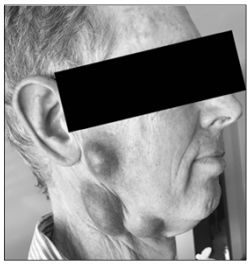
Glandular Tularemia

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

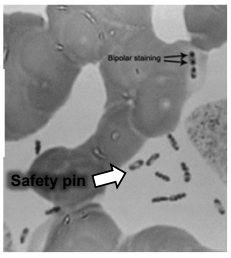
- *Yersinia pestis*
- New Mexico, California, Arizona & Colorado
  - Rodent **flea bite**
  - **Prairie dogs**
- Fever, nausea & swollen, painful lymph nodes
- Sepsis, pneumonia-hematogenous or aerosol in crowded conditions


(Michael Smith, Getty Images)

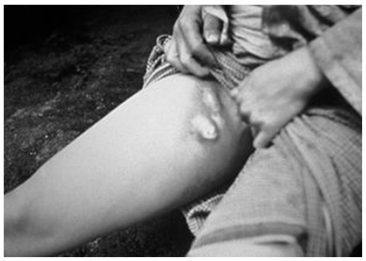

(Eye of Science/Science Source)

PLAGUE

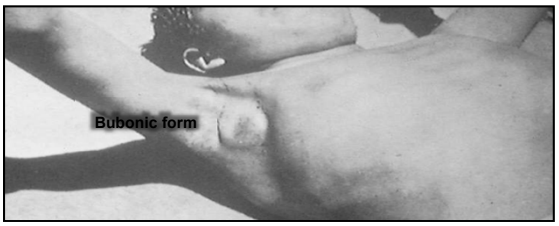
- Gram negative coccobacillus
- **Bipolar-staining** bacilli
- **Safety pin** appearance
  - *Yersinia pestis*: lab hazard
- Treatment: **Streptomycin** >> doxy, cipro

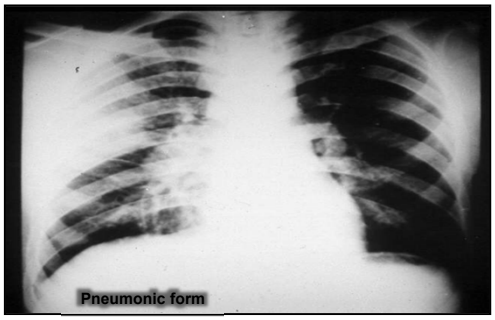


Bubonic form



Wikipedia image



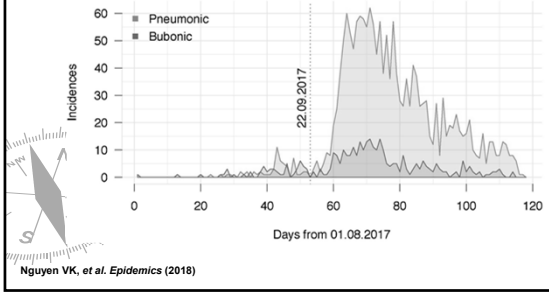


Large Outbreak in Madagascar

- 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

Ingestion of animal products

Question #4

A 41 year old car salesman from Baltimore was admitted for a febrile 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:

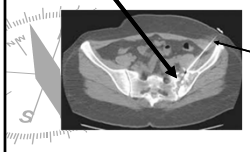
A. Home made sausage from Greece
B. Home made goat cheese from Greece
C. Cole slaw from a Baltimore delicatessen
D. Beef tartar, meat from the farmer's market
E. Lamb kabobs, meat from the farmer's market

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 <u>bone</u>, liver
Epididymo-orchitis[1], endocarditis
sacroiliitis, tenosynovitis, meningitis



Biopsy needle

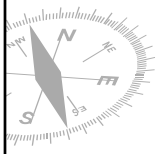
Malodorous perspiration (uncommon) "pathognomonic"[2]

1. Ip CCK, *et al. BMJ Case Rep* 2019;12:e230007. doi:10.1136/bcr-2019-230007
2. 2. Pappas G, *et al. NEJM* (2005)

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

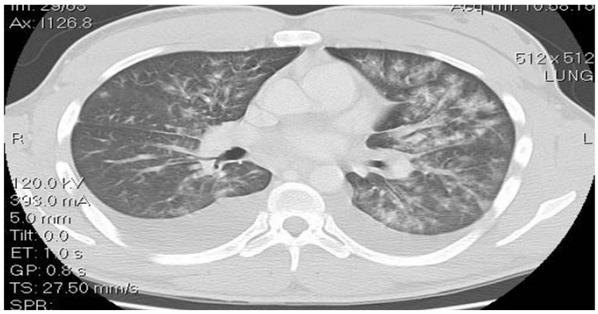


Case

- 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^{o}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

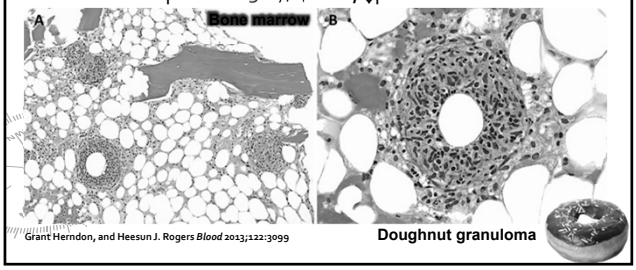


Question #5

Which of the following is the most likely diagnosis?

A. brucellosis
B. anthrax
C. leptospirosis
D. Q fever
E. Visceral leishmaniasis

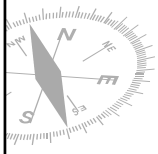
A 54-year-old man with a history of multiple myeloma presented with intermittent fevers, chills, fatigue, & weight loss for 1 month. +splenomegaly, ↑LFTs, ↓plt



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 patient

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 cat exposure, sheep handlers, living downwind of sheep/cattle farms
  - **Q Fever**

Key Clinical Syndromes

Culture negative endocarditis
- Homelessness: *Bartonella quintana*
- Animal exposure: *Coxiella burnetii*

Kaposi-like skin lesions: *Bartonella henselae*

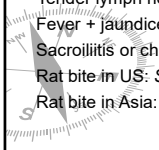
Tender lymph node: bartonellosis, tularemia, plague

Fever + jaundice: leptospirosis

Sacroiliitis or chronic illness w/ stinky sweat: brucellosis

Rat bite in US: *Streptobacillus moniliformis*

Rat bite in Asia: *Spirillum minus*



Other Zoonoses

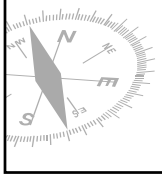
- There are many zoonoses
- Be sure to review them before the boards

Chikeka & Dumler *Clin Microbiol Infect* 2015; 21: 404–415

The End

Thank you!

D.aronoff@vumc.org
@DMAronoff



25

Penicillin Allergy

Dr. Sandra Nelson

25 – Penicillin Allergy
Speaker: Sandra Nelson, MD

Penicillin Allergies

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 have documentation of penicillin allergy
  - Rash most common adverse drug reaction (ADR)
  - Others include "unknown", angioedema, GI symptoms, itching
  - 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

MASSACHUSETTS GENERAL HOSPITAL 3

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

MASSACHUSETTS GENERAL HOSPITAL HARVARD MEDICAL SCHOOL 4

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.

MASSACHUSETTS GENERAL HOSPITAL HARVARD MEDICAL SCHOOL 5

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

MASSACHUSETTS GENERAL HOSPITAL HARVARD MEDICAL SCHOOL 6

25 – Penicillin Allergy
Speaker: Sandra Nelson, MD

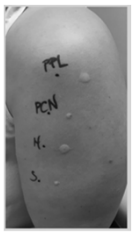
Classification of Drug Allergy (Gell and Coombs)

Type	Immune mechanism	Clinical example
I: Immediate (usually within one hour)	IgE-mediated	Anaphylaxis, Urticaria, Angioedema, Bronchospasm
II: Often <72 hours, but up to 2 weeks	Antibody-dependent (IgG)	Hemolytic Anemia Thrombocytopenia Neutropenia
III: Days to weeks	Immune Complex	Serum Sickness Vasculitis
IV: Days to weeks	Cell mediated	Cutaneous drug reactions - Mild maculopapular - Severe (DRESS, SJS, TEN) Interstitial nephritis Hepatitis

MASSACHUSETTS GENERAL HOSPITAL HARVARD MEDICAL SCHOOL 8

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
  - Epicutaneous and intradermal administration of PLL (penicilloyl polylysine, Pre-Pen) and penicillin G
  - Useful for inpatients and outpatients with a history of IgE mediated reaction
  - Useful for sick patient with unknown reaction
  - Avoid in unstable patients



Shenoy JAMA 2019;321:188

MASSACHUSETTS GENERAL HOSPITAL HARVARD MEDICAL SCHOOL 9

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) or in high risk of IgE mediated reaction
- 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

MASSACHUSETTS GENERAL HOSPITAL HARVARD MEDICAL SCHOOL 10

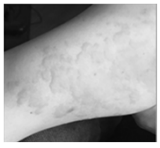
Classification of Drug Allergy (Gell and Coombs)

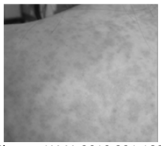
Type	Immune mechanism	Clinical example	Management
I: Immediate (usually within one hour)	IgE-mediated	Anaphylaxis, Urticaria, Angioedema, Bronchospasm	Penicillin skin testing followed by drug challenge
II: Often <72 hours, but up to 2 weeks	Antibody-dependent (IgG)	Hemolytic Anemia Thrombocytopenia Neutropenia	No testing; generally avoid re-use
III: Days to weeks	Immune Complex	Serum Sickness Vasculitis	No testing; generally avoid re-use
IV: Days to weeks	Cell mediated	Cutaneous drug reactions Interstitial nephritis Hepatitis	Varies; for severe reactions and organ involvement avoid re-use

MASSACHUSETTS GENERAL HOSPITAL HARVARD MEDICAL SCHOOL 11

Deciphering Cutaneous Reactions

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



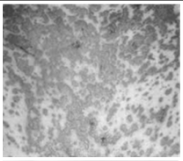


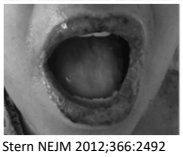
Shenoy JAMA 2019;321:188

MASSACHUSETTS GENERAL HOSPITAL HARVARD MEDICAL SCHOOL 12

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

MASSACHUSETTS GENERAL HOSPITAL HARVARD MEDICAL SCHOOL 13

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.

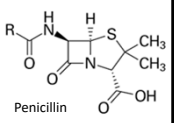
Case #2: Vote

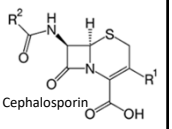
What do you do counsel?

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

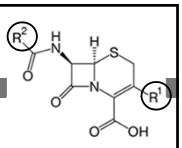
PCN Allergy and other beta-lactams

- 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





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

Thank you and good luck!

26

Staphylococcal Diseases

Dr. Henry Chambers

26 – Staphylococcal Disease

Speaker: Henry Chambers, MD

Staphylococcal Diseases

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

- Equity: Moderna
- Data Monitoring Committee: Merck
- Consultant: Janssen

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 speciation of the blood isolate
C. PET-CT to look for another focus of infection for biopsy
D. Fungal serologies, PPD

Staphylococcus lugdunensis

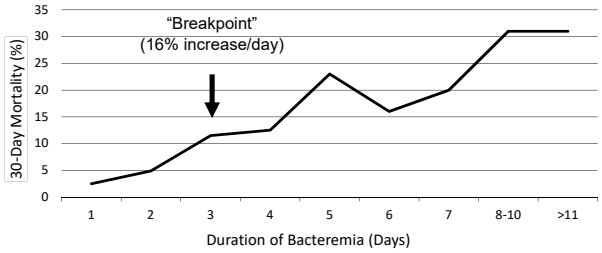
- Coagulase negative….
  - The tube "free" coagulase test is negative
  - The latex "bound" coagulase (i.e., clumping factor) test may be positive and confuse physicians
- Virulent, aggressive, similar to *S. aureus*.
  - Bacteremia, NV and PV endocarditis
  - Bone and joint infection
  - Pacemaker,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

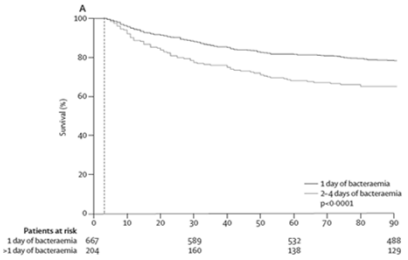
A. MRSA infection
B. Hospital-onset infection
C. Positive blood cultures on appropriate therapy
D. Community-onset infection

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]

Even 2 days of Bacteremia on Therapy is Bad



Lancet Infect Dis 2020; 20: 1409

Risk factors for longer durations of Staph. aureus Bacteremia

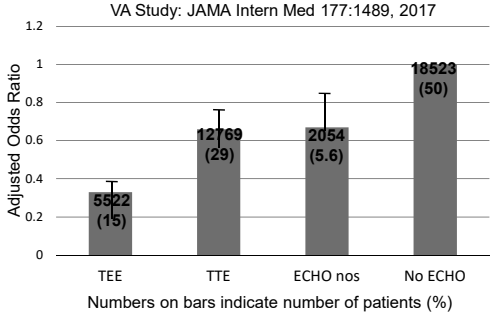
- Factors predictive of longer duration of bacteremia
  - MRSA
  - Delayed source control
- Factors **NOT** associated with longer durations of bacteremia
  - MIC
  - Choice of antimicrobial (specific agent, single or combo)
  - Switching from vancomycin to daptomycin

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

Echocardiography

ECHO and mortality in S. aureus Bacteremia

VA Study: JAMA Intern Med 177:1489, 2017



Numbers on bars indicate number of patients (%)

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

Depends on the pre-test probability

- Consider TTE (sensitivity 70%, specificity 95%) in all patients with SAB
  - Possible exception: HCA + no intracardiac devices + no signs IE + negative BC @ 48-72h
- Obtain TEE (sensitivity 90%, specificity 95%) in high risk patients
  - Embolic events, intracardiac device, IVDU, prior IE
  - Suspected endocarditis, negative TTE

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

Treatment of MSSA Bacteremia

Q3. 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

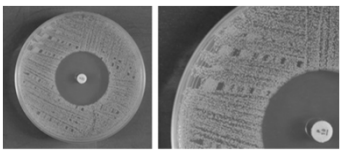
…the current laboratory screening procedures for detecting penicillin susceptibility may not be reliable.

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)

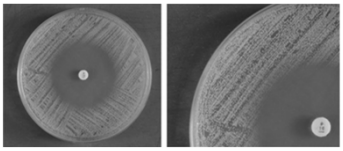
J Clin Micro 54:812, 2016

Zone edge test for β-lactamase

Positive



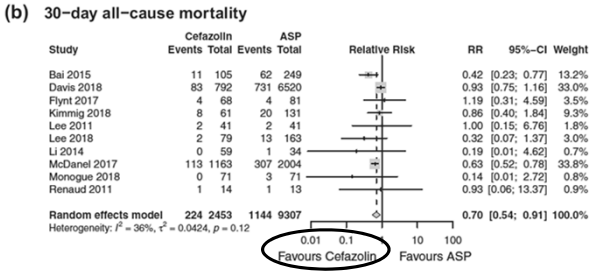
Negative



MSSA Bacteremia: Cefazolin vs. Antistaphylococcal Penicillins

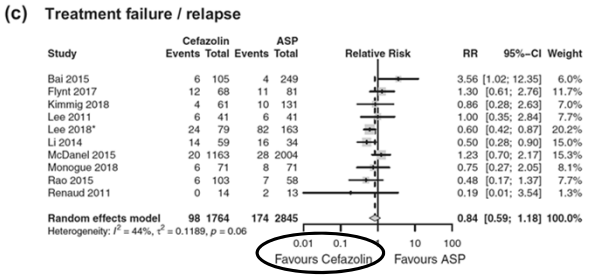
- Efficacy:
  - Penicillinase inoculum effect on cefazolin MICs – does it matter?
- Safety :
  - Adverse events due to ASPs

Cefazolin vs Anti-staphylococcal Penicillins



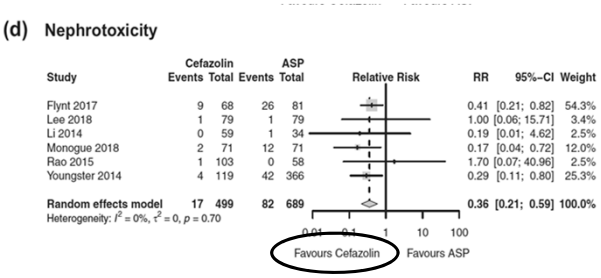
Weis, et al. / Clinical Microbiology and Infection 25 (2019):818e827

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

What about ceftriaxone for MSSA bacteremia?

- Single center, retrospective cohort
  - 38 cefazolin
    - Presumed/proven endovascular: 17 (45%), SSTI: 3 (8%)
  - 33 ceftriaxone
    - Presumed/proven endovascular: 7 (21%), SSTI: 11 (33%)
  - Outcomes
    - Treatment failure*: 11 (29%) cefazolin vs. 18 (55%) ceftriaxone; *P* = .029
    - Mortality: 1 (3%) ceftriaxone vs 4 (11%) cefazolin

* Failure = prolonged IV, unplanned oral therapy, incomplete treatment, relapse, readmission, unplanned surgery

Open Forum Infect Dis. 2018 May 18;5(5):ofy089

What about ceftriaxone for MSSA bacteremia?

- Single center, retrospective cohort
  - 95 cefazolin/oxacillin
    - ICU admission 48%, Endocarditis 43%, SSTI 10%
  - 148 ceftriaxone
    - ICU admission 29%, Endocarditis 28%, SSTI 16%
  - Failure*: 18 (19%) cefazolin/oxacillin vs 31 (21%) ceftriaxone
  - Failure, endocarditis: 4 (10%) cefazolin/oxacillin vs 11 (26%) ceftriaxone, p = 0.11)

* Failure = 90 day mortality, readmission, micro failure

Open Forum Infect Dis. 2020 Aug 13;7(9):ofaa341
See also: Meta-analysis, Antibiotics 2020, 9, 39; doi:10.3390/antibiotics9020039

Summary: MSSA bacteremia

- Cefazolin is better tolerated than ASPs
- AHA recommends 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
- Ceftriaxone efficacy poorly defined, avoid for endocarditis

Treatment of MRSA Bacteremia

Q4. 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

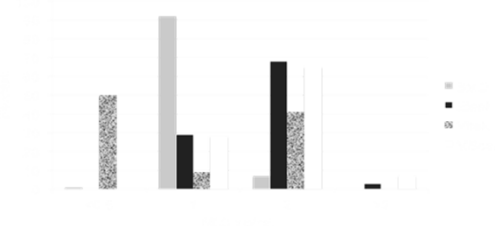
Antibiotic	Indications	Comments
Linezolid	SSTI, HAP, VAP	Serotonin syndrome: avoid use with SSRIs, MAO-Is; bacteriostatic Bone marrow suppression
Telavancin	SSTI, HAP, VAP	Vancomycin derivative Nephrotoxic, black box warning for ClCr ≤ 50 ml/min Artificially prolongs PT, PTT QTc prolongation, teratogenic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



Int J Antimicro Agent 32:378, 2008

MIC is a Poor Predictor of Outcome

- 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, et al. JAMA 312:1552, 2014.

Highlights of Modern Vancomycin Dosing for MRSA Infections

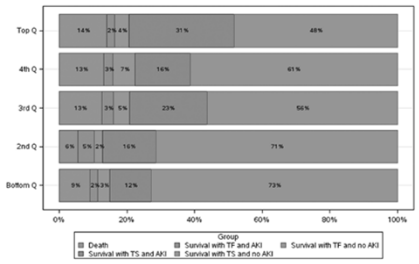
- Use of troughs no longer recommended
- Target AUC/MIC_{MBD} to 400-600 (assume MIC_{BMD} = 1 μg/ml)
  - Bayesian-derived monitoring, 1-2 samples (Cmax, Cmin)
  - 1st order PK equation with C_{max}, C_{min} at near steady-state
  - Continuous infusion: multiply steady-state concentration x 24
- Consider 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

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

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



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

Duration of Therapy of *S. aureus* Bacteremia

Outcomes of *S. aureus* Bacteremia 2 weeks or >2 weeks

Category, N (Days of Rx, IQR)	**Outcome**		
	Success	**Clinical Failure#**	**Non-evaluable**
Uncomplicated, 59 (14-17 days)	73%	15%	11%
Complicated, 37 (17-33 days)	65%	27%	8%

*#Change in Rx, new infection, relapse/persistent bacteremia, death

Holland, et al. JAMA 2018;320:1249

Outcomes of Uncomplicated S. aureus Bacteremia: 14 days vs. >14 days

Outcomes	**14 day Rx (n=21)**	**> 14 days Rx (n=43)**
Death due to SAB	0	0
Relapse	0	2 (5%)
All cause mortality	2 (10%)	2 (5%)
Catheter-associated AE	0	7 (16%)
Adverse drug event	5 (24%)	7 (16%)

Taupin, OFID. 2020; 2020 Sep 29;7(10):ofaa457. doi: 10.1093/ofid/ofaa457

How common is uncomplicated *S. aureus* Bacteremia?

Study	**# eligible**	**# screened**
Taupin	64 (10.4%)	612
14 day Rx	21	
>14 day Rx	43	
Holland (RCT)	116 (1.9%)	~6000*
Uncomplicated SAB	79	
Complicated SAB	37	

*Known or suspected complicated SAB at screening was an exclusion

Duration of Therapy for S. aureus BSI

14 days
- UNCOMPLICATED (uncommon)
- Fever resolves by day 3
- Sterile blood culture after 2-3 days (DOCUMENT!)
- Easily removed focus of infection (no DVT)
- No metastatic infection (e.g., osteo)
- Negative echo, no evidence of endocarditis
- No predisposing valvular abnormalities
- (No implanted prosthetic devices, no DM, no immunosuppression)

4-6 weeks +
- COMPLICATED (usually is)
- Failure to meet one or more of above criteria
- Osteomyelitis, endocarditis, epidural abscess, septic arthritis, pneumonia, complicated UTI

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

Combination Therapy of S. aureus BSI

Q5. Which one of the following combinations have been shown to improve mortality 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. Daptomycin + fosfomycin for MRSA
E. No combination regimen

Overview of Studies of Combination Therapy for SAB

Regimen	Study	Population	Comments	PMID
Adjunctive rifampin	RCT	MRSA, MSSA	No benefit	1929035 29249276
Adjunctive aminoglycoside	Obs., RCT	MRSA, MSSA	1 d shorter SAB, toxic	Various
Adjunctive dapto	RCT	MSSA	No benefit	32667982
Adjunctive β-lactam + vanco/dapto	RCT	MRSA	↑↑ AKI, higher mortality	32044943
Dapto + ceftaroline	Obs., aborted RCT	MRSA	Low quality data	30858203, 31640977, 31404468
Dapto + fosfomycin	RCT	MRSA	No mortality benefit, ↓ micro failure, ↑ AEs	32725216 32887985

Overview of Studies of Combination Therapy for SAB

Consider for salvage therapy, not first line

Regimen	Study	Population	Comments	PMID
Adjunctive rifampin	RCT	MRSA, MSSA	No benefit	1929035 29249276
Adjunctive aminoglycoside	Obs., RCT	MRSA, MSSA	1 d shorter SAB, toxic	Various
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Adjunctive β-lactam + vanco/dapto	RCT	MRSA	↑↑ AKI, higher mortality	32044943
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Dapto + fosfomycin	RCT	MRSA	No mortality benefit, ↓ micro failure, ↑ AEs	32725216 32887985

Once bacteremia clears on a combo salvage regimen, mono or combo follow-on?

263 patients, NVE, osteo, brain abscess (1), ≥4 d MRSA + BC
↓
80 patients, vanco/dapto + ceftaroline
↓
30 evaluable patients
15 combo
15 mono

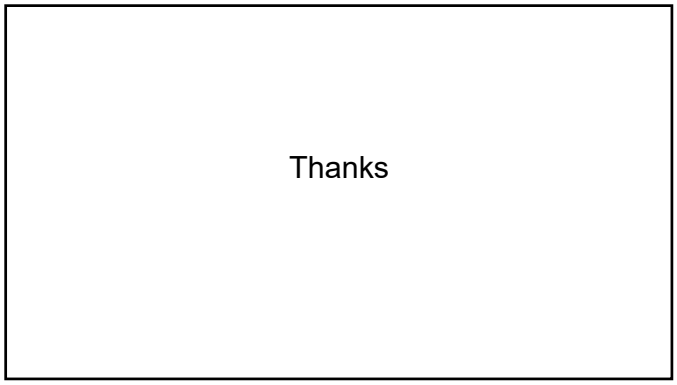
Outcome	Mono	Combo
AKI	6	7
Leukopenia	0	1
Recurrence	1	0
Readmission	2	0
Death	1	3

Infect Dis Ther (2020) 9:77–87

Monotherapy versus combination therapy for *Staph. aureus* bacteremia

- No high quality RCT has demonstrated improved mortality with combination antimicrobial therapy over monotherapy
- Studies suggesting a possible benefit of combination therapy are mostly low quality, retrospective, subject to bias, and based on subjective outcomes (e.g., change in therapy) not mortality, recurrence, metastatic infections*
- Reserve for salvage therapy

Possible exception: Dapto + Fosfo vs Dapto, Pujol, et al. Clin Infect Dis 2021; 72:1517



27

Helicobacter and Clostridioides Difficile

Dr. David Aronoff

27 – Helicobacter and Clostridium Difficile

Speaker: David M. Aronoff, MD

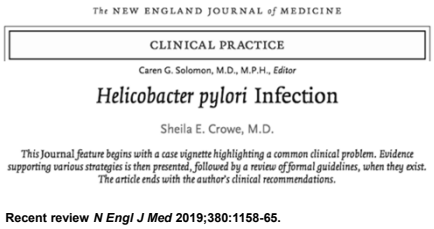
Helicobacter* and *Clostridioides difficile

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

- **Research Grant - Pfizer (*C. difficile* pathogenesis)**

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.

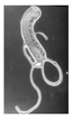
This Journal feature begins with a case vignette highlighting a common clinical problem. Evidence supporting various strategies is then presented, followed by a review of formal guidelines, when they exist. The article ends with the author's clinical recommendations.

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?

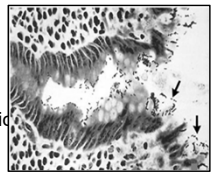
A. Perinatally from mother
B. Ingestion of raw vegetables
C. Ingestion of undercooked meat
D. Ingested tap water from a municipal source
E. Contact with infected secretions from another human

27 – Helicobacter and Clostridium Difficile

Speaker: David M. Aronoff, MD

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

***H. pylori* is a World Health Organization-designated carcinogen & the strongest known risk factor for non-cardia gastric adenocarcinoma**

- #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
Shah SG, et al. Gastroenterology 2021;160:1831–18

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

Question #5

A 23 yo woman presents with persistent epigastric discomfort diagnosed as Hp+ gastritis by endoscopy. Fecal Hp antigen is also positive. Last year she was treated with azithromycin for a respiratory tract infection. 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

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 *Helicobacter pylori* Therapy

1. Ask about abx exposure hx (clarithromycin/metronidazole/fluoroquinolones)
2. Discuss adherence
3. Use high dose PPI (BID dose; increase gastric pH>4-5)
   - *H. pylori* grows optimally at pH 6-8
   - Acidity hinders stability & activity of macrolides, amoxicillin
4. Longer (**14 days**) rather than shorter treatment courses
5. Combination drug therapy is essential
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

Eradication of *Helicobacter pylori*

- Triple therapy with a PPI, clarithromycin, & amoxicillin or metronidazole is **not favored** due to increased prevalence of macrolide resistance (but might still be an option on boards!)
  - Clarithromycin resistance in the US now ≥ 15%
- Use a bismuth-based **quadruple therapy** for 14 days as 1st-line therapy:
  - Bismuth subsalicylate or subcitrate
  - Tetracycline (**not** doxycycline)
  - Metronidazole
  - PPI

Shah SC, *et al. Gastroenterology* 2021;160:1831–1841
Cho J, *et al. Gastroenterol Clin N Am* 50 (2021) 261–282
Hulten KG, *et al. Gastroenterology* 2021

RIFABUTIN-Based Combinations

- 2020: The FDA approved **fixed-dose combination** of omeprazole, amoxicillin & rifabutin (Talicia) for *Hp* treatment in adults
- Omeprazole 10 mg, amoxicillin 250 mg, & rifabutin 12.5 mg
  - The recommended dosage is 4 capsules (with food) every 8 hours for 14 days.

Summary: Omeprazole/Amoxicillin/Rifabutin (*Talicia*)

- A fixed-dose, rifabutin-based, 3-drug combination FDA-approved for treatment of *Helicobacter pylori* infection.
- First rifabutin-based product to be approved for treatment of *H. pylori* infection.
- Rifabutin-based triple therapy has been used for years as a salvage regimen for treatment-refractory *H. pylori* infection.
- Approval was based on the results of two trials in treatment-naive patients; *H. pylori* was eradicated in about 80% of those treated with the combination.
- How the efficacy of *Talicia* compares to that of other regimens used for first-line treatment of *H. pylori* infection is unknown.
- Rates of *H. pylori* resistance to rifabutin have been low; whether more widespread use as part of a first-line regimen would result in higher rates of resistance remains to be established.
- Common adverse effects include diarrhea, headache, rash, and dyspepsia.
- Has the potential to interact with many other drugs.

The Medical Letter (2020)

Eradication of *Helicobacter pylori*

- Fluoroquinolone resistance is common now (>50%)
  - They are not recommended in 1st-line treatment regimens
- Resistance to amoxicillin, tetracycline & rifabutin is **uncommon**
- Clinical significance of resistance to metronidazole not straightforward

Shah SC, *et al. Gastroenterology* 2021;160:1831–1841
Cho J, *et al. Gastroenterol Clin N Am* 50 (2021) 261–282
Hulten KG, *et al. Gastroenterology* 2021

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

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

27 – Helicobacter and Clostridium Difficile

Speaker: David M. Aronoff, MD

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:

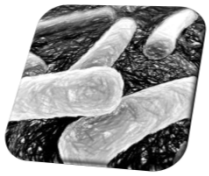
- Quadruple therapy favored over triple therapy
- Increasing emphasis on antibiotic resistance testing
  - Fecal or biopsy **genotypic** testing for clarithromycin, FQ
  - MIC testing for clarithromycin, nitroimidazole, FQ resistance
  - Challenging

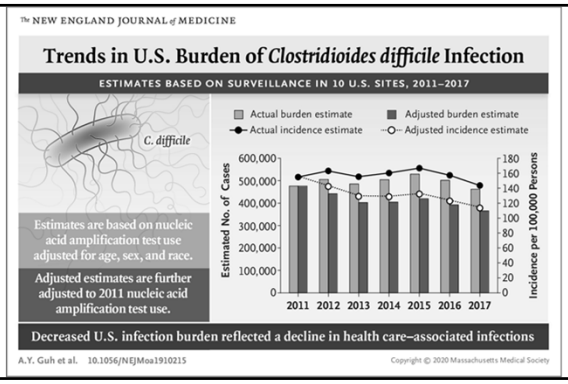
KEY TAKE AWAYS

FOLLOW UP:

- TOC mandatory (stool Hp antigen test, UBT)
- At least 4 weeks after completion of therapy

CLOSTRIDIOIDES DIFFICILE





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

27 – Helicobacter and Clostridium Difficile

Speaker: David M. Aronoff, MD

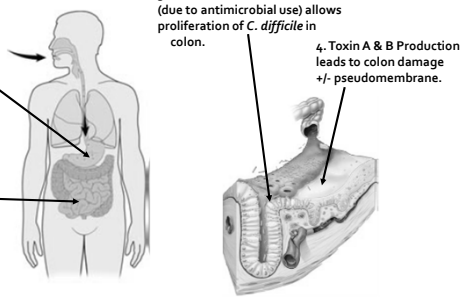
Pathogenesis of CDI

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.

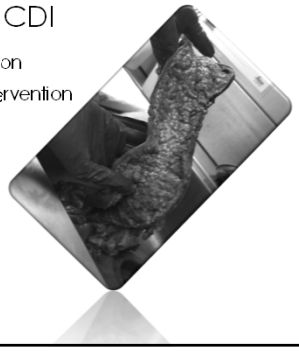
Common Clinical Manifestations

- Watery & mucusy diarrhea up to 10 - 15 times daily
- Lower abdominal pain & cramping
- Low grade fever (15%+)
- Leukocytosis (> 15,000 cells/μl = severe)
- Nausea
- Anorexia
- Malaise

http://year9diseases.wikispaces.com/

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

Magill S, *et al. NEJM* 2018;379:1732-44
Photo from http://www.mckeeassociates.com/blog/2013/07/healthcare-associated-infections-plague-u-s-hospitals/

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

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

- **Good specificity**
- **Rapid**
- **Relatively inexpensive**

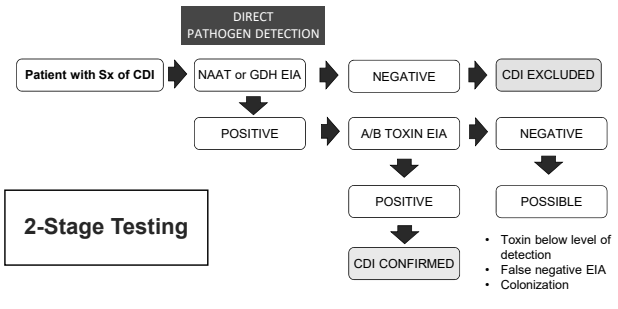
Disadvantages

- **Poor sensitivity**
- **False positives possible**

Usually used in a 2-step protocol with NAAT or GDH

27 – Helicobacter and Clostridium Difficile

Speaker: David M. Aronoff, MD



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
Kelly CR, *et al. Am J Gastroenterol* 2021;00:1–24
Poylin V, *et al. Dis Colon Rectum* 2021; 64: 650–668

Therapy of CDI

Table 1. Recommendations for the Treatment of *Clostridium difficile* Infection in Adults

Clinical Definition	Supportive Clinical Data	Recommended Treatment[a]
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	**VANCOMYCIN 125 mg po QID x 10 d** **FIDAXOMICIN 200 mg po BID x 10 d**
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.

No more metronidazole
(unless mild disease, in young person, +/- cost constraints)

McDonald LC, *et al. Clin Infect Dis.* 2018 Mar 19;66(7):987-994
Kelly CR, *et al. Am J Gastroenterol* 2021;00:1–24
Poylin V, *et al. Dis Colon Rectum* 2021; 64: 650–668

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
Kelly CR, *et al. Am J Gastroenterol* 2021;00:1–24
Poylin V, *et al. Dis Colon Rectum* 2021; 64: 650–668

27 – Helicobacter and Clostridium Difficile

Speaker: David M. Aronoff, MD

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
- ≥65 years old with >1 additional risk factor:
  - Experiencing 2nd episode of CDI within 6 mo
  - Immunocompromised, or severe CDI

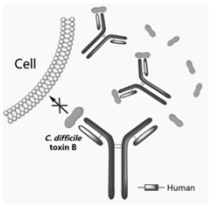


Figure from http://en.pharmacodia.com/web/drug/1_9806.html
McDonald LC, *et al. Clin Infect Dis.* 2018 Mar 19;66(7):987-994
Kelly CR, *et al. Am J Gastroenterol* 2021;00:1–24
Poylin V, *et al. Dis Colon Rectum* 2021; 64: 650–668

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

New Guidelines 2021

Clinical Practice Guideline by the Infectious Diseases Society of America (IDSA) and Society for Healthcare Epidemiology of America (SHEA): 2021 Focused Update Guidelines on Management of *Clostridioides difficile* Infection in Adults[1]

Stuart Johnson,[1] Valéry Lavergne,[2] Andrew M. Skinner,[1] Anne J. Gonzales-Luna,[3] Kevin W. Garey,[3] Ciaran P. Kelly,[4] Mark H. Wilcox[5]

Clinical Infectious Diseases 2021

28

HIV-Associated Opportunistic Infections I

Dr. Henry Masur

28 – HIV-Associated Opportunistic Infections I

Speaker: Henry Masur, MD

Management of AIDS-Related Opportunistic Infections I

Henry Masur, MD, FIDSA, MACP
Clinical Professor of Medicine
The George Washington University

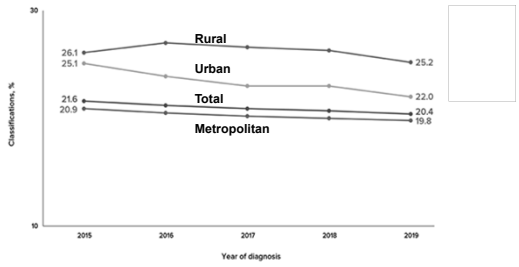
7/5/21

Disclosures of Financial Relationships with Relevant Commercial Interests

None

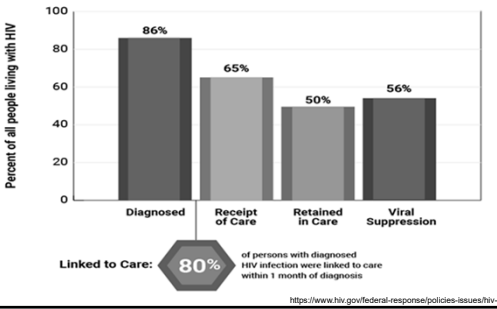
AIDS At Time of Diagnosis 2015-2019, United States

20-25% PWH Continue to Present Late in Disease



https://www.cdc.gov/hiv/library/reports/hiv-surveillance/vol-26-no-2/index.html

Prevalence-based HIV Care Continuum, 2019



https://www.hiv.gov/federal-response/policies-issues/hiv-aids-care-continuum

Causes of Death in Persons With HIV

	DAD Study (1999-2011) N=3909 deaths		London (2016) N=206 deaths	
AIDS-related	1023	(26%)	39	(19%)
Liver-related	515	(13%)	12	(6%)
CVD	429	(11%)	25	(12%)
Non-AIDS cancer	590	(15%)	40	(29%)
Renal	169	(4%)	4	(2%)
Bacterial infection	259	(7%)	14	(7%)

Smith et al Lancet 2014; 384: 241–48
Croxford, HIV Medicine, 2019

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

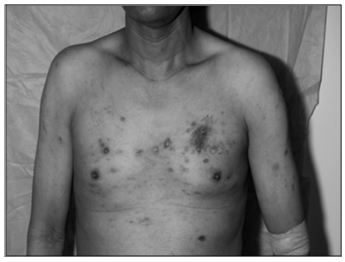
Question #2

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

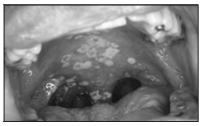


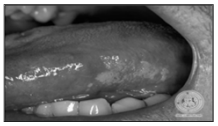
Question #2

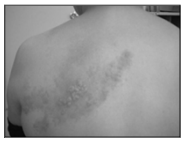
The most likely cause of these skin lesions, if they are not Kaposi sarcoma, is:

A. HHV-6
B. CMV
C. Cryptococcus neoformans
D. Bartonella
E. Rhodococcus

Clinical Indicators of Immunosuppression







Cardinal AIDS-Defining Illnesses

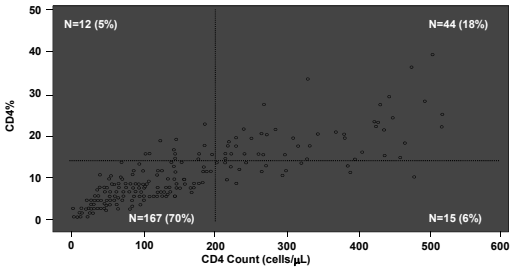
- **Pneumocystis pneumonia**
- **Toxoplasma encephalitis**
- **CMV Retinitis**
- **Disseminated Mycobacterium avium complex/Tuberculosis**
- **Chronic cryptosporidiosis/microsporidiosis**
- **Kaposi Sarcoma**

Susceptibility to Opportunistic Infections Patients with HIV

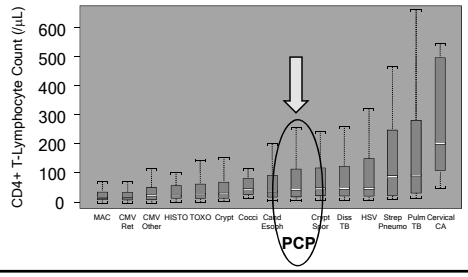
- **CD4 Count**
  - **Current Count is most important**
  - **Prior Nadir count is much less important**
- **Viral Load**
  - **Independent risk factor for OIs**

At What CD4 Counts Do Opportunistic Infections Occur?

Scatterplot of CD4 Number vs CD4 Percent Within 6 Months of HIV-Associated PCP



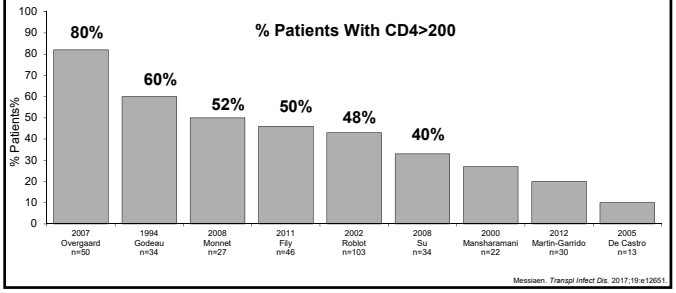
CD4+ Lymphocyte Counts Are Excellent Predictor of the Occurrence of Opportunistic Infections for HIV/AIDS



CD4 Counts in NON-HIV Patients

- **Low CD4 Count**
  - Susceptible to PCP
- **High CD4 Count**
  - Not necessarily protected from PCP

WARNING For Non-HIV Patients
CD4 Count Are Not A Sensitive Indicator of PCP



Messiaen. *Transpl Infect Dis*. 2017;19:e12651.

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**

When to Start ART Following Opportunistic Infection

- **Tuberculosis: 2-8 weeks after initiation RX**
  - **CD4<50-within 2 weeks of diagnosis**
  - **CD4>50-within 8 weeks of diagnosis**
- **Cryptococcal Meningitis: 4-6 weeks after initiation RX**
  - Sooner if mild and if CD4<50
  - Later if severe
- **"Untreatable" OIs, i.e., PML, Cryptosporidiosis**
  - **Start immediately**

Primary and Secondary OI Prophylaxis

These Are Guidelines But They Are Based on 1980-1990 ART

- **Primary Prophylaxis**
  - **PCP (CD4 <200, ~~oral candida, prior AIDS Defining~~)**
  - **Toxo (CD4 <100, old or new positive anti Toxo IgG)**
  - **Cocci (CD4<250, new 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**

Prophylaxis NOT Routinely Recommended in US

Primary	Secondary
• Candida	Candida*
• Cryptococcus	
• HSV	HSV*
• VZV	VZV*
• CMV	
• MAC	

***Secondary Prophylaxis would be reasonable if recurrences were frequent or severe**

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)

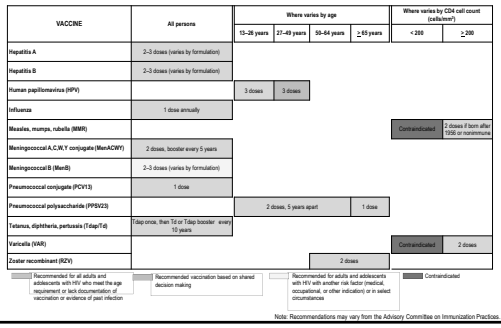
Secondary Prophylaxis/Chronic Maintenance	
– PCP	>200 x 3 months
– Toxo	>200 x 6 months
– Crypt	>200 x 6 months
– MAC	>100 x 6 months + 12 m Rx
– CMV	>100 x 3-6 months*

Primary Coccidiomycosis Prophylaxis 2021 OI Guideline

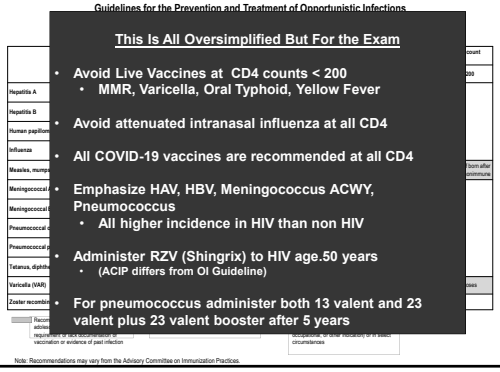
Testing
- **Once or twice yearly testing for seronegative patients**

Primary Prophylaxis
- **Do not administer in endemic area if serology negative**
- **Within the endemic area**
  - New positive IgM or IgG serology and
  - CD4 count is <250 cells (BIII) and
  - No Active Disease
- **Regimen**
  - Fluconazole 400mg qd until CD4>250 and fully suppressed viral load

Guidelines for the Prevention and Treatment of Opportunistic Infections in Adults and Adolescents with HIV



Guidelines for the Prevention and Treatment of Opportunistic Infections



Who Should be Vaccinated for HBV

- **Patients without chronic HBV or without immunity to HBV (i.e., anti-HBs <10 international units/mL)**
- **Patients with isolated anti-HBc and negative HBV DNA**
  - Vaccinate with one standard dose of HBV vaccine and check anti-HBs titers 1 to 2 months afterward
  - If the anti-HBs titer is ≥100 IU/mL, no further vaccination is needed
  - If the titer is <100 IU/mL, then complete series of HBV vaccine (single-dose or double-dose) followed by anti-HBs testing
  - If titers are not available, then give complete vaccine series
- **Note**
  - In patients with low CD4 cell counts, vaccination should not be deferred until CD4 count reaches >350 cells/μL, because some patients with CD4 counts <200 cells/μL do respond to vaccination

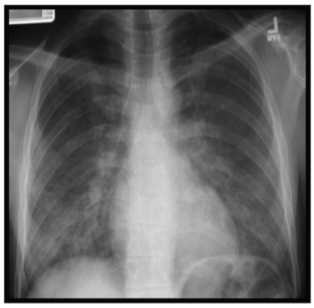
Who Are HBV Non Responders

- **Definition**
  - • Anti-HBs <10 international units/mL 1 month after vaccination series
- **Options: Not testable**
  - Switch to other recombinant vaccine, ie GSK to Merck or vice versa
  - Double dose of recombinant vaccine
  - Four dose regimen
  - Heplisav adjuvant vaccine

Post Exposure to HBV for PWH

- **Prior vaccine with documented response**
  - Nothing needed
- **Prior vaccine with NO response measured**
  - Administer single dose
- **No prior vaccine**
  - HBIG if within 7 days of percutaneous and 14 days of sexual exposure
    - Might not be necessary for patients on tenofovir or lamivudine
  - Full vaccine series simultaneously with HBIG
  - https://www.cdc.gov/mmwr/volumes/67/rr/rr6701a1.htm

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)**

Approach to Diagnosis and Therapy of Pneumonia in PWH

Parameter	Example
• Rapidity of Onset	> 3 days: PCP, TB, <3 days: Bacteria, viral
• Temperature	Afebrile: Neoplasm, PE, CHF
• Sputum	Scant: PCP, Virus, TB Purulent: Bacteria
• Physical Exam	Normal: PCP Consolidation: Bacteria
• Xray	Suggestive But Never Diagnostic

Pneumococcal Disease in Persons with HIV Infection

- **CD4<200**
  - Frequency enhanced
  - 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

Are There Strategies for Reducing Bacterial Pneumonias in Patients with HIV Infection?

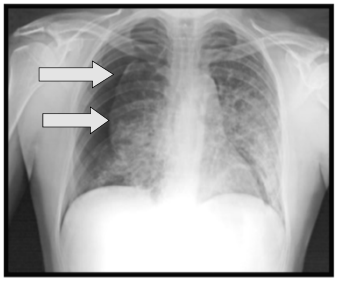
Strategies to Reduce Incidence of Pneumonia for Patients with HIV

- **Patient Focused Strategies**
  - Antiretroviral Therapy
  - Pneumococcal vaccine
  - Influenza vaccine
  - Tobacco cessation
- **Environmental Strategies**
  - Immunize contacts and community (esp children)
    - Pneumococcal and Hemophilus vaccines
    - Influenza vaccine

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



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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

Host Susceptibility to PCP

- **CD4 < 200 cells/μL --(90% of cases)**
- **CD4% <14**

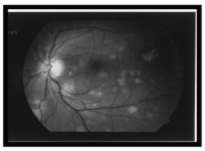
Clinical Features of PJP in Pre-AIDS Era, (n=168)

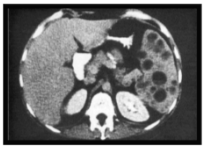
No Feature is Present 100% of Initial Presentations

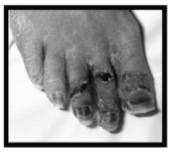
Symptom	% Patients
• Dyspnea	91%
• Fever	66%
• Cough	47%
Productive	7%
Non-productive	40%
• Signs	
– Cyanosis	39%
– Rales	33%

Walzer, Ann Intern Med 1974

Uncommon Manifestations of PCP

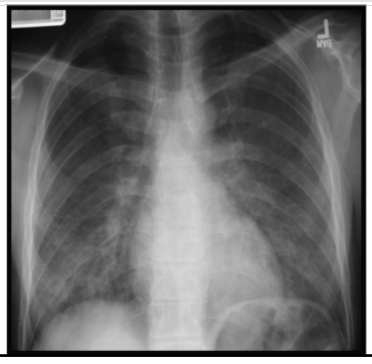




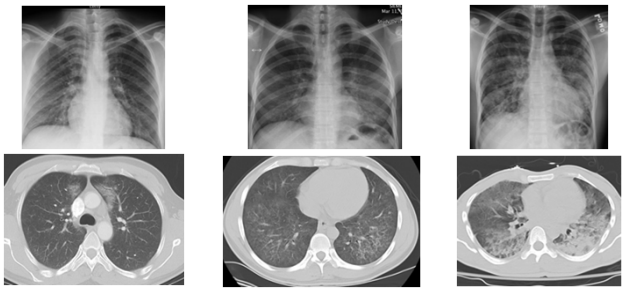


Imaging of PCP

- **Early-CT is never normal!**
  - Reticular (interstitial)
  - Nodular (interstitial)
  - Ground Glass (sparing periphery)
- **Later-Progression from Interstitial**
  - Consolidation (late finding)
  - Upper Lobe Cysts (thin walled)
  - Pneumothorax
    - (cyst and bronchopleural fistula)



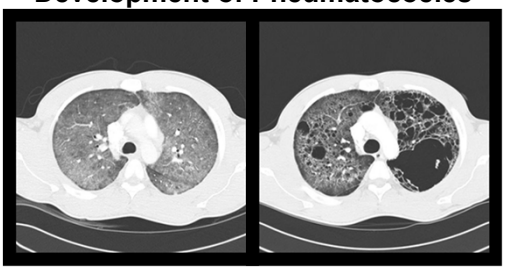
HIV Related PCP



Asymptomatic
Incidental Finding

⇩

Development of Pneumatocoeles



May 23 June 13

Radiologic Patterns Associated with Documented Pneumocystis Pneumonia

- **Most Frequent**
  - **Diffuse symmetric interstitial infiltrates progressing to diffuse alveolar process**
    - **Butterfly pattern radiating from hilum**

Radiologic Patterns Associated with Documented Pneumocystis Pneumonia

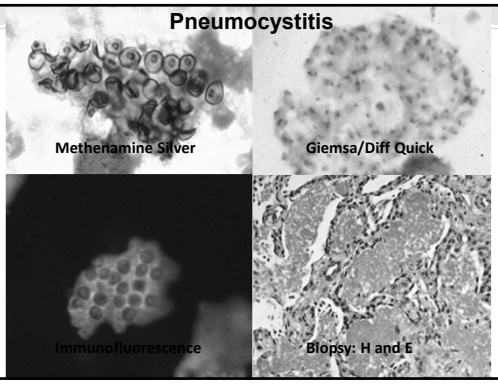
- **Other Patterns Recognized**
  - **(Other concomitant infectious or neoplastic disease processes?)**
  - **Lobar infiltrates**
  - **Upper lobe infiltrates**
  - **Pneumothorax**
  - **Solitary nodules**
  - **Cavitating lesions**
  - **Infiltrates with effusions**
  - **Asymmetric or unilateral processes**
  - **Normal chest x-ray**

Diagnosis of Pneumocystis Pneumonia

Specimen Acquisition	Organism Detection
Open lung biopsy	Methenamine silver
Transbronchial biopsy	Immunofluorescence
Bronchoalveolar lavage	Giemsa / Diff Quik
Induced sputum	PCR

1957 ↓ 2021

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

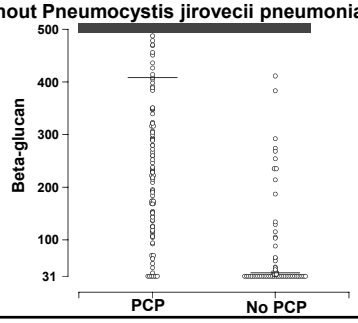
Negative BAL PCR rules out PCP

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-elevated in many lung diseases
- **Beta Glucan**
  - Sensitive but not specific
  - Maybe useful for
    - Heightened suspicion of PCP if BAL or sputum not feasible
    - Following response to Rx

Distribution of β-glucan Results at Baseline in Those With and Without Pneumocystis jirovecii pneumonia (PCP)



Sax PE. *Clin Infect Dis* 2011

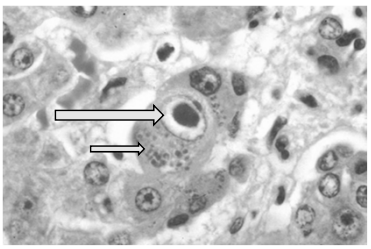
Question #4

- **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 #4

A patient with HIV infection newly diagnosed (CD4=10, VL= 200,000 copies/uL) was started on the following medications: efavirenz, emtricitabine, tenofovir, dapsone,fluconazole clarithromycin.

Ten days later the patient returns with headache, shortness of breath, a normal chest CT

Pulse oximetry shows an O2 saturation of 85%

A stat ABG is ordered which shows pH 7.40, pO2=96mmHg, pCO2 =39mm Hg, O2 Sat 96%.

The ABG lab reports methemoglbinemia = 25%

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 #4

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

Pulse oximetry shows an O2 saturation of 85%

A stat ABG is ordered which shows pH 7.40, pO2=96mmHg, pCO2 =39mm Hg, O2 Sat 80%.

The ABG lab reports Methemoglobin at 25%

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

Answer #4

Methemoglobemia = Methemoglobin>3%

Causes: Many: Dapsone and topical anesthetics notorious
Also chloroquine, primaquine, sulfa, nitrofurantoin

Therapy: Stop drug +/- methylene blue, ascorbic acid, transfusions

A patient wit… copies/uL) was started on th… ovir, dapsone, clarithromyc…

Ten days late… n, a normal chest CT

Pulse oxime…

A stat ABG … 39mm Hg, O2 Sat 96%.

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

Answer #4

Methemoglobemia = Methemoglobin>3%

Unlike normal hemoglobin, methemoglobin does not bind oxygen and as a result cannot deliver oxygen to the tissues

Symptoms: Headache to dyspnea to delirium and organ ischemia to death start occurring at methg >10%; >30% is life threatening

Detection
Too complicated for IDBR due to improving technology
Many systems measure methemoglobinemia directly
look for high P02, low O2 Sat and…report of methemoglobin

Causes: Many: Dapsone and topical anesthetics notorious
Also chloroquine, primaquine, sulfa, nitrofurantoin

Therapy: Stop drug +/- methylene blue, ascorbic acid, transfusions

A patient wit… copies/uL) was started on th… ovir, dapsone, clarithromyc…

Ten days late… n, a normal chest CT

Pulse oximet…

A stat ABG … 39mm Hg, O2 Sat 96%.

The most lik…

A. Pneumo…
B. Pulmon…
C. Flucona…
D. Dapson…
E. Clarithro…

Question #5

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.

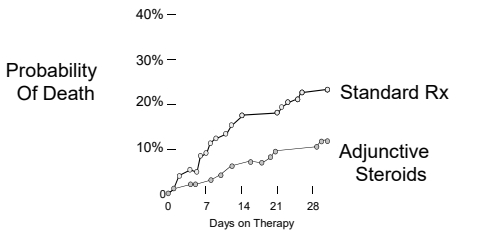
What Non cardiac toxicity of pentamidine would be most likely

A. Hyponatremia
B. Seizure
C. Hypoglycemia
D. Hypertensive crisis and stroke
E. Pulmonary embolus

Therapy for Pneumocystis Pneumonia

- **Specific Therapy**
  - **First Choice**
    - **Trimethoprim-Sulfamethoxazole**
  - **Alternatives**
    - **Parenteral Pentamidine**
    - **Atovaquone**
    - **Clindamycin-Primaquine**
- **Adjunctive Corticosteroid Therapy**
  - Moderate to Severe PCP
    - Room air p02 less than 70mmHg or A-a gradient >35mm Hg

Likelihood of Death in Patients with Moderate-Severe PCP Receiving Corticosteroids (n=251)



(Bozette, NEJM 5/90)

A Question That Could Be on Boards

- What drugs should only be given after screening for Glucose-6-Phosphate Dehydrogenase
- Drugs
  - Primaquine
  - Dapsone
  - And…..fluoroquinolones, Nitrofurantoin, Nalidixic acid, tafenoquine

A Question That Could Be on Boards

- What drugs should only be given after screening for Glucose-6-Phosphate Dehydrogenase
  - G6PD is common and nationality is increasingly difficult to define as a predictor
  - Males have more severe hemolysis since this is X linked
- Presentation
  - Hemolysis, jaundice, back and abdominal pain 2-4 days post drug exposure
  - Smear shows hemolytic pattern and "Heinz bodies"
  - Hemoglobinuria, high retic count
- Drugs
  - Primaquine
  - Dapsone
  - And…..fluoroquinolones, Nitrofurantoin, Nalidixic acid, tafenoquine
- Screening
  - Qualitative assay is used in urgent situations before drug administration
    - Testing after hemolysis can be misleading
  - Other management issues are too complicated for ID boards

How to Manage Patients Who Are Failing TMP-SMX

- Average Time to Clinical Improvement
  - 4-8 Days
- Radiologic Improvement
  - Lags clinical improvement

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
- Unrecognized
- Immune Reco

Patients Failing TMP-SMX Not Testable!

- Whether to Switch
- When to Switch
- What to Switch To
- How to Manage Steroid Dosing

Can *Pneumocystis Jiroveci* Become Resistant to TMP-SMX?

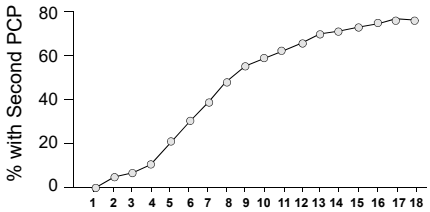
Toxicities of TMP-SMX and Pyrimethamine-Sulfadiazine

Drug	Toxicities
TMP-SMX	↓WBC, ↓plat, ↑LFT, ↑Creat, ↑Amylase, rash, fever, pruritus, "Sepsis" syndrome-distributive shock Hyperkalemia (TMP) Cross reactivity: dapsone (± 50%)
Pyrimethamine-Sulfadiazine	Similar to TMP-SMX Folinic acid necessary (not folate) to prevent cytopenias

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	Poor absorption if low fat diet Rash, N + V, diarrhea, LFT

Without ART or Chemoprophylaxis
Second Episodes of HIV Associated PCP Are Amazingly Common



Fischl/ACTG 002, 10/88

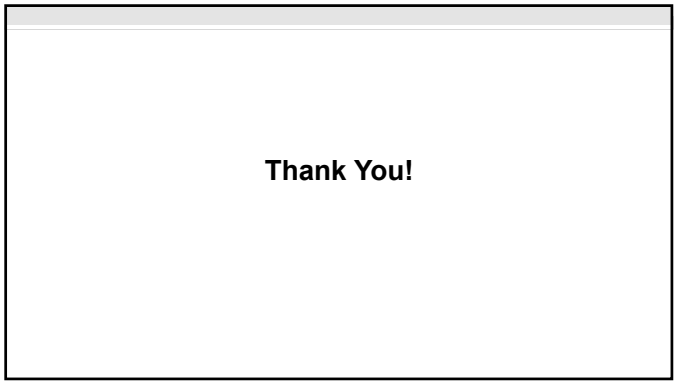
Indications for Primary and Secondary PCP Prophylaxis

Start	CD4 < 200 cells/uL (14%) ~~Oral candidiasis~~ ~~AIDS Defining Illness~~ ~~Prior PCP~~
Stop	CD4 >200 cells/µL x 3 M (Consider: CD4 100-200 and VL<50 x 3M)
Restart	CD4<200 cells/µL

Whether prophylaxis is needed at CD4 100-200 with suppressed viral load is too controversial for exam

Primary or Secondary Prophylaxis Agents for Pneumocystis Pneumonia

- **First Choice**
  - TMP-SMX
- **Other Options**
  - Aerosol pentamidine **OR**
  - Atovaquone **OR**
  - (Monthly IV pentamidine) **OR**
  - (Dapsone)



Monday, August 23, 2021

AM Moderator: Whitley
PM Moderator: Bennett

#	Start		End	Presentation	Speaker
29	9:30 AM	-	10:00 AM	**Daily Question Preview Day 3**	*Richard Whitley, MD (Moderator)*
30	10:00 AM	-	10:30 AM	**Sexually Transmitted Infections: Genital Ulcers Diseases (GUD)**	*Khalil Ghanem, MD*
31	10:30 AM	-	11:00 AM	**CMV, EBV, HHV6 and HHV8 in Immunocompetent and Immunocompromised Patients**	*Camille Kotton, MD*
	11:00 AM	-	11:30 AM	***BREAK with FACULTY CHAT***	
32	11:30 AM	-	12:30 PM	**Sexually Transmitted Infections: Other Diseases and Syndromes**	*Khalil Ghanem, MD*
33	12:30 PM	-	1:00 PM	**HSV and VZV in Immuno-competent and Immunocompromised Hosts**	*Richard Whitley, MD*
34	1:00 PM	-	1:45 PM	**Board Review Day 3**	*Drs. Whitley(Moderator), Kotton, Dhanireddy, Ghanem, Rose, Thomas, and Tunkel*
	1:45 PM	-	2:15 PM	***BREAK with FACULTY CHAT***	
35	2:15 PM	-	3:00 PM	**Kitchen Sink: Syndromes Not Covered Elsewhere**	*Stacey Rose MD*
36	3:00 PM	-	4:00 PM	**Immunizations: Domestic, Travel, and Occupational**	*Shireesha Dhanireddy, MD*
37	4:00 PM	-	4:45 PM	**Acute Hepatitis**	*David Thomas, MD*
	4:45 PM	-	5:15 PM	***BREAK with FACULTY CHAT***	
38	5:15 PM	-	5:45 PM	**Viral and Bacterial Meningitis**	*Allan Tunkel, MD*
39	5:45 PM	-	6:45 PM	**Chronic Hepatitis**	*David Thomas, MD*
40	6:45 PM	-	7:15 PM	**Brain Abscess, Cavernous Sinus Thrombosis, and Subdural and Epidural Empyema**	*Allan Tunkel, MD*
	7:15 PM	-	7:45 PM	***END OF THE DAY FACULTY CHAT***	

29

Daily Question Preview 3

Dr. Richard Whitley (Moderator)

29 – Daily Question Preview: Day 3

Moderator: Richard Whitley, MD

Daily Question Preview: Day 3

Moderator: Richard Whitley, MD

PREVIEW QUESTION

3.1 **A pregnant woman living with HIV(CD4 260 cells/mm3; 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.

PREVIEW QUESTION

3.1 **Which of the following antibiotics is most appropriate?**

A) Azithromycin

B) Benzathine penicillin G

C) Ceftriaxone

D) Doxycycline

PREVIEW QUESTION

3.2 **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.

PREVIEW QUESTION

3.2 **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

3.3 **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.

29 – Daily Question Preview: Day 3

Moderator: Richard Whitley, MD

PREVIEW QUESTION

3.3 **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

PREVIEW QUESTION

3.4 **A 30-year-old man with HIV 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.

PREVIEW QUESTION

3.4 **Which of the following empiric antibiotic regimens is most appropriate?**

A) Ceftriaxone 500mg IM + Azithromycin 1g PO X1

B) Ceftriaxone 500mg IM + Doxycycline 100mg PO BID X 7d

C) Ceftriaxone 500mg IM + Azithromycin 1g PO weekly X 3wks

D) Ceftriaxone 500mg IM + Doxycycline 100mg PO BID X 21d

E) Ceftriaxone 500mg IM + Doxycycline 100mg PO BID X 7d + oral valacyclovir

PREVIEW QUESTION

3.5 **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

PREVIEW QUESTION

3.6 **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.**

PREVIEW QUESTION

3.6 **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

29 – Daily Question Preview: Day 3

Moderator: Richard Whitley, MD

PREVIEW QUESTION

3.7 What complication would you be most concerned about?

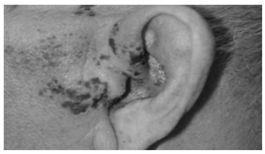
A) Facial paralysis

B) Keratitis

C) Encephalitis

D)Optic neuritis

E) Oculomotor palsies



PREVIEW QUESTION

3.8 A 34-year-old male with a history of injection drug use presents to the emergency room with a 2-day history of progressive muscle weakness and blurry vision.

He also notices some difficulty swallowing.

On examination, vital signs are normal, but the patient is noted to have ptosis and sluggish pupillary responses as well as slurred speech.

PREVIEW QUESTION

3.8 Which of the following treatment(s) are recommended?

A) Plasmapheresis

B) Naloxone

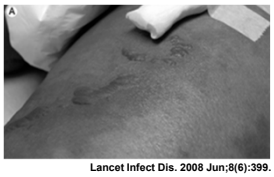
C) Tetanus antitoxin

D) Botulinum antitoxin

PREVIEW QUESTION

3.9 A 44 year-old male with a history of cirrhosis due to Hepatitis B and alcoholism presents with fever, lethargy and leg swelling. On exam, he is febrile, hypotensive and tachycardic.

Skin exam is as pictured.



Lancet Infect Dis. 2008 Jun;8(6):399.

PREVIEW QUESTION

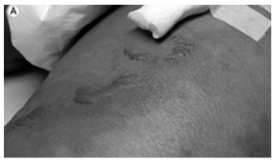
3.9 The patient's clinical syndrome was most likely caused by which of the following exposures?

A) Rat bite

B) Tick bite

C) Consumption of raw oysters

D) Consumption of raw egg



Lancet Infect Dis. 2008 Jun;8(6):399.

PREVIEW QUESTION

3.10 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.

29 – Daily Question Preview: Day 3

Moderator: Richard Whitley, MD

PREVIEW QUESTION

3.10 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

3.11 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.

PREVIEW QUESTION

3.11 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

PREVIEW QUESTION

3.12 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

PREVIEW QUESTION

3.13 42-year-old female has malaise and RUQ pain; she just returned from 2 months working 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; Hb 13.4 g/dl; TB 3.2 mg/dl; WBC 3.2k nl differential.

PREVIEW QUESTION

3.13 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

29 – Daily Question Preview: Day 3

Moderator: Richard Whitley, MD

PREVIEW QUESTION

3.14 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)

PREVIEW QUESTION

3.14 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

3.14 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

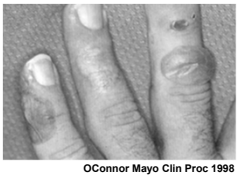
D) Herpes simplex virus type 2

E) Human herpesvirus 6

PREVIEW QUESTION

3.15

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

PREVIEW QUESTION

3.15 The most likely dx is:

A) Cirrhosis due to HCV and alcohol

B) Necrolytic acral erythema

C) Porphyria cutanea tarda

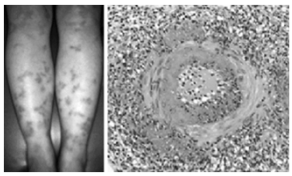
D) Essential mixed cryoglobulinemia

E) Yersinia infection

PREVIEW QUESTION

3.16

A 46-year old-woman HBsAg pos, anti-HCV neg



Chen Rheum 2014

29 – Daily Question Preview: Day 3

Moderator: Richard Whitley, MD

PREVIEW QUESTION

3.16 The most likely dx is:

A) Necrolytic acral erythema

B) Porphyria cutanea tarda

C) Essential mixed cryoglobulinemia

D) Polyarteritis nodosa

E) Secondary syphilis vasculitis

PREVIEW QUESTION

3.17 A 54-year-old 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; creatinine 1.2 mg/dl; HBsAg pos; anti-HBc pos. HIV neg

PREVIEW QUESTION

3.17 Which of the following is the next appropriate step:

A) Treat with oral regimen for 8-12 weeks

B) Check HCV 1a resistance test

C) Elastography

D) Confirm HCV antibody test

PREVIEW QUESTION

3.18 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.

PREVIEW QUESTION

3.18 What do you recommend?

A) Hold rituximab

B) Hold prednisone

C) Entecavir 0.5 mg

D) HCV PCR

E) HBV DNA

30

Sexually Transmitted Infections: Genital Ulcers Diseases (GUD)

Dr. Khalil G. Ghanem

30 – Sexually Transmitted Infections: Genital Ulcers Diseases (GUD)

Speaker: Khalil Ghanem, MD

Sexually Transmitted Infections: Genital Ulcer Diseases

Khalil G. Ghanem, MD, PhD
Professor of Medicine
Division of Infectious Diseases
Johns Hopkins University School of Medicine

Disclosures of Financial Relationships with Relevant Commercial Interests

- None

INCLUDED PHOTOS

Please note: all photos are freely available from the following website unless otherwise noted:
http://www.cdc.gov/std/training/clinicalslides/slides-dl.htm

GENITAL ULCER DISEASES (GUD)

- Syphilis (*Treponema pallidum*)
- HSV-2
- HSV-1
- Chancroid *(Haemophilus ducreyi)*
- Lymphogranuloma venereum (LGV) *(Chlamydia trachomatis)*
- Granuloma inguinale (Donovanosis) *(Klebsiella granulomatis)*

PAIN AND GUD

Which ulcers are PAINFUL?

- HSV
- Chancroid

Which ulcers are PAINLESS?

- Syphilis*
- LGV (but lymphadenopathy is PAINFUL)
- Granuloma inguinale

*** >30% of patients have multiple painful lesions**

"KEY WORDS" IN GUD

- SYPHILIS: Single, **painless** ulcer or chancre at the inoculation site with heaped-up borders & clean base; painless bilateral LAD **(>30% of patients have multiple painful lesions)**
- HSV: multiple, **painful**, superficial, vesicular or ulcerative lesions with erythematous base

"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

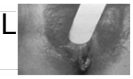
Which of the following diagnostic tests is **inappropriate** to obtain?

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 mainly in secondary syphilis)
- Treponemal tests are almost always reactive in late syphilis (once positive always positive) irrespective

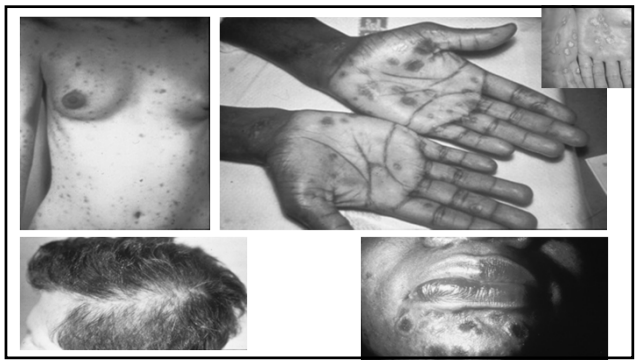
EARLY SYPHILIS: CLINICAL MANIFESTATIONS



- 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

30 – 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

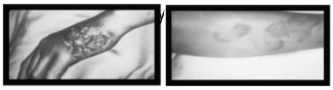
Cardiovascular

- 15-30 years after latency
- Men 3X> women
- Aortic aneurysm; aortic insufficiency; coronary artery stenosis; myocarditis

Up to 30% of patients with cardiovascular and late benign syphilis will have concomitant neurological involvement- perform CSF exam!

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, tinnitus or vertigo)
  - Congenital (early and late)
  - Acquired (secondary and late stages)
  - **CSF examination is normal in >90% of cases of otic syphilis**

***No need for a CSF examination in patients who only have ocular or otic symptoms/signs

SYPHILIS SEROLOGICAL TESTING

Nontreponemal tests

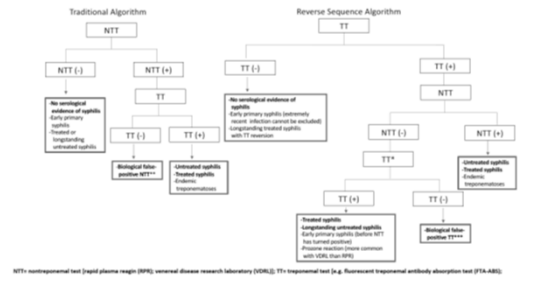
- RPR (serum) or VDRL (serum or CSF)
- False+: endemic treponematoses, old age, pregnancy, autoimmune disease (APS), viral infections
- Reactive result must be confirmed with treponemal test
- False negative: PROZONE effect
- Four-fold (i.e. 2-dilution) decline after treatment = CURE (irrespective of the end-titer)
- **Titers will decline with or without treatment**

Treponemal tests

- MHA-TP, TPPA, FTA-Abs, EIAs, CIA
- Detect IgG +/- IgM antibodies against treponemal antigens
- **Once reactive, always reactive even after appropriate therapy**
- False + may occur with endemic treponemal infections (e.g. yaws, pinta, bejel), with Lyme disease, or rarely in autoimmune conditions

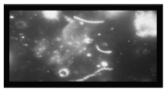
30 – Sexually Transmitted Infections: Genital Ulcers Diseases (GUD)

Speaker: Khalil Ghanem, MD



SYPHILIS: DIAGNOSTICS

- Darkfield microscopy or PCR 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*



NEUROSYPHILIS: DIAGNOSTICS

- 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/Otic 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; **<u>may induce early labor</u>**

QUESTION #2

A pregnant woman living with HIV(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.

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
  - PWH more susceptible to early neurosyphilis
- Testing and therapy similar to HIV-uninfected
- Serological failure is more likely among PWH
- Serological response may be slower among PWH
- Follow-up is more frequent (every 3 months)

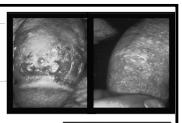
SYPHILIS & PREGNANCY

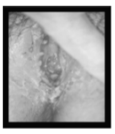
- Screen all women at 1st prenatal visit
- Screen all high risk women and those women living in high-prevalence areas twice in the 3rd trimester: at 28 weeks and again at the time of delivery
- Screen all women who deliver a stillborn infant after 20 weeks' gestation
- **Pregnant penicillin-allergic 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 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
- HSV suppressive therapy in PWH with a history of HSV and who are starting ART- but only if their CD4 <200 cells/mm^3

HSV: DIAGNOSTICS IN PATIENTS WITH GENITAL ULCERS

- Tzanck smear (40% sensitive)
- Culture (sensitivity 30-80%)
  - Mainly used for antiviral susceptibility testing
- Antigen detection (~70% sensitive)
- PCR (FDA cleared, >90% sensitive)
  - **Preferred diagnostic test when a lesion is present**

30 – Sexually Transmitted Infections: Genital Ulcers Diseases (GUD)

Speaker: Khalil Ghanem, MD

HSV: DIAGNOSTICS IN ASYMPTOMATIC PATIENTS

- Use Glycoprotein G-based type-specific EIA assays
  - 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 EIA index value cutoff; for an EIA cutoff <3, a second confirmatory test that uses a different HSV antigen must be performed (HSV Biokit or HSV Western Blot)**
**** Assay has low sensitivity**

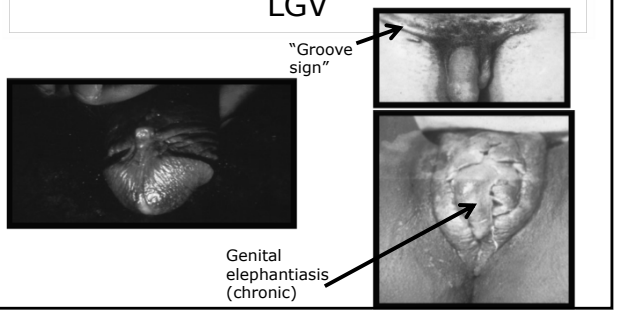
HSV: PREGNANCY

- 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

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



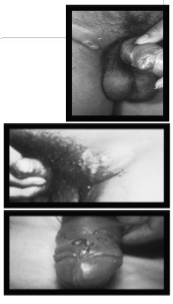
LGV DIAGNOSIS & THERAPY

- **Routine NAATs** do not distinguish between serotypes D-K and L1-L3 (LGV). **Multiplex PCR** can be performed for specific serotypes but is NOT commercially available. Serology is NOT standardized and is NOT recommended
- Therapy: **doxycycline 100mg PO BID X 3* weeks (preferred)** or azithromycin 1g PO q week X 3 weeks (alternate)

*Small observational study suggests that in mild LGV proctitis, 1 week of doxycycline or 2g of azithromycin is sufficient

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



30 – Sexually Transmitted Infections: Genital Ulcers Diseases (GUD)

Speaker: Khalil Ghanem, MD

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)

GUD	Pain	Characteristics	Diagnosis	Treatment
HSV 1 & 2	Painful	Multiple, superficial, vesicular/ulcerative, erythematous base	-NAATs -Culture (sensitivity ~70%) -Serology	-Acyclovir etc. -Foscarnet (resistant HSV) -Cidofovir parenteral or topical (resistant HSV)
Syphilis (T. pallidum)	Painless	Single, well circumscribed, heaped-up borders, clean base	- Serology - PCR	-Penicillin (preferred) -Doxycycline (alternate for early and late latent)
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 (preferred) -Azithromycin (alternate)
Granuloma Inguinale (Klebsiella granulomatis)	Painless	Progressive "serpiginous" without LAD; beefy red with white border & highly vascular	- Biopsy	-Doxycycline -Azithromycin -Bactrim

31

CMV, EBV, HHV 6, and HHV 8 in Immunocompetent and Immunosuppressed Patients

Dr. Camille Kotton

31 – CMV, EBV, HHV6 and HHV8 in Immunocompetent and Immunocompromised Patients

Speaker: Camille Kotton, MD

CMV, EBV, HHV6 and HHV8 in Immunocompetent and Immunocompromised Patients

Camille Nelson Kotton, MD, FIDSA, FAST
Clinical Director, Transplant and Immunocompromised Host Infectious Diseases
Massachusetts General Hospital
Harvard Medical School

Disclosures of Financial Relationships with Relevant Commercial Interests

Company	Role	Details
Biotest	Consultant	Scientific advisory board, medical education (CMV immunoglobulins)
Hookipa	Consultant	CMV Vaccine trial
Merck	Consultant	Clinical trial adjudication, scientific advisory board (CMV)
Oxford Immunotec	Consultant	Scientific advisory board (CMV), medical education (TB)
Takeda	Consultant	Clinical trial adjudication, scientific advisory board (CMV)

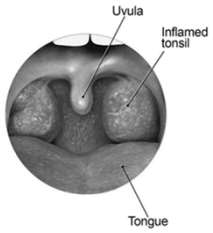
Human Herpesviruses Family

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)**

3

"Mononucleosis Syndrome"

- Clinical Features:
  - Fever
  - Malaise
  - Myalgias, arthralgias
  - Pharyngitis
  - Lymphadenopathy
  - Hepatomegaly / splenomegaly
- Laboratory Findings:
  - Lymphocytosis (>50%; >4500/mm3)
  - Atypical lymphocytes (>10%)
  - Abnormal LFTs



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Differential Features of Most Common Causes of Mononucleosis Syndrome

	EBV	CMV	Toxo	HIV
Fever	++++	++++	++	++++
Myalgias / Arthralgias	++	+++	+	+++
Lymphadenopathy	++++	+	++++	+++
Sore throat	++++	++	+	+++
Exudative pharyngitis	++++	+	0	0
Headache	+++	++	+	++
Rash	+	+	+	+++
Splenomegaly	+++	++	+	++
Hepatomegaly	+	++	+	0
Atypical lymphocytes	++++	+++	+	++
Elevated LFTs	++++	+++	0	+

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Differential Diagnosis of Pharyngitis

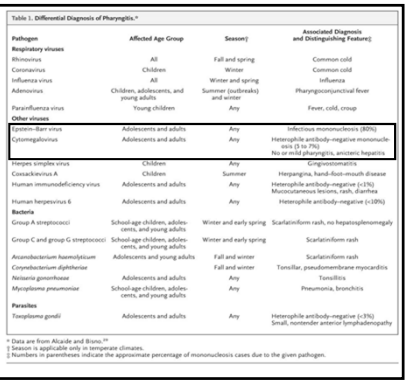

Table 1. Differential Diagnosis of Pharyngitis.*

Pathogen	Affected Age Group	Season†	Associated Diagnosis and Distinguishing Feature‡
Respiratory viruses			
Rhinovirus	All	Fall and spring	Common cold
Coronavirus	Children	Winter	Common cold
Influenza virus	All	Winter and spring	Influenza
Adenovirus	Children, adolescents, and young adults	Summer (outbreaks) and winter	Pharyngoconjunctival fever
Parainfluenza virus	Young children	Any	Fever, cold, croup
Other viruses			
Epstein–Barr virus	Adolescents and adults	Any	Infectious mononucleosis (80%)
Cytomegalovirus	Adolescents and adults	Any	Heterophile antibody–negative mononucleosis (3 to 7%) No or mild pharyngitis, anicteric hepatitis
Herpes simplex virus	Children	Any	Gingivostomatitis
Coxsackievirus A	Children	Summer	Herpangina, hand–foot–mouth disease
Human immunodeficiency virus	Adolescents and adults	Any	Heterophile antibody–negative (<1%) Mucocutaneous lesions, rash, diarrhea
Human herpesvirus 6	Adolescents and adults	Any	Heterophile antibody–negative (<10%)
Bacteria			
Group A streptococci	School-age children, adolescents, and young adults	Winter and early spring	Scarlatiniform rash, no hepatosplenomegaly
Group C and group G streptococci	School-age children, adolescents, and young adults	Winter and early spring	Scarlatiniform rash
Arcanobacterium haemolyticum	Adolescents and young adults	Fall and winter	Scarlatiniform rash
Corynebacterium diphtheriae		Fall and winter	Tonsillar, pseudomembrane myocarditis
Neisseria gonorrhoeae	Adolescents and adults	Any	Tonsillitis
Mycoplasma pneumoniae	School-age children, adolescents, and young adults	Any	Pneumonia, bronchitis
Parasites			
Toxoplasma gondii	Adolescents and adults	Any	Heterophile antibody–negative (<3%) Small, nontender anterior lymphadenopathy

* Data are from Alcaide and Bisno.[3]
† Season is applicable only in temperate climates.
‡ Numbers in parentheses indicate the approximate percentage of mononucleosis cases due to the given pathogen.

Luzuriaga K, Sullivan JL. N Engl J Med 2010;362:1993-2000.

31 – CMV, EBV, HHV6 and HHV8 in Immunocompetent and Immunocompromised Patients

Speaker: Camille Kotton, MD

Non-ID causes of mononucleosis syndrome with atypical lymphocytosis

- Drug hypersensitivity syndrome
- Can be induced by several drugs:
  - anticonvulsants such as **phenytoin, carbamazepine**
  - antibiotics such as **isoniazid, minocycline**

Epstein Barr Virus

Epstein Barr Virus: Epidemiology

- Majority of infections are asymptomatic in early childhood
- Adolescent seroprevalence:
  - Resource limited regions >95%
  - Higher resource regions ~40-50%
- Primary infection in adolescents or adults results in ~50% symptomatic dz (infectious mononucleosis)
- 500 cases/100,000 population/year in USA
  - incidence rate for those 15--19yo estimated 200 – 800 cases per 100,000
- Occasionally transmitted by transfusion or organ/stem cell transplant

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EBV Infection: Pathogenesis

- Gamma herpesvirus; HHV-4
- Infectious virus intermittently shed from oropharyngeal epithelial cells
  - Up to 6 months or longer after disease, then intermittently
- Transmission by saliva ("kissing disease"), sexual transmission possible
- Long incubation period – 4 to 8 weeks
- Latently infected memory B lymphocytes serve as lifelong viral reservoirs
  - EBV is capable of transforming B lymphocytes, resulting in malignancy
- EBV reactivation mostly asymptomatic

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Infectious Mononucleosis

- Etiology - primary Epstein-Barr virus infection
- Transmission - saliva (due to prolonged shedding for months)
- Clinical – viral prodrome with **fever**, malaise, headache
  - **Pharyngitis** with tonsillar exudate
  - Symmetrical cervical **adenopathy**, posterior > anterior
  - Palatal petechiae, periorbital edema, and rash (maculopapular, urticarial, or petechial)
  - Splenomegaly in 15 to 65% of cases
  - Acute symptoms persist 1-2 weeks, fatigue can last for months
- Lab - lymphocytosis with atypical lymphocytes
- Diagnosis - serologic. Non-specific heterophile Ab ("monospot"); specific Ab (VCA, EBNA)
- Therapy - supportive, no antiviral therapy, steroids for upper-airway obstruction, hemolytic anemia, and thrombocytopenia (rash with ampicillin)
- Prevention - no vaccine

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Complications of Primary EBV Infection/Infectious Mononucleosis

- Splenic rupture in 0.5-1%, male > female, mostly w/in 3 weeks (up to 7)

****avoid contact sports for 4 weeks minimum****

- Prolonged fatigue/malaise (>6 mo. in 10%)
- Airway obstruction from massive adenopathy
- Hepatitis, rarely with fulminant hepatic failure
- Pneumonitis
- Peritonsillar abscess

Heme syndromes:

- Neutropenia
- TTP-HUS
- DIC
- Acquired hypogammaglobulinemia
- X-linked lymphoproliferative disease (EBV as trigger)
- Hemophagocytic lymphohistiocytosis (HLH) (est 50% of all HLH cases from EBV)

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31 – CMV, EBV, HHV6 and HHV8 in Immunocompetent and Immunocompromised Patients

Speaker: Camille Kotton, MD

Neurologic Complications of Primary EBV Infection/Infectious Mononucleosis (1 to 5% of cases)

- Viral meningitis
- Encephalitis
- Optic neuritis
- Transverse myelitis
- Facial nerve palsies
- Guillain–Barre syndrome
- Acute cerebral ataxia
- Hemiplegia
- Sleep disorders
- Psychoses

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Laboratory Findings in EBV Infectious Mononucleosis

- CBC - elevated lymphocytes, often >50%
- Atypical lymphocytes = range 10-90% (manual differential only)
  - >=10% atypical lymphocytes in a pharyngitis patient --> sensitivity of 75% and specificity of 92% for the diagnosis of infectious mononucleosis (Ebell MH Am Fam Physician 2004)
- Total white blood cell count averages 12,000 to 18,000/microL
- Elevated liver function tests
  - AST, ALT (90%), alkaline phosphatase (60%)
  - Elevated bilirubin less common (45%, but jaundice in <10%)
- EBV viral load/PCR - *not necessary for routine mononucleosis*, may be useful in transplant or other immunocompromised patients

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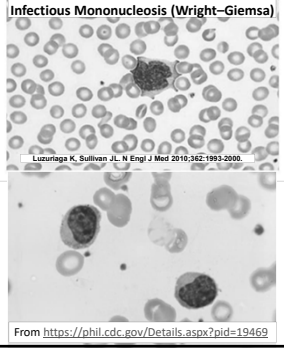
An Atypical Lymphocyte in a Patient with Infectious Mononucleosis (Wright–Giemsa)



From https://phil.cdc.gov/Details.aspx?pid=19469

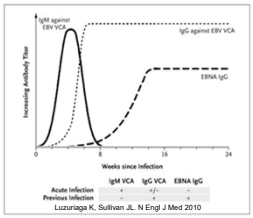
- Large pleomorphic, non-malignant peripheral blood lymphocytes
- **CD8+ cytotoxic T cells** activated by exposure to viruses (e.g., CMV, EBV, HIV, etc.) or other antigens (e.g., toxo)

General features:

- Low nuclear / cytoplasmic ratio
- Indented or lobulated nuclei with nucleoli
- Cytoplasm often basophilic; can be "sky blue"
- Cytoplasmic vacuoles and granules

EBV Serology

- **Viral capsid antigen (VCA)**
  - Anti-VCA IgM appears early in EBV infection then disappears in 4-6 weeks
  - Anti-VCA IgG appears in the acute phase of EBV infection, peaks at two to four weeks after onset, declines slightly then **persists for the rest of a person's life**.
- **EBV nuclear antigen (EBNA)**
  Antibody to EBNA, determined by the standard immunofluorescent test, is not seen in the acute phase of EBV infection but slowly **appears two to four months after onset of symptoms and persists for the rest of a person's life.**
- **Early antigen (EA)**
  Anti-EA IgG appears in the acute phase of illness and generally falls to undetectable levels after three to six months. In many people, detection of antibody to EA is a sign of active infection. However, 20% of healthy people may have antibodies against EA for years.
- **Monospot test**
  The Monospot test is not recommended for general use, poorly sensitive/specific. The antibodies detected by Monospot can be caused by conditions other than infectious mononucleosis.
- The antibody response occurs rapidly during primary EBV infection



Luzuriaga K, Sullivan JL. N Engl J Med 2010

https://www.cdc.gov/epstein-barr/laboratory-testing.html

EBV after Solid Organ Transplantation

- High risk for EBV syndromes and proceeding to post-transplant lymphoproliferative disorder (PTLD), especially if donor seropositive/recipient seronegative (D+R-)
  - Best to monitor periodically for the first two years after transplant
- If EBV viremia, reduce immune suppression whenever possible
- No evidence that any current antiviral therapy is helpful
  - Valganciclovir only works in lytic phase (small %)
- WHO pathology classification of a tissue biopsy remains the gold standard for PTLD diagnosis
- PTLD treatment may include (in order): reduction of immunosuppression, rituximab, and cytotoxic chemotherapy

Allen and Preiksaitis, Post-transplant lymphoproliferative disorders, Epstein-Barr virus infection, and disease in solid organ transplantation: Guidelines from the American Society of Transplantation Infectious Diseases Community of Practice, Clin Trans 2019

Question

An 14-year-old female presents to your office with sore throat, fever, and malaise, with lymphadenopathy and pharyngitis on physical exam.

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?

	VCA IgM	VCA IgG	EBNA IgG	EA IgG
A	+	+	+	+
B	+	+	-	+
C	-	+	+	+
D	-	-	+	-

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31 – CMV, EBV, HHV6 and HHV8 in Immunocompetent and Immunocompromised Patients

Speaker: Camille Kotton, MD

CMV

Epidemiology of CMV Infection

- Age-specific peaks in incidence:
  - Children in USA: 10-15% infected before age 5
  - Young adults at onset of sexual activity
  - ~50% adults are CMV IgG+ (NHANES, *Bate et al, Clin Infect Dis 2010*)
- Seroprevalence of CMV correlates inversely with socioeconomic development
  - In the developing world, CMV seroprevalence approaches 100%.
- Transplant:
  - Organ: highest risk is donor seropositive, recipient seronegative (D+R-)
  - Stem cell: highest risk is D-R+ (opposite)
  - Superinfection can occur (organ transplant D+R+ higher risk than D-R+)

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Estimation of the worldwide seroprevalence of cytomegalovirus: A systematic review and meta-analysis

Mohamed Zuhair[1] | G. Suzanne A. Smit[2,3,4] | Gabriel Wallis[1] | Faiz Jabbar[1] | Colette Smith[5] | Brecht Devleesschauwer[6] | Paul Griffiths[1,5]

Estimated global cytomegalovirus seroprevalences in women of reproductive age

TABLE 1 Estimated cytomegalovirus mean seroprevalence % and corresponding 95% uncertainty interval in the different World Health Organisation regions and globally per population group

Regions	General Population	Women of Reproductive Age	Blood and Organ Donors
European region	66 (56-74)	70 (63-76)	69 (65-77)
Region of the Americas	75 (64-84)	79 (69-87)	78 (67-87)
South-east Asian region	86 (77-93)	89 (82-94)	88 (81-94)
African region	88 (80-93)	90 (85-94)	90 (84-94)
Western Pacific region	88 (81-93)	91 (86-94)	90 (85-94)
Eastern Mediterranean region	90 (85-94)	92 (88-95)	92 (87-95)
Global	83 (78-88)	86 (83-89)	86 (82-89)

Cytomegalovirus: the troll of transplantation

Balfour HH, Jr. Arch Intern Med. 1979;139(3):279-80

Remember the tale of "The Three Billy Goats Gruff?" The transplant patient, like the billy goats, initially is on rocky ground and wants to cross the bridge over the rushing river to greener pastures on the other side. Cytomegalovirus is the troll under the bridge, hidden in shadows and often undetectable even by the most sophisticated diagnostic techniques. As we immunosuppress patients to help them cross the bridge, the troll comes out and threatens to devour them. Like the two smaller billy goats in the story, we clinicians are passing the buck to stall for time, hopeful that in the near future our patients, armed with either a vaccine or an effective antiviral agent, will be strong enough to throw the voracious CMV troll off the bridge and back into obscurity.

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Transmission & Pathogenesis of CMV

- Beta herpesvirus
- Infection transmitted via:
  - body fluids (urine, semen, cervical secretions, saliva, breast milk)
  - transplanted tissue (blood, organs, stem cell transplant)
    - Reduced with routine use of blood filtered/WBC-depleted
- Primary infection usually asymptomatic/subclinical
  - Mononucleosis syndrome in <10%
- Viral replication in WBCs, epithelial cells (kidney, salivary glands, etc.)
- Following primary infection, prolonged viremia (weeks) and viruria (months) persist despite humoral and cellular immune responses.
  - Ongoing shed is important factor in transmission
- No vaccine available; several under development

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CMV Mononucleosis Syndrome

- 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 (80%).
  - Rash in up to 30% (variety of appearances)
  - May be clinically indistinguishable from mono syndrome caused by other pathogens
  - Complications: colitis, hepatitis, encephalitis, GBS, anterior uveitis
- Symptoms may persist > 8 weeks
- Diagnosis: IgM/IgG seroconversion (CMV blood PCR - can be confusing)
- Antiviral therapy not indicated (except for severe complications or in immunocompromised)

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31 – CMV, EBV, HHV6 and HHV8 in Immunocompetent and Immunocompromised Patients

Speaker: Camille Kotton, MD

CMV: Congenital infection

- Leading cause of nonhereditary sensorineural hearing loss
  - Can cause other long-term neurodevelopmental issues, including cerebral palsy, intellectual disability, seizures, vision impairment
- Congenital CMV 0.6% prevalence in developed countries
  - 40,000 children/year in USA
- Primary maternal CMV infection - 30-40% risk
  - Having children in daycare is major risk
  - Infants more likely to have symptoms at birth & long-term sequelae
- Reactivation maternal CMV infection - 0.9-1.5% risk
- Hearing loss similar in both primary and reactivation cohorts
- Newborn screening under evaluation, sensitivity of dried blood spots for detecting congenital CMV infection is 73-78%

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CMV INFECTION AFTER ORGAN TRANSPLANT: A SPECTRUM OF DISEASE

Direct Effects

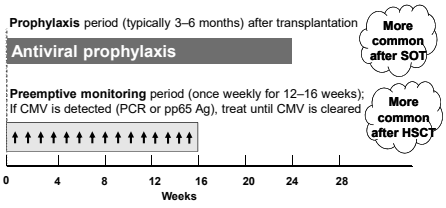
Asymptomatic Viremia

CMV Viral Syndrome
- Flu-like syndrome: fever, malaise, myalgia
- Leukopenia, thrombocytopenia

Tissue-Invasive Disease
- GI diseases: Colitis, Hepatitis
- Pneumonitis
- Myocarditis
- Myocarditis
- Nephritis
- Encephalitis, retinitis

Torres-Madriz G, Boucher HW. Clin Infect Dis. 2008;47(5):702-711;
Kotton CN, CMV: Prevention, Diagnosis and Therapy, AJT 2013

PREVENTION: Prophylaxis vs. Preemptive Therapy



Humar A, Snydman D; AST Infectious Diseases Community of Practice. *Am J Transplant.* 2009;9 (Suppl 4):S78-S86.

CMV Diagnostics

- Serology
  - To diagnose acute infection, detect IgM or IgM-->IgG seroconversion
  - CMV IgG establishes donor/recipient serostatus/risk in transplantation (no IgM)
  - Serology has no role in diagnosis of acute infection in transplant setting
- Molecular diagnostics
  - Quantitative PCR – detects CMV DNA in blood, other fluids, tissues
    - Lower (somewhat) sensitivity of blood PCR for CMV GI disease, pneumonitis, retinitis
    - Variations between whole blood and plasma, different testing platforms – pick one and use that to trend results, don't compare across different specimen types/testing platforms
- Histopathology of biopsied tissue
  - Basophilic intranuclear inclusion bodies surrounded by a clear halo – "owl's eye" cells
  - CMV-specific immunohistochemical stains
- Viral culture
  - Specimens: BAL, GI biopsy, etc.
  - Tissue culture: slow; cytopathic effect in 3-21 days (shell vial technique is faster); expensive; sensitivity/specificity not optimal (viral shed vs true infection)

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TREATMENT for Transplant Recipients: Consensus Recommendations (Kotton et al, CMV Guidelines, Transplantation 2018)

- For initial and recurrent episodes of CMV disease, VGCV (900 mg every 12 hours) or intravenous GCV (5 mg/kg every 12 hours) are recommended as first-line treatment in adults with normal kidney
- Valganciclovir is recommended in patients with mild to moderate CMV disease
- Intravenous GCV is recommended in life-threatening & severe disease; after clinical response, intravenous GCV may be transitioned to VGCV
- In patients without concomitant rejection, reduction of immunosuppression is suggested in the following settings: severe CMV disease, inadequate clinical response, high viral loads, and cytopenia
- During the treatment phase, weekly plasma CMV DNA testing is recommended using an assay calibrated to the WHO standard (IU/ml) to monitor response. Also renal function.
- Antiviral treatment dosing should be continued for a minimum of two weeks, until clinical resolution of disease and eradication of CMV DNAemia below a specific threshold (LLOQ < 200 IU/ml) on one or two consecutive weekly samples
- Adjunctive immunoglobulin therapy is not routinely recommended

Risk Factors and Rates for Resistant Virus

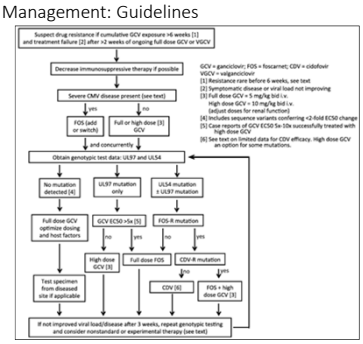
Risk Factors
- **Inadequate antiviral drug dose or delivery**
- **Prolonged antiviral drug exposure**
- **Ongoing active viral replication (often seen w/ lack of prior CMV immunity D+/R-)**
- **Strongly immunosuppressive therapy**
- **Drugs with lower barrier to resistance**

Rates
- **Among solid organ recipients the usual incidence of resistance after ganciclovir therapy is 5% to 12%, but up to 18% in lung and 31% in intestinal and multivisceral organ transplant recipients**
- **Incidence of resistance is lower, in the 0% to 3% range, with 100 to 200 days of ganciclovir or valganciclovir prophylaxis in D+/R- kidney recipients (IMPACT trial, Humar AJT)**

31 – CMV, EBV, HHV6 and HHV8 in Immunocompetent and Immunocompromised Patients

Speaker: Camille Kotton, MD

Resistant CMV Management: Guidelines



Kotton CN, et al. *Transplantation*. 2018;102(6):900-931.

Pseudotumor presentation of CMV disease: Diagnostic dilemma and association with immunomodulating therapy

Olivia C. Smibert[1,2] | Cody C. Allison[3] | Marcel Doerflinger[3] | Marc Pellegrini[3] | Danny Rischin[4] | Alesha Thai[4] | Monica A. Slavin[2,5] | Camille N. Kotton[3]

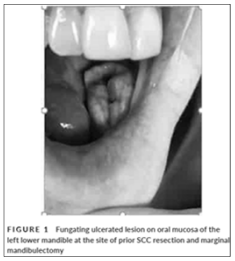


FIGURE 1 Fungating ulcerated lesion on oral mucosa of the left lower mandible at the site of prior SCC resection and marginal mandibulectomy

"Cytomegalo-tumor"

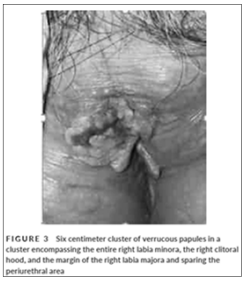


FIGURE 3 Six centimeter cluster of verrucous papules in a cluster encompassing the entire right labia minora, the right clitoral hood, and the margin of the right labia majora and sparing the periurethral area

A kidney transplant recipient (D+R-) gets 6 months of valganciclovir prophylaxis. Three months later, presents with fevers, malaise, low WBC, atypical lymphocytes, low platelets, hepatitis. What do you recommend?

A. Could be many things – send for many different cultures and viral load testing
B. This is probably CMV – send CMV viral load testing and routine cultures, and start treatment with valganciclovir 900mg po twice a day (renally adjusted as needed) (plan if not better, will check additional diagnostics)
C. Call a transplant ID colleague for guidance

HHV-6

Human Herpesvirus Type 6

- Beta herpesvirus, discovered in 1986
- Two subgroups:
  - HHV-6A – uncommon pathogen, little known about clinical impact or epidemiology
  - HHV-6B – frequent infection in healthy children, etiology of roseola (exanthem subitem), & cause of reactivation disease
- Primary infection common in first year of life, >60% infected by 12 months
- Transmission by saliva; incubation period ~9 days (5-15 days)
- Replicates and establishes latency in mononuclear cells, esp. activated T-lymphocytes
- Can integrate into human germline cells (1%); chromosomally inherited, will be viral load/PCR high level positive forever; can reactivate from integrated state
- No vaccine available or under development

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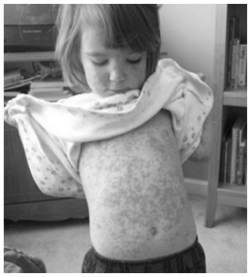
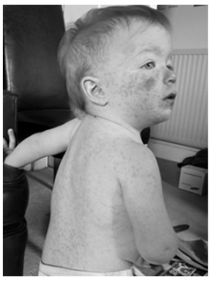
Exanthem subitum (roseola, sixth disease)





Slide courtesy of John W. Gnann Jr., MD, Medical University of South Carolina

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31 – CMV, EBV, HHV6 and HHV8 in Immunocompetent and Immunocompromised Patients

Speaker: Camille Kotton, MD

Human Herpesvirus Type 6: Normal hosts

- Associated syndromes
  - Exanthem subitum (roseola infantum, sixth disease)
    - children <4 y.o.; high fever for 5 days (febrile seizures), followed by a rash
  - Primary infection in adults (very rare) – mononucleosis syndrome
  - *Reactivation disease in transplant patients, esp. encephalitis and pneumonitis*
  - Mesial temporal lobe epilepsy association
  - Not the cause of MS, chronic fatigue, myocarditis, some others
- Diagnosis
  - Classic rash and clinical setting (early childhood)
  - IgG seroconversion
  - PCR from plasma (cell free), CSF, tissue → *immunocompromised patients*
- Therapy
  - Supportive care

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HHV-6: Immunocompromised Hosts

- Associated syndromes
  - Reactivation disease in transplant patients
  - Encephalitis – mostly allogeneic HCT recipients (1-3%), often in first 60 days
  - Bone marrow suppression (maybe also GVHD?)
  - Pneumonitis (rare, harder to prove)
- Diagnosis
  - PCR from plasma (cell free), CSF, tissue
    - High prevalence of viral DNA in peripheral blood mononuclear cells limits the use of PCR to discriminate between latency and active infection, chromosomal integration can be confusing
    - CSF typically normal or only mildly abnormal, slightly elevated WBC and protein, HHV-6 PCR 15,000-30,000 copies/ml
  - Encephalitis – MRI, EEG
- Therapy
  - Ganciclovir or foscarnet; likely decide based on toxicities; cidofovir last choice
  - Treat encephalitis; not all need treatment, not low level HHV-6+ in blood
  - Reduce immunosuppression if possible

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HHV-8

Human Herpesvirus Type 8

- Gamma herpesvirus, discovered 1994
- Kaposi sarcoma-associated herpesvirus (KSHV)
- Four variants have been described:
  - classic
  - endemic (Africa, Mediterranean regions)
  - iatrogenic or immunosuppression-associated
  - epidemic or AIDS- associated
- HHV-8 seroprevalence in the US (highly variable internationally):
  - 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, some with febrile rash syndrome

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HHV-8 Associated Diseases

- Kaposi sarcoma. 4 types:
  - Classic: indolent cutaneous proliferative disease, mainly affecting the lower extremities of elderly men of Mediterranean and Ashkenazi Jewish origin
  - Endemic: all parts of equatorial Africa, affecting both children and adults, can be more aggressive than classic
  - Transplant-associated: more often donor-derived (D+R-), can be reactivation
  - Epidemic/AIDS-related): KS is the most common tumor arising in people living with HIV; an AIDS-defining illness
- Primary effusion lymphoma (body cavity-based lymphoma)
  - Non-Hodgkin B-cell lymphoma, usually in HIV+. Involves pleural, pericardial, or peritoneal spaces
- Castleman's disease (HIV+ and HIV-)
  - 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.

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HHV-8 Diagnosis and Treatment

- Diagnosis
  - HHV-8 IgG
  - HHV-8 PCR on plasma, tissue
  - Biopsy/pathology for primary effusion lymphoma, Castleman's disease, etc
    - HHV-8 immunohistochemistry
- Treatment
  - Reduction of immunosuppression (watch for rejection)/start antiretroviral therapy
  - mTor inhibitors (sirolimus/rapamycin, etc) for transplant patients
  - Antiviral therapies +/- efficacy, not usually recommended, can be considered
  - Intralesional therapy or adjuvant chemotherapy may be required if unresponsive to these conservative measures or for more aggressive disease
  - Kaposi's sarcoma treated as a cancer

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31 – CMV, EBV, HHV6 and HHV8 in Immunocompetent and Immunocompromised Patients

Speaker: Camille Kotton, MD

Antiviral Prophylaxis & Treatment Agents

*acyclovir/valacyclovir/famciclovir and letermovir for prophylaxis only

**foscarnet, cidofovir not usually used for prophylaxis

Antiviral agent	EBV	CMV	HHV-6	HHV-8	HSV	Varicella	BK	Adeno-virus
Commercially available								
ganciclovir IV/valganciclovir PO		x	x	+/-	x	x		
acyclovir/valacyclovir/famciclovir*		high dose +/-			x	x		
letermovir		x						
foscarnet**		x	x	+/-	x	x		
cidofovir**		x	x	+/-	x	x	poor	+/- (IC50)
Novel/investigational antiviral agents (SOT)								
brincidofovir (not available)	*x*	*x*			*x*	*x*	*x*	*x*
maribavir	*In vitro*	x						

Summary: EBV, CMV, HHV-6, HHV-8

- Common childhood infections
- All human herpesviruses establish latency
- Serology useful, viral load detection more helpful in immunocompromised
- Infection from donor → recipient usually major risk factor
- Varied spectrum of clinical manifestations, from infectious syndromes to malignancies (EBV, HHV-8)
- Antiviral prophylaxis/treatment – best for CMV, more limited utility for others
- No vaccines available

Questions? ckotton@mgh.Harvard.edu

MASSACHUSETTS GENERAL HOSPITAL
TRANSPLANT CENTER

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Sexually Transmitted Infections: Other Diseases and Syndromes

Dr. Khalil G. Ghanem

32 – Sexually Transmitted Infections: Other Diseases and Syndromes

Speaker: Khalil Ghanem, MD

Sexually Transmitted Infections: Other Diseases and Syndromes

Khalil G. Ghanem, MD, PhD
Professor of Medicine
Division of Infectious Diseases
Johns Hopkins University School of Medicine

Disclosures of Financial Relationships with Relevant Commercial Interests

- None

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

A man with persistent urethritis following doxycycline therapy is tested and found to be positive for *Mycoplasma genitalium.* Which of the following is the most appropriate therapy?

A. Azithromycin 1g orally
B. Azithromycin 500mg orally X1 followed by 250 mg daily on the subsequent 3 days
C. Doxycycline 100 mg orally twice daily for 14 days
D. Moxifloxacin 400 mg orally daily for 10 days

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

- Asymptomatic
- Urethritis
- Epididymitis (70% of cases in young men)
- Proctitis
- Conjunctivitis
- Pharyngitis (rare)
- **Reactive arthritis (urethritis, conjunctivitis, arthritis, skin lesions)**

WOMEN

- Asymptomatic
- Cervicitis
- Urethritis
- **Pelvic inflammatory disease**
- Bartholinitis
- Proctitis
- 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: **doxycycline 100mg PO BID X 7d is preferred;** alternate is 1 g oral azithromycin
  - L1-L3 serotypes (if moderate to severe proctitis): **Doxycycline 100 mg PO BID X3 weeks** (preferred); alternate is 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 persons treated for chlamydia infection 3 months later (REINFECTION rates are high)

AZITHROMYCIN VS. DOXYCYCLINE

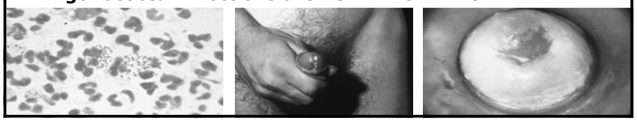
- **Urogenital** *C. trachomatis*
  - RCT in correctional facility: azithromycin=97% vs. doxycycline=100% (noninferiority of azithromycin was **not** established) Geisler NEJM 2015
- **Rectal** *C. trachomatis*
  - 2 Recent RCTs: Efficacy difference in favor of doxycycline of 20% Dombrowski CID 2021; Lau NEJM 2021

GONORRHEA: TAKE-HOME POINTS

- Drug resistance: IM ceftriaxone 500 mg is now the preferred regimen
- Pharyngeal gonorrhea: ceftriaxone is the only drug that is recommended; test of cure 7-14 days after treatment
- Disseminated gonococcal infection: patients may NOT have symptoms of urethritis
- Gonococcal conjunctivitis: 1g of ceftriaxone

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**



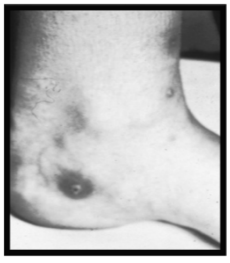
SCREENING FOR GONORRHEA

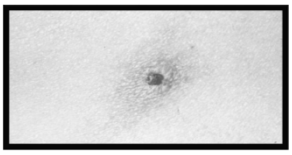
- HIV-infected men and women
- Sexually active MSM (**at all sites of exposure**)
- Individuals with new or multiple sexual partners
- Sexually active women <25
- Sexually active individuals living in areas of high *N. gonorrhoeae* prevalence
- Individuals with a history of other sexually transmitted 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 usually 5-7 days; longer with arthritis

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

- The only first-line option for uncomplicated gonorrhea is **ceftriaxone** (**500 mg** IM x1)
  - >5% of isolates in the US in 2019 had elevated MICs to azithromycin so it was abandoned as first-line therapy

St Cyr MMWR 2020

GONORRHEA THERAPY (CONT.)

- Second-line agents for **urogenital** or **rectal infections**:
  - Cefixime (800mg PO X1)
  - Gentamicin 5mg/kg IM+ 2g azithromycin
  - **Azithromycin 2g PO X1 is no longer recommended**
- **There are NO second-line recommendations for pharyngeal gonorrhea**- it's ceftriaxone or bust!
  - Gentamicin and cefixime have lower efficacy for pharyngeal infections Ross JDC, et al. *Lancet* 2019
  - All pharyngeal infections: must do a test of cure within 2 weeks after ceftriaxone therapy

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GONORRHEA THERAPY CONTINUED

- **DGI**: Ceftriaxone 1g IM or IV until clinically better (can also use cefotaxime and ceftizoxime); then, can complete 7-day course of therapy with a PO cephalosporin (once results of antibiotic susceptibility testing are available)
- **Gonococcal conjunctivitis**: Ceftriaxone 1g IM X1

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 extragenital 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 hpf
- More common etiologies:
  - *Chlamydia trachomatis* (25% cases)
  - ***Mycoplasma genitalium* (30% of cases)**
  - *Trichomonas vaginalis* (10-25% of cases; mainly MSW not MSM)
  - *Ureaplasma urealyticum* (controversial; do NOT test for this bacterium)
  - HSV
- Less common etiologies: anaeobes; enterobacteriaceae, Haemophilus, *Staphylococcus saprophyticus*, adenovirus
- NGU treatment: **doxycycline 100mg PO BID X 7d is now the preferred regimen**

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

- 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
- Test men with persistent urethritis or epididymitis; consider testing women with persistent cervicitis or PID (discuss with patient); consider testing in men and women with persistent proctitis symptoms
- FDA-cleared diagnostic test now available
  - Combined molecular diagnostic with molecular detection of macrolide resistance is not yet FDA cleared (it is available in Europe and Australia)

M. GENITALIUM THERAPY

- Doxycycline 100mg PO BID X 7days (success rate ~30%)
- Azithromycin 1g PO X1 (success rate now <50%)
  - Azithromycin should NOT be used unless you know the organism is sensitive to the macrolides
- **Moxifloxacin 400mg POX 7-14 days is now the drug of choice**
  - Emerging resistance to fluoroquinolones (13.6% moxifloxacin resistance) Emerg Infect Dis. 2017;23(5):809-812
- Pristinamycin was highly effective in treating macrolide- and quinolone-resistant strains (not FDA approved)

Clin Infect Dis. 2015 ;60(8):1228-36

SUMMARY: URETHRITIS APPROACH

- All men presenting with urethritis should be tested for both GC and CT and treated with one week of oral doxycycline
- If the GC and CT tests are negative and the patient has persistent symptoms:
  - If the patient is a MSW: Test for *M genitalium* and trichomonas and treat based on results
  - If the patient is a MSM: Test for *M genitalium* and treat based on results (trichomonas is rare in MSM)

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: Treat all women with metronidazole 500mg PO BID X 7 days OR tinidazole 2g PO X1 [do NOT use topical gel formulations]
  - Recent clinical trial in HIV- women: 7 days of metronidazole superior to 2g single dose Kissinger et al. Lancet Inf Dis 2019
- Therapy: Treat all men with metronidazole 2g PO X1 OR tinidazole 2g PO X1
- 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 women with HIV annually**

TRICHOMONAS & NITROIMIDAZOLES

- **Tinidazole** has a longer serum half-life and achieves higher tissue concentrations than metronidazole; MICs to tinidazole lower than to metronidazole
- Can use 2g of oral tinidazole to treat both men and women
- If patient fails Rx with metronidazole & reinfection is excluded:
  - Option 1: Tinidazole 2 g PO X1
- If patients fails option 1 above:
  - Option 2: Metronidazole 2g PO QD X 5d
  - Option 3: 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 OR Secnidazole 2g PO X1 dose
  - *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; **screening asymptomatic pregnant women for BV if high risk for pre-term delivery (e.g., history of premature delivery) is no longer recommended**

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 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 in the 2021 CDC STI Treatment Guidelines (online at cdc.gov)
- 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 500mg 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 man with HIV 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 500mg IM + Azithromycin 1g PO X1
B. Ceftriaxone 500mg IM + Doxycycline 100mg PO BID X 7d
C. Ceftriaxone 500mg IM + Azithromycin 1g PO weekly X 3wks
D. Ceftriaxone 500mg IM + Doxycycline 100mg PO BID X 21d
E. Ceftriaxone 500mg 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+)

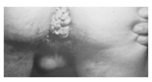
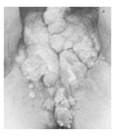
OTHER CAUSES

- Campylobacter
- Shigella
- Entamoeba
- CMV
- *Giardia lamblia** (mainly enteritis; especially among MSM)

PROCTITIS THERAPY

- **Ceftriaxone 500mg IM X1 + Doxycycline 100mg PO BID X 7-21 days <u>depending on extent of symptoms</u>**
- **Treat for 21d**: Moderate to severe symptoms- (e.g., pain, bloody discharge +/- ulcers)
- Treat for HSV: Painful perianal ulcers or mucosal ulcers are detected on anoscopy
- Azithromycin is 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

32 – Sexually Transmitted Infections: Other Diseases and Syndromes

Speaker: Khalil Ghanem, MD

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)

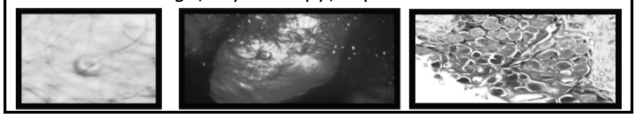
*FDA approved a supplemental biologics licensure application in 6/2020: prevention of oropharyngeal and other head and neck cancers caused by HPV types targeted by the vaccine

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

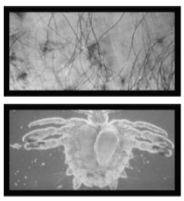
MOLLUSCUM CONTAGIOSUM

- Poxvirus
- 1 to 5mm lesions; painless papules; CENTRAL UMBILICATION
- Not necessarily sexually transmitted
- Molluscum bodies: intracytoplasmic inclusions
- Rx: curettage; cryotherapy; topical cidofovir

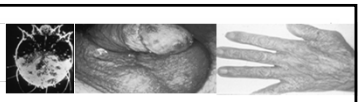


PEDICULOSIS PUBIS

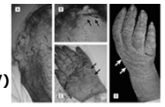
- Pediculosis pubis= pubic lice= crabs (*Pthirus pubis*)
  - Nits confined to upper shaft=old infection (no need for retreatment)
  - Maculae ceruleae (blue gray macules)
  - Permethrin 1% cream OR Pyrethrins with piperonyl butoxide (topical)
  - Resistance increasing; consider malathion 0.5% lotion 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

33

Herpes Viruses: HSV and VZV in Immunocompetent and Immunosuppressed Patients

Dr. Richard Whitley

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

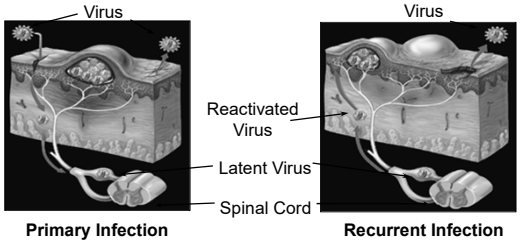
Disclosures of Financial Relationships with Relevant Commercial Interests

- Member, Board of Directors at Gilead Sciences, rotated off in May of 2021
- Chairperson: NIAID COVID-19 Vaccine DSMB
- Chairperson: Merck Letermovir DMC and GSK IDMC for Zoster
- Scientific Advisory Board: Treovir, LLC
- Member, Board of Directors at Evrys Bio
- Member, Board of Directors at Virios Therapeutics

Herpes Viruses: The Family

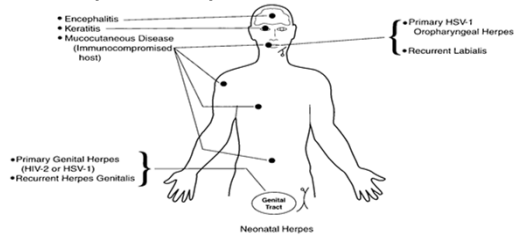
- Herpes simplex virus, type 1 (HSV-1)
- Herpes simplex virus, type 2 (HSV-2)
- Varicella zoster virus (VZV)
- Cytomegalovirus (CMV)
- Epstein Barr virus (EBV)
- Human herpesvirus 6 (HHV 6 A and B)
- Human herpesvirus 7 (HHV 7)
- Human herpesvirus 8 (HHV 8)

Viral Latency and Reactivation

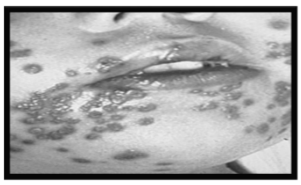


Netter FH. ©2001 by Icon Learning Systems.

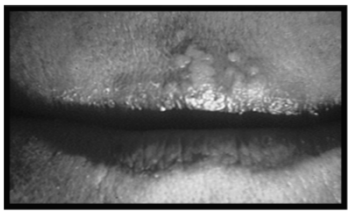
Clinical Manifestations of Herpes Simplex Virus Infections



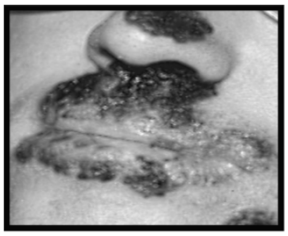
Primary Herpes Simplex Virus Infection: Cutaneous Lesions



Herpes Simplex Labialis

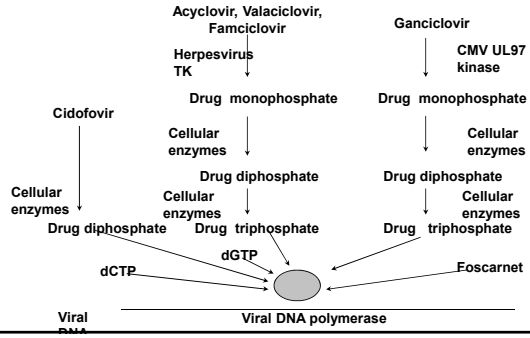


Immunocompromised Host



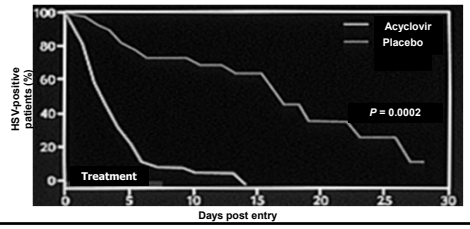
Most Widely Used Systemic Anti-HSV and VZV Drugs

- 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

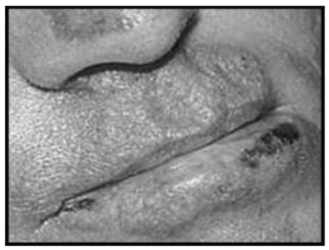
Time to cessation of viral shedding with acyclovir



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

Global Prevalence of HSV-2 Infection

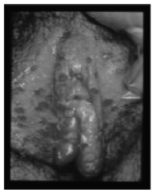
Total estimated number of people (in millions) infected with HSV-2 in 2012 by WHO region, gender and age range.
Source: WHO, as published in PLOS ONE (21 Jan 2015)

Acyclovir Therapy of Genital Herpes

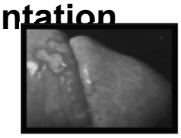
Summary of clinical benefit for treatment of:

- Primary
- Recurrent
- Suppressive

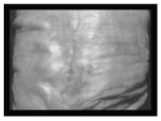
Spectrum of HSV Clinical Presentation



First infection

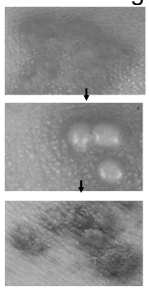


Classical recurrence



Atypical recurrence

Progression of Lesions



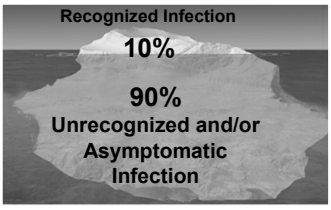
Early Redness/Swelling

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.

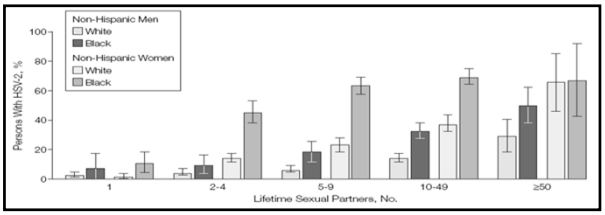
Changes in Weighted Herpes Simplex Virus 2 Seroprevalance Age 14 to 49 years

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

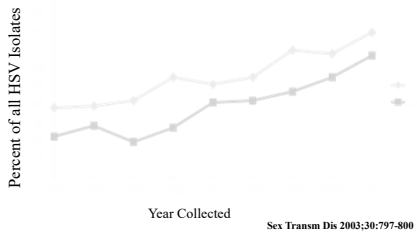
JAMA, August 23/30, 2006 Vol 296 No 8 pg 968

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%

Transmission — 70%

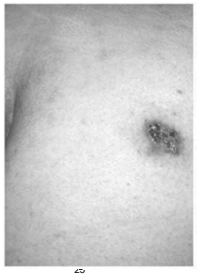
Corey L. *Sex Transm Dis.* 1994;21(S38-S44.
Mertz GJ, et al. *Ann Intern Med.* 1992;116:197-202.

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

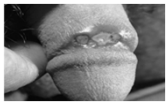


- The patient had been to her doctor 3 times over the past 8 months with this pruritic and mildly painful rash on her right buttock. She had been told that it was an irritation from riding a bicycle.
- What is the key to the diagnosis?
  - A. the fact that lesions recurred
  - B. site of involvement is not unusual
  - C. trauma can induce reactivation

Photo courtesy of Dr. Robert, 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.

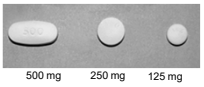


Which of the following diagnostic tests is most likely to yield the specific diagnosis?

A. Serum RPR
B. Serum FTA-Abs
C. Darkfield microscopy
D. Glycoprotein-G 1 serum antibodies
E. PCR on lesion swab

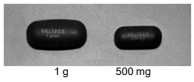
Oral Antiviral Therapies

- Famciclovir [Famvir®]



500 mg 250 mg 125 mg

- Valaciclovir [Valtrex®]



1 g 500 mg

800 mg 600 mg 200 mg

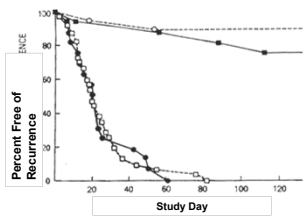
- Acyclovir [Zovirax®]

Valtrex® and Zovirax® are registered trademarks of GlaxoSmithKline.

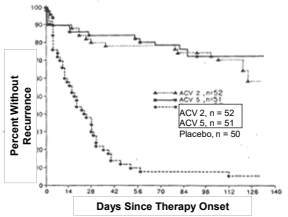
Impact of Acyclovir Therapy on Primary Genital HSV Infection

	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

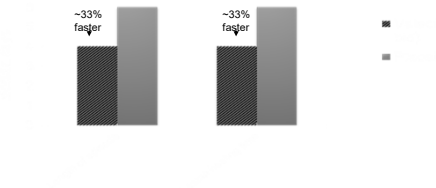
Second Generation Anti-Herpetic Medications

- Valacyclovir (prodrug of acyclovir)
- Famciclovir (prodrug of penciclovir)

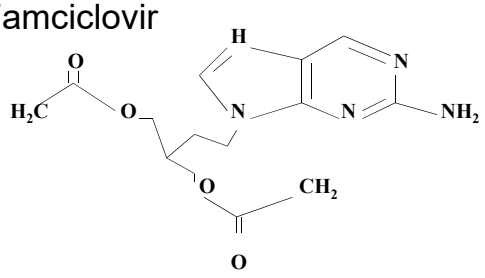
Acyclovir/Valacyclovir Kinetics

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

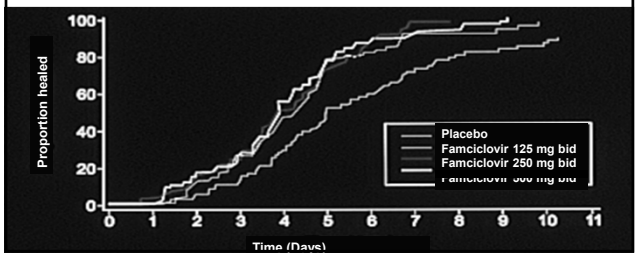
Therapy of Recurrent Genital Herpes: Duration of Disease



Famciclovir



Famciclovir Therapy of Recurrent Genital Herpes



Shorter and Shorter Therapy

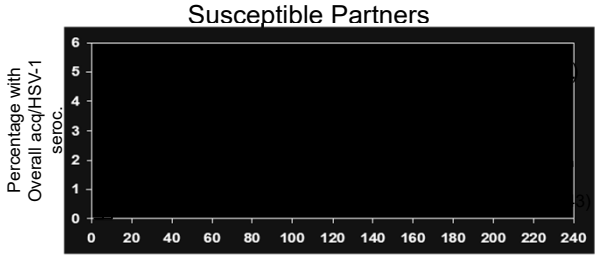
- Genital Herpes
  - Valacyclovir: three days
  - Famciclovir: one day
- Labial Herpes
  - Valacyclovir: two days
  - Famciclovir: one day

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.

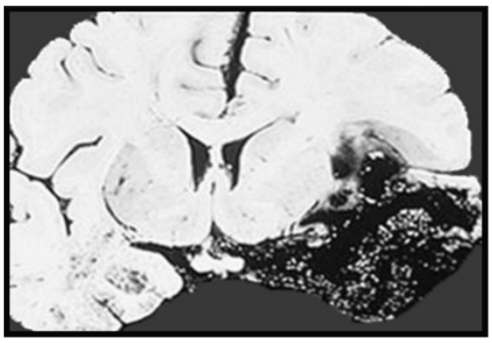
Recommended Treatment for Recurrent Episodes

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

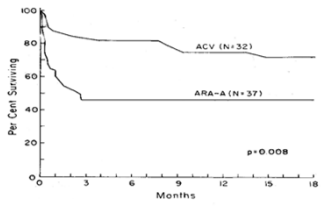
ORFamciclovir 500 mg once, followed by 250 mg twice daily for 2 days

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

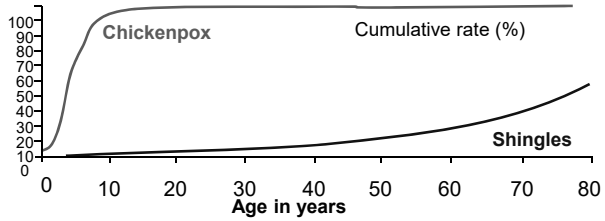
Age	Glasgow Coma Scale	
	<6	>6
<30	0	60
>30	0	36

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

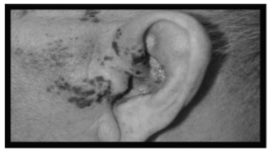
Treatment of Chicken Pox: Adults (>18 Years) < 24 Hour Duration

	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?



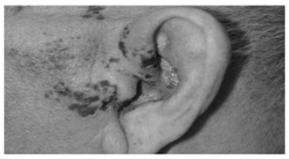
Answer

- 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

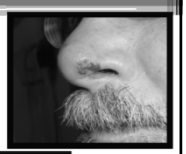
What complication is it most likely to be associated with this illness?

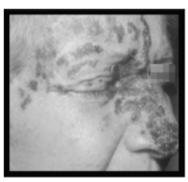
A. Deafness
B. Vertigo
C. Optic neuritis
D. Keratitis
E. Stroke

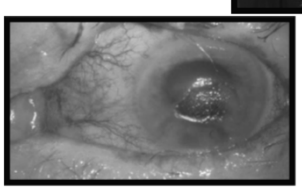
www.medscape.com

Hutchison's Sign

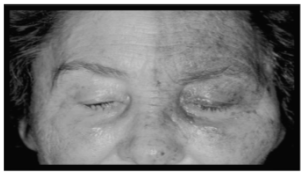
Zoster Involving nasociliary branch, Cranial Nerve VII which inervates the tip of the nose and the cornea







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**

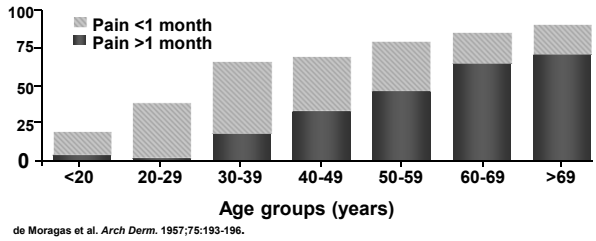
NATURAL HISTORY OF ZOSTER IN THE NORMAL HOST

- **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

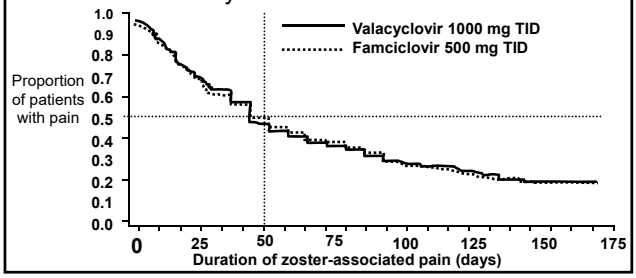
- Accelerate cutaneous healing
- Accelerate loss of pain acute / chronic
- Prevent complications

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

Question 6

A 32 year previously healthy female is referred by an ophthalmologist for treatment of acute retinal necrosis, diagnosed in her office earlier that day. You recommend which of the following as initial therapy:

- A. sulfadiazine and pyrimethamine
- B. ganciclovir IV
- C. acylovir PO
- D. acyclovir IV
- E. foscarnet IV

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

34

Board Review Session 3

Drs. Whitley (Moderator), Kotton, Dhanireddy, Ghanem, Rose, Thomas, and Tunkel

34 – Board Review Day 3

Speaker: Drs. Whitley (Moderator), Kotton, Dhanireddy, Ghanem, Rose, Thomas, and Tunkel

Board Review: Day 3

Moderator: Dr. Whitley
Faculty: Drs. Kotton, Dhanireddy, Ghanem, Rose, Thomas, and Tunkel

BOARD REVIEW DAY 3

#31 **45-year-old HIV infected man switched to monthly cabotegravir and rilpilvirine injections. Aside from some pain in the injection sites he had no complaints.**

However, his routine lab testing showed ALT 568 IU/ml and AST 672 IU/L and total bilirubin of 2.3 mg/dl.

Other labs weren't significantly changed from baseline.

He was in a stable relationship with one male partner and did not endorse using illicit drugs.

BOARD REVIEW DAY 3

#31 **What test is most likely to explain the hepatitis?**

A) Cabotegravir metabolite level

B) Rilpilvirine level

C) HCV RNA level

D) HBV DNA level

E) Electron microscopy of hepatocytes mitochondria

BOARD REVIEW DAY 3

#32 **You are asked by your occupational health service about a 22-year-old incoming medical student who had never been vaccinated for HBV since he recently emigrated to the US.**

At his initial visit to occupational medicine as a first-year student he reported having hepatitis B since birth which was never treated. His family immigrated to the US and his mother is the presumed source of infection.

He is otherwise well.

Occupational medicine reports that he is HBsAg positive, has an HBV DNA level of 8.2 log IU/ml, and an ALT of 22 IU/L.

BOARD REVIEW DAY 3

What is the best advice regarding the student's participation in clinical rotations now and in the future?

#32

A) His HBV status is not relevant to his clinical rotations or career choice regardless of whether he is treated

B) His HBV status should preclude him from an interventional career (e.g., surgery) regardless of whether he is treated

C) He should be treated and restricted from clinical rotations until his HBeAg converts to negative at which point he can resume all activities

D) He should be treated with an approved regimen and allowed to complete clinical training once his HBV DNA < 1000 IU/L when he can resume all clinical activity

E) He should be treated and restricted from clinical rotations until his HBV DNA < 1000 IU/L but he should never be involved in interventional procedures (e.g., surgery)

BOARD REVIEW DAY 3

#33 **A 35-year-old sexually active man has burning with urination and clear urethral discharge for the past two weeks.**

Urine culture and urine NAAT for Neisseria gonorrhoeae, Chlamydia trachomatis and Trichomonas vaginalis are negative.

34 – Board Review Day 3

Speaker: Drs. Whitley (Moderator), Kotton, Dhanireddy, Ghanem, Rose, Thomas, and Tunkel

BOARD REVIEW DAY 3

#33 **Urine PCR should be performed for which of the following?**

A) ***Mycoplasma pneumoniae***

B) ***Mycoplasma genitalium***

C) ***Mycoplasma hominis***

D) ***Treponema pallidum***

E) ***Chlamydia pneumoniae***

BOARD REVIEW DAY 3

#34 **A 35-year-old male agricultural specialist visited Zimbabwe for 3 weeks to assess farm productivity. One day after his return to the United States, he developed fever, headache, diffuse myalgias and joint pains in his hands, elbows, shoulders, knees, and feet. He had a macular non-pruritic rash on his face and neck that faded over several days. His fingers and wrists were swollen but not erythematous. His wrists were so sore he could not use his computer or carry his briefcase.**

He stayed home from work for 4 days until his fever abated without therapy, but his joint pains persist 3 weeks later, and he consults you.

BOARD REVIEW DAY 3

#34 **He relates that he took mefloquine weekly during his stay in India but stopped it when the fever and rash began.**

On his exam he is not febrile and he has no rash, joint findings, or other abnormalities you can detect.

Laboratory:

- **CBC and blood chemistries are normal.**
- **Malaria smear is pending.**

BOARD REVIEW DAY 3

#34 **The most likely cause of this man's illness was which of the following:**

A) Nipah virus

B) Hepatitis A

C) Chikungunya

D) Mefloquine hypersensitivity

E) Dengue

BOARD REVIEW DAY 3

#35 **You are called by a family physician about a patient, a 17-year-old whom she saw two days earlier for severe sore throat and malaise of five days duration.**

The patient was well until he developed the sore throat accompanied by low grade fever and "feeling tired and sick." He doesn't know anyone else who is sick. He is sexually active with a single partner and always uses condoms.

On exam, his temperature was 100.8°F; pulse 86, BP 112/78. He had periorbital edema and bilateral anterior and posterior cervical nodes that were more prominent posteriorly. His throat was red with small exudates. The spleen tip was palpable.

BOARD REVIEW DAY 3

#35 **A rapid strep test performed in the family physician's office was negative.**

The doctor thought the young man had mononucleosis and ordered a CBC and Monospot test (heterophile antibody).

The WBC count was 12,000; there were 32% lymphocytes and 12% atypical lymphocytes and the platelet count was slightly low at 120,000.

The Monospot test was negative.

34 – Board Review Day 3

Speaker: Drs. Whitley (Moderator), Kotton, Dhanireddy, Ghanem, Rose, Thomas, and Tunkel

BOARD REVIEW DAY 3

#35 Which one of the following is most likely responsible for the young man's illness?

A) Cytomegalovirus

B) HIV

C) Epstein-Barr virus

D) Toxoplasma

E) Human herpes virus 6

BOARD REVIEW DAY 3

#36 A 28-year-old female emergency room nurse cares for a child with fever and rash who is later determined to have measles. Because the diagnosis was not under consideration at the time of clinical presentation, the child was not placed on airborne precautions, and the nurse did not wear an N-95 respirator when caring for the patient.

The nurse is originally from Nigeria and prior MMR (measles-mumps-rubella) vaccination records are not readily obtainable.

BOARD REVIEW DAY 3

#36 You are asked to provide recommendations for post-exposure prophylaxis for the nurse. Which of the following would you advise?

A) Vitamin A

B) MMR vaccine and immunoglobulin (IG) within six days of exposure

C) MMR vaccine within 72 hours of initial measles exposure, or immunoglobulin (IG) within six days of exposure

D) Valacyclovir intravenously every 12 hours

E) Ribavirin

BOARD REVIEW DAY 3

#37 A 27-year-old man with no significant past medical history presents complaining of a rash and "ringing" in both his ears.

He was well until one week earlier when he noticed a rash on his back and abdomen. The rash is not pruritic.

Five days prior to presentation, he noted "ringing" in his right ear followed shortly thereafter by similar symptoms in his left ear.

He denies any other complaints.

BOARD REVIEW DAY 3

#37 Physical examination reveals a macular non-blanching rash limited to his abdomen and back.

Anogenital and neurological examinations are unremarkable. There is no obvious hearing loss on examination.

However, an immediate evaluation by an otolaryngologist found bilateral sensorineural hearing loss. Abnormal laboratory results include a reactive serum treponemal CIA and a reactive serum RPR with a titer of 1:512.

BOARD REVIEW DAY 3

#37 Which of the following is the most appropriate next step?

A) A single intramuscular dose of 2.4 MU of penicillin G benzathine

B) An intramuscular dose of 2.4 MU penicillin G benzathine weekly for 3 consecutive weeks

C) A CSF examination

D) Doxycycline 200 mg orally twice daily for two weeks

E) Intravenous aqueous penicillin G 18-24 million units daily for 10-14 days

34 – Board Review Day 3

Speaker: Drs. Whitley (Moderator), Kotton, Dhanireddy, Ghanem, Rose, Thomas, and Tunkel

BOARD REVIEW DAY 3

#38 A 35 y/o male reports that he spent this past week at a shelter where he was told there were several cases of active hepatitis A. You call the shelter and they confirm that they have diagnosed 6 cases among their clients during the past week.

Your patient feels well, has no complaints and a normal examination. He reports that he never received immunizations of any sort that he can remember.

You don't have ready access to serologic testing for hepatitis A antibody, so that screening is not an option even if you thought it were useful.

BOARD REVIEW DAY 3

#38 In order to protect him from hepatitis A, what would you recommend:

A) Hyperimmune hepatitis A immune globulin

B) Immune serum globulin

C) Hepatitis A vaccine

D) Both hepatitis A vaccine and immune serum globulin

E) No post exposure prophylaxis

BOARD REVIEW DAY 3

#39 A 48-year-old with rheumatoid arthritis on TNF- alpha inhibitors presents in the Fall of 2016 for routine follow-up.

He states he NEVER gets the influenza vaccine because he develops severe hives if he eats eggs and is immunosuppressed.

On further questioning he states he can eat baked goods cooked with eggs and has no allergic sequelae.

BOARD REVIEW DAY 3

#39 What would you advise this patient about influenza vaccination:

A) He should be given the Live Attenuated Influenza Vaccine

B) He may safely receive Inactivated trivalent or quadrivalent Influenza Vaccine

C) He should not receive any influenza vaccine due to his egg allergy

D) The only safe option is to receive Flucelvax (ccIIV), the mammalian Cell Culture Inactivated Influenza Vaccine or Flublok (rIIV), the Recombinant Influenza Vaccine

BOARD REVIEW DAY 3

#40 You are consulted to see a 31-year-old woman on the neurology service who was admitted yesterday after an apparent transient ischemic episode.

She was febrile on admission and reported having had fever for more than a week along with night sweats.

On review of systems, she noted a five-pound weight loss in the last week along with pain in both calf muscles after walking about a half mile.

She works in a shelter for homeless people.

BOARD REVIEW DAY 3

#40 On exam, she has a temperature of 101.6˚F; pulse 100; BP 84/66. There is no rash and no murmur.

She is tender bilaterally over her carotid arteries and has diminished peripheral pulses throughout.

Her neurological exam is normal.

Blood cultures from admission are negative at 24 hours.

Chest x-ray and routine labs are normal except for a WBC count of 12,300 with 77% polymorphonuclear neutrophils.

34 – Board Review Day 3

Speaker: Drs. Whitley (Moderator), Kotton, Dhanireddy, Ghanem, Rose, Thomas, and Tunkel

BOARD REVIEW DAY 3

#40 Which one of the following is the most likely diagnosis?

A) Culture-negative endocarditis

B) Temporal arteritis

C) Moyamoya disease

D) Takayasu's arteritis

E) Atrial myxoma

BOARD REVIEW DAY 3

#41 A 52-year-old homeless man who often lives in shelters is hospitalized in Boston for fever, chills, loss of appetite, and weakness in the left arm and leg.

He denies intravenous drug abuse, animal exposure, and receiving any form of medical attention or medications over the past year.

BOARD REVIEW DAY 3

#41 Physical examination reveals a pale disheveled man with a temperature of 38.3˚C, several conjunctival petechiae, a small hemorrhagic lesion in the right retina, a grade 2/6 systolic ejection murmur, and a grade 2/6 diastolic decrescendo murmur heard along the left sternal border.

The spleen tip is palpable.

There are no skin lesions, but a nurse found some lice in his clothing.

Motor strength in the left arm and leg is diminished and the Babinski response is positive on the left.

BOARD REVIEW DAY 3

#41 A trans-thoracic echocardiogram reveals an oscillating mass on the non-coronary cusp of the aortic valve.

Three sets of blood cultures, each with 10 mL of blood for aerobic and anaerobic culture were drawn on the first and second hospital days and remain negative after 7 and 6 days of incubation, respectively.

BOARD REVIEW DAY 3

#41 The most likely cause of this patient's endocarditis is:

A) Coxiella burnetii

B) Chlamydophila (Chlamydia) psittaci

C) Abiotrophia defectiva

D) Bartonella quintana

E) Histoplasma capsulatum

BOARD REVIEW DAY 3

#42 A 25-year-old female with acute myelogenous leukemia is currently in complete remission and is being scheduled for an allogeneic stem cell transplantation in the near future.

The patient's CMV IgG is positive, and her identified donor's CMV IgG is negative.

34 – Board Review Day 3

Speaker: Drs. Whitley (Moderator), Kotton, Dhanireddy, Ghanem, Rose, Thomas, and Tunkel

BOARD REVIEW DAY 3

#42 Which of the following would you recommend regarding prevention of CMV infection post-transplantation, assuming her serum CMV PCR is being monitored weekly and remains undetectable?

A) Letermovir prophylaxis

B) Brincidofovir prophylaxis

C) Acyclovir prophylaxis

D) Monthly IVIG prophylaxis

E) Valganciclovir prophylaxis

BOARD REVIEW DAY 3

#43 A 75-year-old man presents with a 2-day history of fever, dysphasia, and personality change. One day prior to admission, his family noted that he was lethargic.

On presentation, vital signs were temperature 101F, pulse 110, respirations 14, and blood pressure 120/70 mmHg.

He was unresponsive.

Neck was supple and there were no obvious focal neurologic abnormalities.

BOARD REVIEW DAY 3

#43 The peripheral WBC was 9,000/mm^3.

- In the emergency room, the patient was treated empirically with vancomycin, ampicillin, ceftriaxone, and acyclovir.
- He was then sent for an emergent non-contrast CT scan of the head, which was negative. Cerebrospinal fluid (CSF) examination revealed a WBC 100/mm3 (98% lymphs), glucose 80 mg/dL, and protein 100 mg/dL.
- CSF Gram stain was negative.

BOARD REVIEW DAY 3

#43 Which of the following tests will most likely identify the etiology of the patient's encephalitis?

A) CT scan of the head with contrast

B) Brain MRI

C) Serum IgG antibody

D) CSF IgG antibody

E) CSF polymerase chain reaction

BOARD REVIEW DAY 3

#44 A 30-year-old man is thrown from his motorcycle and suffers a depressed skull fracture with intracranial hemorrhage.

He is taken to the OR where the hemorrhage is evacuated. He initially does well, but 5 days later develops fever of 39C, worsening headache and transiently loses consciousness.

A non-contrast CT of the head reveals stable appearance of the hemorrhage. Cerebrospinal fluid analysis shows a WBC count of 1500/mm3 (95% segs), RBC count of 1000/mm3, glucose of 40 mg/dL, and protein of 300 mg/dL.

The Gram stain is negative.

BOARD REVIEW DAY 3

#44 Which of the following should be initiated?

A) Vancomycin + cefepime

B) Vancomycin + trimethoprim-sulfamethoxazole

C) Cefepime + gentamicin

D) Meropenem

E) Supportive care as this is a chemical meningitis

34 – Board Review Day 3

Speaker: Drs. Whitley (Moderator), Kotton, Dhanireddy, Ghanem, Rose, Thomas, and Tunkel

BOARD REVIEW DAY 3

#45 **A 42-year-old man from New York City developed fever, dyspnea, and increasing pulmonary infiltrates four weeks post-cadaveric single lung transplant.**

He had been receiving standard 3 drug immunosuppression, but has also required high dose steroids for acute organ rejection.

He received standard anti-infective prophylaxis.

On bronchoscopy, diffuse alveolar hemorrhage was noted from both lungs.

BOARD REVIEW DAY 3

#45 **Biopsy of the transplanted lung showed no evidence of rejection.**

BAL stains for bacteria, fungi and mycobacteria were negative. PCR of blood for CMV was negative.

The transplant center was notified that the recipient of the other lung had developed a similar syndrome. The donor was a 20-year-old recent immigrant from Guatemala who died of a gunshot wound.

His mother thought he had been healthy.

BOARD REVIEW DAY 3

#45 **Assuming this infection was acquired from the transplanted lung, which organism appears most likely:**

A) Balamuthia mandrillaris

B) Rabies

C) Cryptococcus neoformans

D) Nocardia brasiliensis

E) Strongyloides stercoralis

35

Kitchen Sink: Syndromes Not Covered Elsewhere

Dr. Stacey Rose

35 – Kitchen Sink: Syndromes Not Covered Elsewhere

Speaker: Stacey Rose, MD

Kitchen Sink: Syndromes Not Covered Elsewhere

Stacey R. Rose, MD, FACP
Assistant Dean of Clinical Curriculum, School of Medicine
Assistant Professor, Infectious Diseases Section
Baylor School of Medicine

Disclosures of Financial Relationships with Relevant Commercial Interests

- **None**

Session plan

- Case-based discussions of topics not extensively covered in other sessions
- Highlight points likely to be assessed on ID Boards (rather than comprehensive overview)

3

Question 1

- A 51-year old male with past medical history significant for insulin dependent diabetes presents with a six-month history of progressive athralgias, abdominal pain, diarrhea, weight loss, and low grade fevers.
- Work up thus far:

Negative blood cultures x 2
Negative Rheumatoid factor
Normal metabolic panels
Mild normocytic anemia

4

Question 1

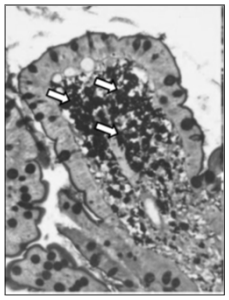
- Which of the following tests will most likely yield the diagnosis?

a) Anti-streptolysin O Antibody
b) Anti-nuclear Antibody
c) Stool ova and parasite
d) Duodenal biopsy

5

Whipple's disease

- Caused by *Trophyrema whipplei* (gram variable bacterium, difficult to cultivate)
- More common in middle aged, Caucasian men
- Diagnosis often delayed due to indolent clinical presentation
- Most commonly diagnosed via duodenal biopsy, stained with PAS
- PCR increasingly used



Periodic acid-Schiff-diastase (PAS-D)-stained duodenal biopsy specimens with PAS-D-positive granules in the foamy macrophages (arrows).

Dolmans RAV, Boel CHE, Lacle MM, Kusters JG. 2017. Clinical manifestations, treatment, and diagnosis of Tropheryma whipplei infections. Clin Microbiol Rev 30:529–555. https://doi.org/10.1128/CMR.00033-16.

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35 – Kitchen Sink: Syndromes Not Covered Elsewhere

Speaker: Stacey Rose, MD

Whipple's: clinical presentations

TABLE 1 Clinical manifestations of *Tropheryma whipplei* infection[a]

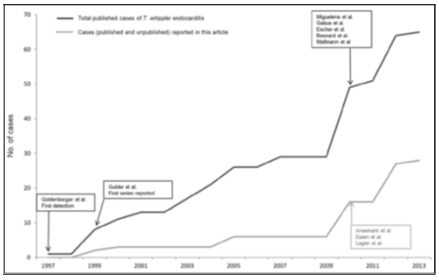
Classic Whipple's disease (% incidence)	Chronic localized infections[b]	Acute infections[b]
Weight loss (79–99)	Endocarditis	Gastroenteritis
Gastroenteritis (63–85)	Encephalitis	Pneumonia
Abdominal pain (23–60)		Bacteremia
Arthritis (20–83)		
Neurological symptoms (6–63)		

[a]See text for references.
[b]Values for relative incidence are unknown.

Dolmans RAV, Boel CHE, Lacle MM, Kusters JG. 2017. Clinical manifestations, treatment, and diagnosis of Tropheryma whipplei infections. Clin Microbiol Rev 30:529–555. https://doi.org/10.1128/CMR.00033-16.

7

Whipple's endocarditis



- Increasingly recognized (PCR on heart valves)
- Analysis of > 1000 cardiac valves in Germany concluded that *T. whipplei* was the most common pathogen associated with *culture negative endocarditis*

Fenollar F, Célard M, Lagier JC, Lepidi H, Fournier PE, Raoult D. Tropheryma whipplei endocarditis. Emerg Infect Dis. 2013;19(11):1721-1730. doi:10.3201/eid1911.121356
Geissdörfer W, Moos V, Moter A, et al. High frequency of Tropheryma whipplei in culture-negative endocarditis. *J Clin Microbiol*. 2012;50(2):216-222. doi:10.1128/JCM.05531-11

8

Whipple's: treatment

No gold standard

Options:

- Ceftriaxone or meropenem plus prolonged co-trimoxazole (~1 year)

OR

- Doxycycline plus hydroxychloroquine (12-18 mos)

Symptoms improve, but relapse is common without prolonged treatment / suppression

Dolmans RAV, Boel CHE, Lacle MM, Kusters JG. 2017. Clinical manifestations, treatment, and diagnosis of Tropheryma whipplei infections. Clin Microbiol Rev 30:529 –555. https://doi.org/10.1128/CMR.00033-16
Principles and Practice of Infectious Diseases, 9th ed

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- Cause: *Trophyrema Whipplei*
- Epidemiology: middle aged, Caucasian males
- Clinical presentation: classic – ***arthralgia, diarrhea, weight loss***
- Localized infection including ***endocarditis*** (increasingly recognized)
- Diagnosis with ***duodenal biopsy*** (***PAS*** stain; foamy macrophages) or ***PCR*** of infected tissue
- Prolonged treatment needed to prevent relapse

Whipple's disease

Take home points

10

Question 2

- A 20 year-old female school teacher presents to her primary care doctor with fever and pain / swelling in multiple joints (knees, elbows and wrists). The pain seems to move from joint to joint.
- She is generally healthy, but reports being ill ~3 weeks prior with sore throat and headache which resolved without specific treatment. She has no skin rashes and no lymphadenopathy.
- She denies travel.
- She is sexually active with one male partner, using barrier protection (condoms)
- Labs are notable for elevated ESR and CRP and + ASO titer; pregnancy and HIV tests (4th generation Ag/Ab) are negative.

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Question 2

- Which of the following is the best explanation for her symptoms?

a. Acute HIV infection
b. Mononucleosis due to Epstein Barr Virus
c. Acute rheumatic fever
d. Lemierre's syndrome

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REVISED JONES CRITERIA

For patients with evidence of prior GAS infection*,

Acute Rheumatic fever =

2 MAJOR

OR

1 MAJOR plus 2 MINOR

Major	Minor
Arthritis (usually migratory polyarthritis)	Arthralgia
Carditis (clinical or subclinical)	Fever
Chorea	Elevated ESR or CRP
Erythema marginatum	Prolonged PR interval (unless carditis is a major criterion)
Subcutaneous nodules	

*e.g. rapid strep test; culture; anti-streptolysin-O titer (ASO)

Revision of the Jones Criteria for the diagnosis of acute rheumatic fever in the era of Doppler echocardiography: a scientific statement from the American Heart Association. Circulation. 2015

Question 3

- A 34 year old male with a history of injection drug use presents to the emergency room with a 2 day history of progressive muscle weakness and blurry vision. He also notices some difficulty swallowing.
- On examination, vital signs are normal, but the patient is noted to have ptosis and sluggish pupillary responses as well as slurred speech.

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Question 3

- Which of the following treatment(s) are recommended?

A. Plasmapheresis
B. Naloxone
C. Tetanus antitoxin
D. Botulinum antitoxin

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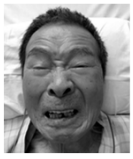
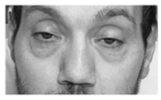
Explanation



Tetanus: sardonic smile



Botulism: ptosis

- Plasmapheresis – for Lambert-Eaton syndrome, immune attack of neuromuscular junction (chronic; associated with lung cancer)
- Naloxone – for opioid intoxication (respiratory suppression, *constricted* pupils)
- Tetanus antitoxin – for tetanus (rigid paralysis)
- Botulinum antitoxin – for botulism

https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(19)31137-7/fulltext
https://www.nejm.org/doi/pdf/10.1056/NEJMcp1003352

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Botulism

https://phil.cdc.gov/details.aspx?pid=2107

- Caused by **Clostridium botulinum* (gram positive, strict anaerobe with subterminal spore; found in soil)
- Symptoms due to TOXINS which prevent release of acetylcholine in neuromuscular junction
- Leads to flaccid paralysis of motor and autonomic nerves, beginning with the cranial nerves (*descending* weakness)
- DX: culture or detection of toxin

**other neurotoxin producing species of Clostridium: C. butyricum, or C. baratii*

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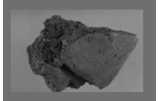
Botulism

Foodborne

Infant



Wound (black-tar heroin)

Iatrogenic

Peak CM, Rosen H, Kamali A, et al. Wound Botulism Outbreak Among Persons Who Use Black Tar Heroin — San Diego County, California, 2017–2018. MMWR Morb Mortal Wkly Rep 2019
https://www.cdc.gov/botulism/
Principles and Practice of Infectious Diseases, 9th ed.

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Botulism treatment

Supportive care	Antitoxin
• Ventilatory support for respiratory compromise • Wound debridement	• Botulinum anti-toxin (adults) Or • Botulinum immune globulin (infants)

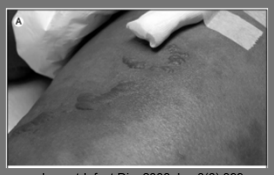
https://www.cdc.gov/botulism/
Principles and Practice of Infectious Diseases, 9th ed.

- Cause: *Clostridium botulinum* toxin impedes acetylcholine release from neuromuscular junction
- Epidemiology: food (home canned veggies / fruits / fish); infant (honey); wound (black-tar heroin); iatrogenic (rare)
- Clinical presentation: *descending flaccid paralysis*, starting with *cranial nerves* (ptosis, blurred vision, slurred speech)
- Diagnosis: clinical; confirmed by culture or ID of toxin
- Treatment: *antitoxin* plus supportive care; wound debridement

Botulism

Take home points

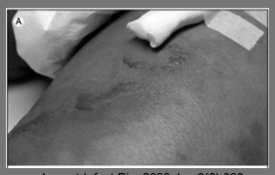
Question 4



Lancet Infect Dis. 2008 Jun;8(6):399.

- A 44 year-old male with a history of cirrhosis due to Hepatitis B and alcoholism presents with fever, lethargy and leg swelling. On exam, he is febrile, hypotensive and tachycardic. Skin exam is as pictured.

Question 4

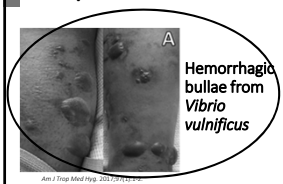


Lancet Infect Dis. 2008 Jun;8(6):399.

- The patient's clinical syndrome was most likely caused by which of the following exposures?

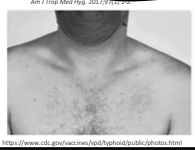
A. Rat bite
B. Tick bite
C. Consumption of raw oysters
D. Consumption of raw egg

Explanation



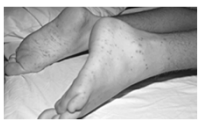
Hemorrhagic bullae from *Vibrio vulnificus*

Am J Trop Med Hyg. 2017;97(1):3-5.



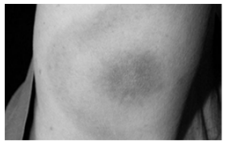
Rose spots from *Salmonella typhi*

https://www.cdc.gov/vaccines/vpd/typhoid/public/photos.html



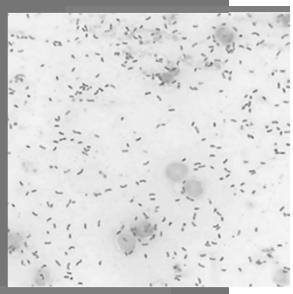
Petechial rash from *Streptobacillus moniliformis* (rat bite fever); fever, rash, migratory arthritis

CMAJ. 2006 Aug 15;175(4):354.



Erythema migrans due to *Borrelia burgdorferi* (tick borne)

https://www.cdc.gov/lyme/signs_symptoms/rashes.html

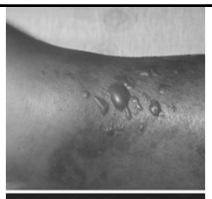


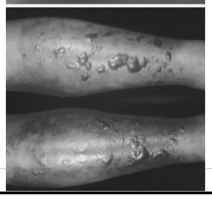
Vibrio vulnificus

- Gram-negative, curved bacillus
- Halophilic (salt loving) – *brackish water*
- Cause: *consumption of raw seafood (oysters) or contamination of open wound*
- At risk: *liver disease* (cirrhosis); iron overload; renal disease; immunosuppression
- High mortality

Beatty NL, Marquez J, Al Mohajer M. Skin Manifestations of Primary *Vibrio vulnificus* Septicemia. *Am J Trop Med Hyg.* 2017;97(1):1-2.

Clinical presentation and treatment





- Abrupt onset
- Fever, hypotension
- Rapidly progressive skin lesions: erythema → ***hemorrhagic bullae*** → necrosis
- Bacteremia common
- Treatment:
  - Fluoroquinolone plus 3rd generation cephaloporin
  - Debridement

Principles and Practice of Infectious Diseases, 9th ed.

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- Epidemiology: consumption of raw seafood; contamination of wound (organism lives in warm, brackish water)
- At risk: liver disease, iron overload (also renal; immune suppression)
- Clinical presentation: rapidly progressive skin lesions with *hemorrhagic bullae; fever, hypotension, sepsis*
- Diagnosis: clinical; blood cultures usually positive
- Treatment: fluoroquinolone plus 3rd generation cephalosporin; debridement

Vibrio vulnificus

Take home points

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Question 5

- A 23-year-old otherwise healthy college student presents to the university clinic with a non-productive, intermittent cough for 3 weeks. She describes spells during which she coughs repeatedly for several minutes. On two occasions she vomited after coughing.
- She reports episodes of sweating but has had no fever or other constitutional symptoms.
- She has tried several cough medicines, but nothing seems to help. She knows several other students who have been "coughing for weeks," and says the showers in her dorm are "covered with mold."

27

Question 5

- She is afebrile and has a completely normal exam.
- Her CBC is normal; chest x-ray is normal.
- Specific nasopharyngeal culture for *Bordetella pertussis* is negative.

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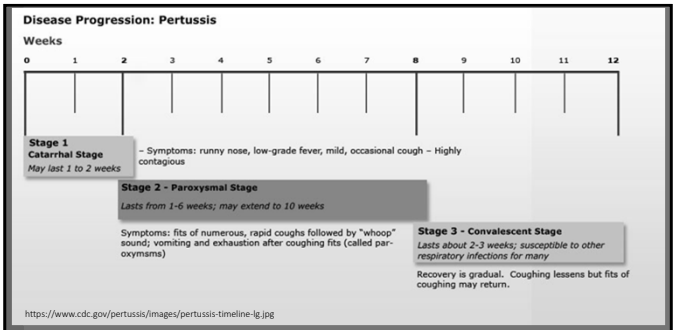
Question 5

- Which one of the following is the most likely cause of her illness?

A. Bordetella pertussis
B. Chlamydophila pneumoniae
C. Respiratory syncytial virus
D. Mycoplasma pneumoniae

29



Pertussis: clinical stages

35 – Kitchen Sink: Syndromes Not Covered Elsewhere

Speaker: Stacey Rose, MD

Pertussis diagnosis – no perfect test

Clinical case criteria (in absence of alternate dx):

- cough illness lasting ≥2 weeks, with at least one of the following:
  - Paroxysms of coughing; **OR**
  - Inspiratory whoop; **OR**
  - Post-tussive vomiting; **OR**
  - Apnea (with or without cyanosis)

Test	*Sensitivity (%)*	*Specificity (%)*	*Advantages*	*Disadvantages*
Culture	15	100	Specific; confirms diagnosis; most useful in first two weeks	Fastidious growth requirements; delayed results; inaccurate in late stages of disease
Polymerase chain reaction	45	85	Confirms diagnosis; rapid results; most accurate in early stages of disease	Sensitivity declines in late stages of disease
Serology	65	89	Accurate in late stages of disease	Cannot confirm acute infection (can be positive because of past infection or immunization); testing method not standardized

https://www.cdc.gov/nndss/conditions/pertussis/case-definition/2020/
Am Fam Physician. 2013 Oct 15;88(8):507-514.

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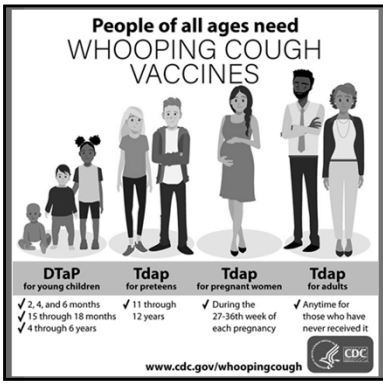
Treatment and post exposure prophylaxis

- TREAT with **macrolide** (e.g. azithromycin) if **within 3 weeks of onset**
- Treat within 6 weeks of onset for infants or pregnant women

- **POST EXPOSURE PROPHYLAXIS (PEP) given to household members and contacts at risk of severe infection (within 3 weeks of exposure)**

https://www.cdc.gov/pertussis/

32



Pertussis Vaccination

for adults:
-wound mgmt.
-*each* pregnancy
-booster q 10 yrs

- Epidemiology: in past infants / kids; now young adults (waning immunity?)
- ***Severe disease: infants, pregnant women***, lung disease
- Clinical presentation: ***cough*** lasting 2+ weeks plus ***paroxysmal cough***, ***inspiratory whoop***, ***post-tussive vomiting or apnea***
  Stages:
  - *catarrhal*: URI
  - *paroxysmal*: coughing fits / whoop
  - *convalescent*: gradual lessening of cough
- Diagnosis: clinical; culture (insensitive), PCR, serology (late)
- Treat with ***macrolide within 3 wks*** of onset
- ***PEP*** for household contacts / at risk of severe dz ***within 3 wks*** of exposure

Bordatella pertussis

Take home points

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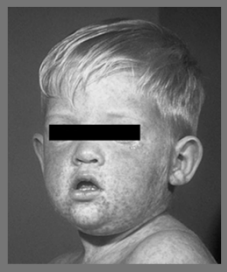
Question 6



- A 25-month old child is brought to the emergency room for ***fever, rash and fussiness***. The rash ***started on the face and spread to trunk*** and extremities within 1-2 days.
- 10 days ago, the family returned to the United States following a 1-month trip to Tanzania (where the parents conduct research as university professors).
- The child's 4-year old sibling is also ill, with cough and watery eyes, but does not have a rash.
- The parents do not believe in vaccination for their children due to fear of adverse effects (autism).

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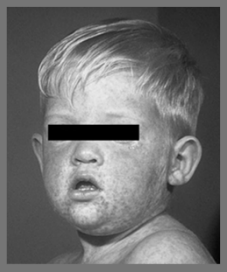
Question 6



- Which of the following could have prevented the development of the patient's illness?

A. Varicella zoster virus vaccination
B. Measles, mumps, rubella vaccination
C. Mefloquine prophylaxis
D. Influenza vaccination

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35 – Kitchen Sink: Syndromes Not Covered Elsewhere

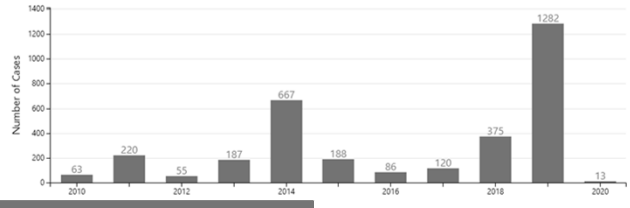
Speaker: Stacey Rose, MD

Measles (Rubeola) in the US

Mostly in <u>unvaccinated</u> individuals, related to international travel or an imported case

Number of measles cases reported by year

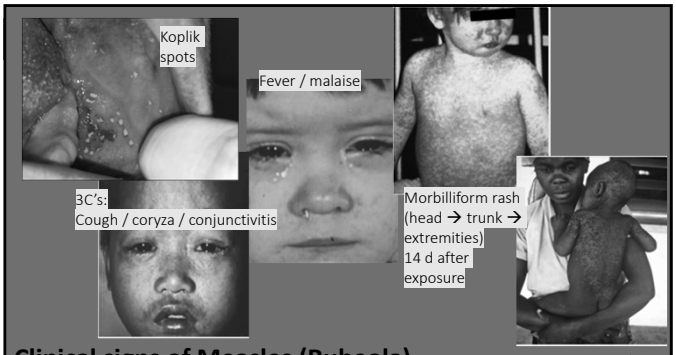
2010-2020*(as of December 31, 2020)



https://www.cdc.gov/measles/cases-outbreaks.html

37

Clinical signs of Measles (Rubeola)



Principles and Practice of Infectious Diseases, 9th ed.
https://www.cdc.gov/measles/symptoms/photos.html

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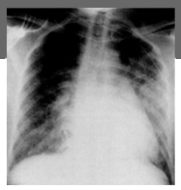
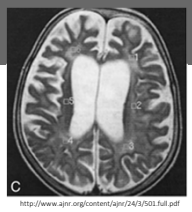
Complications of measles



Chest. 1993 May;103(5):1625-6



http://www.ajnr.org/content/ajnr/24/3/501.full.pdf

Acute

- 1 of 1000 children – death from respiratory / neurologic complications

Delayed

- rare but fatal - Subacute Sclerosing Pan-Encephalitis (SSPE)
- 7 yrs after infection; degenerative disease, seizures

Principles and Practice of Infectious Diseases, 9th ed.
https://www.cdc.gov/measles/

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Diagnosis

Don't wait for confirmation: isolate patients with suspected infection (airborne)

Clinical – high suspicion in unvaccinated individuals

Serum: measles-specific IgM antibody

*Respiratory specimen (nasopharyngeal swab): measles RNA by real-time polymerase chain reaction (RT-PCR)

https://www.cdc.gov/measles/

*may also be detected in urine

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Prevention: Measles-mumps-rubella (MMR) Vaccination

CHILDREN
1st dose: 12-15 mos
2nd dose: 4-6 years

ADULTS born after 1957 without evidence of immunity (at least one dose)

COLLEGE STUDENTS without evidence of immunity
(two doses, 28 d apart)

INTERNATIONAL TRAVELERS (6 mos and older) without evidence of immunity

Principles and Practice of Infectious Diseases, 9th ed.
https://www.cdc.gov/measles/

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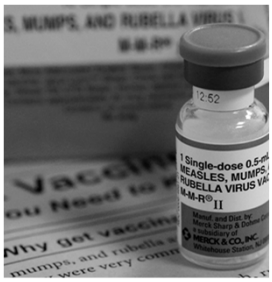
Immunity and post exposure prophylaxis

Who is immune to measles?	What is the recommendation for PEP?
• written documentation of adequate vaccination • Lab evidence of immunity • Lab confirmation of measles infection • Born before 1957	• Non-immune persons with measles exposure should receive ***either*** **MMR vaccine** (within 72 hours of exposure) **or Immune globulin (IG)** within 6 days of exposure • **Do not co-administer** MMR vaccine and IG (invalidates vaccine)



Principles and Practice of Infectious Diseases, 9th ed.
https://www.cdc.gov/measles/
https://www.washingtonpost.com/health/2019/04/29/how-does-measles-spread-other-frequently-asked-questions-about-measles/

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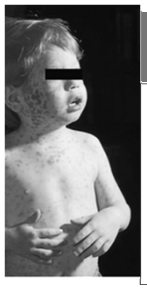
35 – Kitchen Sink: Syndromes Not Covered Elsewhere

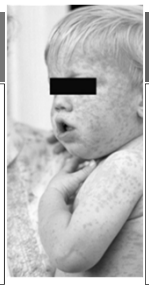
Speaker: Stacey Rose, MD

"German measles" (Rubella) vs. Measles (Rubeola)



German Measles (Rubella)

- Caused by RNA virus of *Togaviridae* family
- Often **mild** / asymptomatic
- Viral prodrome → maculopapular rash which spreads from head to extremities, +/- **arthritis**
- Transmitted in utero (**congenital** rubella): deafness, cataracts, glaucoma, heart disease, cognitive defects



Measles (Rubeola)

- Caused by RNA virus of Paromyxovirus family
- **Severe** disease with complications including death
- Viral prodrome → **cough / coryza / conjunctivitis, fever, Koplik spots** → maculopapular rash which spreads from head to extremities

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- Cause: Rubeola (RNA virus of Paramyxovirus family)
- Epidemiology: worldwide distribution; *in US, seen in unvaccinated persons due to travel or exposure to imported case*
- Clinical presentation: three C's (*cough, coryza, conjunctivitis*), Koplik spots, morbilliform rash spreading from head → trunk → extremities (14 d after exposure)
- Diagnosis: clinical; serum IgM; PCR on respiratory swab (or urine)
- Treatment: supportive care, Vit A for severe cases in children
- Post-exposure ppx: vaccination (within 72 h) or IG (within 6 days)

Measles (Rubeola)

Take home points

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Question 6

- A 19 year old male, previously healthy, complained of abdominal pain and nausea after eating leftovers from a restaurant.
- Within several hours, his symptom progressed to include weakness, headache and neck stiffness.
- Five hours later, he had developed purplish skin discolorations and a friend brought him to the emergency room for evaluation.

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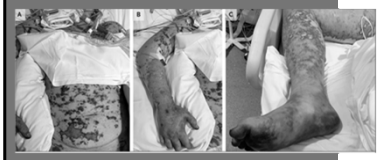
Question 6



- Upon arrival to the hospital, he was noted to be febrile (40.4 degrees Celsius), tachycardic (HR 166), and tachypneic (RR 28), with BP 120/53, and with rapidly progressive reticular, purpuric rash.
- Within 24 hours, gram stain of blood cultures showed gram-negative diplococci.

N Engl J Med. 2021 Mar 11;384(10):953-963.

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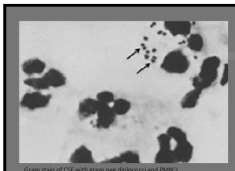
Question 6

- Which of the following is the most likely diagnosis?

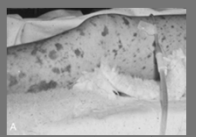
A. Meningococcemia
B. Disseminated *Streptococcus pneumonia*
C. Disseminated gonorrhea
D. Secondary syphilis

N Engl J Med. 2021 Mar 11;384(10):953-963.

47



Gram stain of CSF with gram neg diplococci and PMN's
https://www.cdc.gov/meningitis/lab-manual/chpt06-culture-id.html



Principles and Practice of Infectious Diseases, 9th ed

Invasive meningococcal disease (*N. meningitidis*)

- Main manifestations:
  - *meningococcemia*
  - *acute meningitis*
- **Petechial or purpuric rash** in 40-80% of meningococcemia cases
- Fulminant disease **can progress to death within hours**
- Treat with 3rd generation cephalosporin (**ceftriaxone or cefotaxime**) and supportive care

Principles and Practice of Infectious Diseases, 9th ed.
https://www.cdc.gov/meningococcal/clinical-info.html

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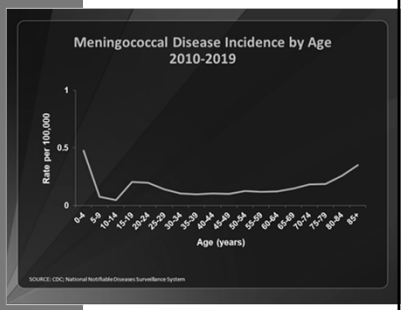
35 – Kitchen Sink: Syndromes Not Covered Elsewhere

Speaker: Stacey Rose, MD

Epidemiology

In the US, infants, young adults, and adults >80 years of age have the highest rates of meningococcal disease



https://www.cdc.gov/meningococcal/surveillance/index.html

Transmission and risk factors

https://www.cdc.gov/meningococcal/about/causes-transmission.html

Transmission: person to person (respiratory droplets, oral secretions) from asymptomatic carriage or invasive disease

HOST factors: asplenia; terminal complement deficiencies (native or acquired, such as use of complement inhibitors: eculizumab or ravulizumab)

ENVIRONMENTAL factors: crowded conditions (dorms, military barracks; Hajj and Umrah pilgrimages); daycare / preschool facilities; microbiologists

ANTIBIOTIC	CONSIDERATIONS
Rifampin	Drug interactions
Ceftriaxone	Recommended in pregnancy
Ciprofloxacin	Not generally recommended for persons < 18 yrs
Azithromycin	Limited data

https://www.cdc.gov/vaccines/pubs/surv-manual/chpt08-mening.html

Chemoprophylaxis for:

- Household members
- Childcare center contacts
- Anyone directly exposed to an infected person's oral secretions (kissing; mouth to mouth resuscitation; intubation) within 7 d before symptom onset
- HCW with exposure to respiratory secretions of infected patient

BOX 1. Meningococcal vaccination recommendations — Advisory Committee on Immunization Practices, United States, 2020

ACIP recommends MenACWY vaccination for the following groups:

- Routine vaccination for adolescents aged 11 or 12 years, with a booster dose at age 16 years.
- Routine vaccination of persons aged ≥2 months at increased risk for meningococcal disease (dosing schedule varies by age and indication, and interval for booster dose varies by age at time of previous vaccination):
  - Persons with certain medical conditions including anatomic or functional asplenia, complement component deficiencies (e.g., C3, C5-C9, properdin, factor H, or factor D), complement inhibitor (e.g., eculizumab [Soliris] or ravulizumab [Ultomiris]) use, or human immunodeficiency virus infection.
  - Microbiologists with routine exposure to *Neisseria meningitidis* isolates.
  - Persons at increased risk during an outbreak (e.g., in community or organizational settings, and among men who have sex with men [MSM]).
  - Persons who travel to or live in countries in which meningococcal disease is hyperendemic or epidemic.
  - Unvaccinated or undervaccinated first-year college students living in residence halls.
  - Military recruits.
- Booster doses for previously vaccinated persons who become or remain at increased risk.

ACIP recommends MenB vaccination for the following groups:

- Routine vaccination of persons aged ≥10 years at increased risk for meningococcal disease (dosing schedule varies by vaccine brand; boosters should be administered at 1 year after primary series completion, then every 2–3 years thereafter):
  - Persons with certain medical conditions, such as anatomic or functional asplenia, complement component deficiencies, or complement inhibitor use.
  - Microbiologists with routine exposure to *N. meningitidis* isolates.
  - Persons at increased risk during an outbreak (e.g., in community or organizational settings, and among MSM).
- Vaccination of adolescents and young adults aged 16–23 years with a 2-dose MenB series on the basis of shared clinical decision-making. The preferred age for MenB vaccination is 16–18 years. Booster doses are not recommended unless the person becomes at increased risk for meningococcal disease.
- Booster doses for previously vaccinated persons who become or remain at increased risk.

Abbreviations: ACIP = Advisory Committee on Immunization Practices; MenACWY = quadrivalent (serogroups A, C, W, Y) meningococcal conjugate vaccine; MenB = serogroup B meningococcal vaccine.

https://www.cdc.gov/mmwr/volumes/69/rr/pdfs/rr6909a1-H.pdf

Immunization

- Recommendations revised in 2020

Summary:

- MenACWY for all adolescents plus persons at increased risk due to host or environmental factors
- MenB for those at increased risk due to host or environmental factors; shared decision making for others

- Epidemiology:
  - Host (*asplenia*; *complement deficiencies*; *complement inhibitors* – eculizumab or ravulizumab)
  - Environmental (crowded conditions – dorms, barracks, day care)
  - Person to person transmission from oral / respiratory droplets
- Clinical presentation: *acute meningitis* or *meningococcemia*; rapidly progressive, *petechial / purpural rash*
- Treatment: ceftriaxone or cefotaxime; immunize for prevention and during outbreaks
- Chemoprophylaxis for close contacts within 7 d of exposure: *rifampin*, *ceftriaxone* (pregnancy), or *ciprofloxacin* (adults)

Invasive meningococcal disease (*Neisseria meningitidis*)

Take home points

Kitchen Sink summary

Whipple's:

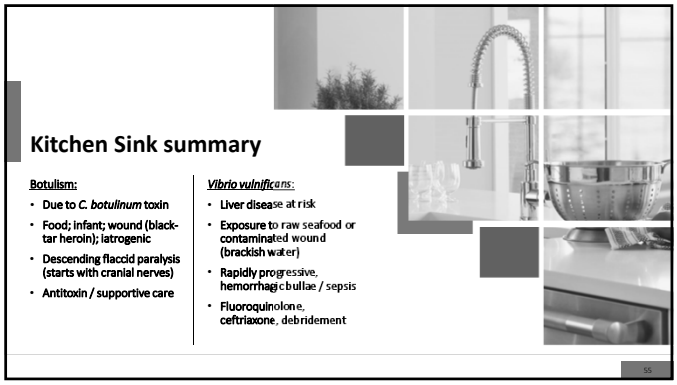
- Classic: arthralgia, diarrhea, weight loss
- Dx with duodenal bx (PAS+, foamy macrophages)
- or PCR of tissue (heart valve for endocarditis)

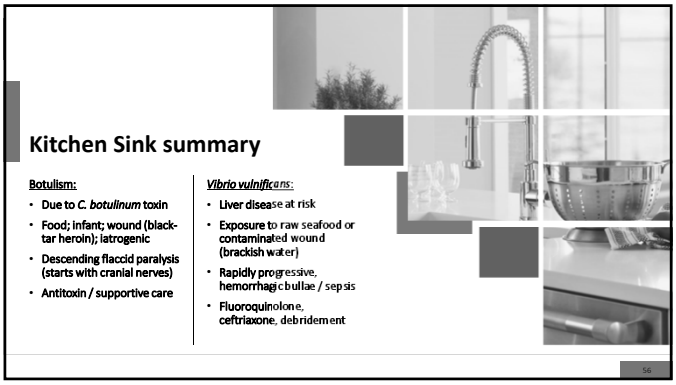
Acute Rheumatic fever:

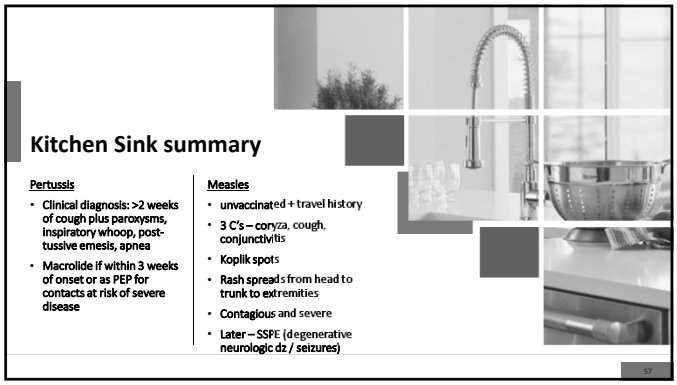
- Kids / young adults with migratory polyarthritis, carditis, chorea, subcutaneous nodules, erythema marginatum following GAS pharyngitis
- Monthly IM penicillin prophylaxis for 10 years or to age 40 if carditis + residual valvular disease

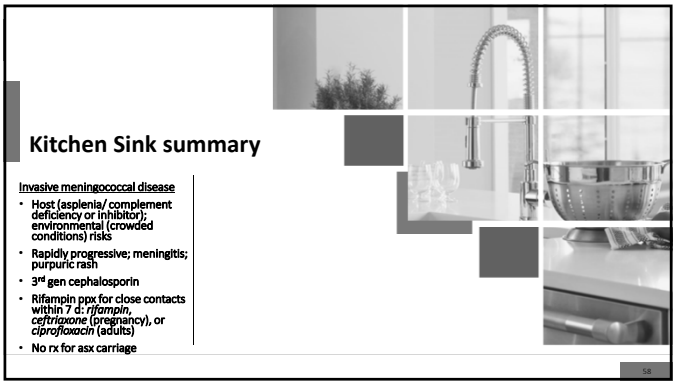
35 – Kitchen Sink: Syndromes Not Covered Elsewhere

Speaker: Stacey Rose, MD









36

Immunizations: Domestic, Travel, and Occupational

Dr. Shireesha Dhanireddy

36 – Immunizations: Domestic, Travel, and Occupational

Speaker: Shireesha Dhanireddy, MD

Immunizations:
Domestic, Travel, and Occupational

Shireesha Dhanireddy, MD
Professor, Allergy & Infectious Diseases
University of Washington

Disclosures of Financial Relationships with Relevant Commercial Interests:

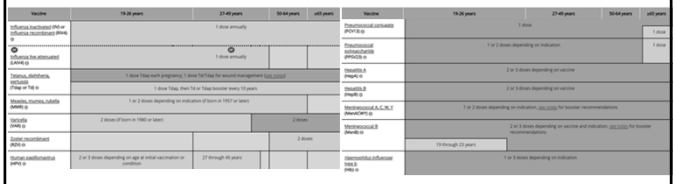
- **None**

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

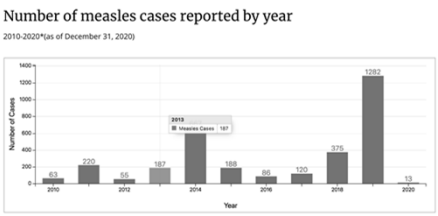
Question: Measles Vaccine

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

- 90% of cases in unvaccinated or unknown states individuals
- As of June 2021, 2 confirmed cases of measles in US in 2021
- Vaccine very effective!
  - 93% effective after 1 dose
  - 97% effective after 2 doses
  - Immunity is felt to be lifelong*



Measles Vaccine

<u>Evidence of presumptive immunity</u>

- 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: HPV Vaccine

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

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 for everyone through age 26 if not previously vaccinated
- **Vaccine not recommend for everyone older than 26 years**

BUT

- **May consider for ages 27 through 45 through shared decision making**

* Vaccination series may be started at 9 years of age

MMWR 2019;68:698-702

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: 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 (years)	Disease Incidence Cases/100,000 (number of cases)	Death Rate Deaths/100,000 (number of deaths)
<1	17.7 (702)	0.20 (8)
1	12.6 (500)	0.20 (8)
2–4	5.07 (606)	0.13 (16)
5–17	1.23. (659)	0.00 (0)
18–34	2.33 (1,757)	0.08 (60)
35–49	6.48 (3,982)	0.46 (284)
50–64	14.8 (9,326)	1.47 (932)
65–74	18.0 (4,952)	2.17 (597)
75–84	29.0 (4,042)	4.53 (631)
≥85	45.4 (2,856)	11.4 (718)
Total	9.14 (29,382)	1.01 (3,254)

Gierke R et al. CDC Vaccine Preventable Diseases Surveillance Manual

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

36 – Immunizations: Domestic, Travel, and Occupational

Speaker: Shireesha Dhanireddy, MD

Pneumococcal Vaccine Schedule in PWH

Pneumococcal Vaccine-Naïve Adults — ≥ Age 65

PCV13 → (≥ 8 wks) PPSV23 → (≥ 5 yrs) PPSV23 → (≥ 5 yrs) PPSV23

PPSV23-Immunized Adults — ≥ Age 65

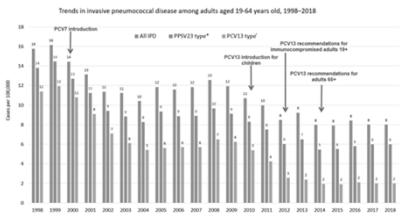
PPSV23 → (≥ 1 yr) PCV13 → (≥ 8 wks) PPSV23 → (≥ 5 yrs) PPSV23

(≥ 5 yrs)

PPSV23 → (≥ 5 yrs) PPSV23 → (≥ 1 yr) PCV13 → (≥ 8 wks) PPSV23

(≥ 5 yrs)

Pneumococcal Vaccine in Adults Age ≥ 65 Yrs



https://www.cdc.gov/pneumococcal/surveillance.html

Revised recommendations in 2019

- Indirect effects of vaccinating children greater than direct effects in vaccinating adults
- PPSV23 still recommended for all adults in this age group
- Shared decision making recommended for use of PCV-13 in this age group (if not immunocompromising condition, CSF leak, cochlear implant if not previously vaccinated)

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® 10 mcg/mL or Engerix® 20 mcg/mL : 3 dose series (0, 1, 6 months) 10 µg/mL IM

OR

- Heplisav®: 2-dose series (0, 1 month) 20 µg in 0.5 mL IM

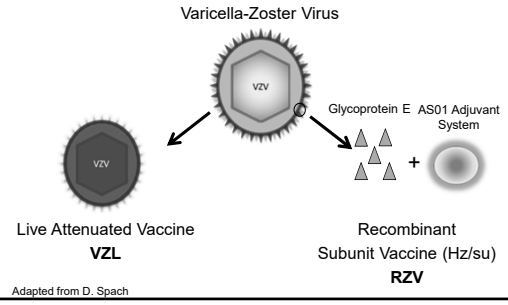
Anti-HBs should be assessed 1-2 months after completion of series. If anti-HBs < 10mIU/mL, then considered non-responder

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?

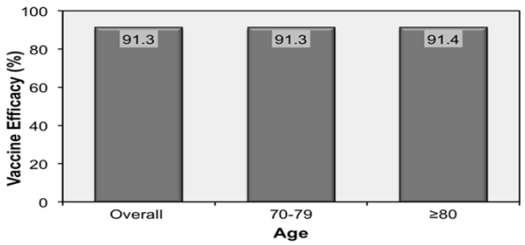
A. Vaccine not indicated given her history of zoster
B. Vaccine not indicated as she has received ZVL
C. Check VZV titer to confirm history. If negative, proceed with vaccination
D. Recommend recombinant zoster vaccine

Zoster Vaccines



Adapted from D. Spach

RZV Efficacy Against First Episode of Zoster in Immunocompetent Patients ≥50



Cunningham AL, et al. N Eng J Med. 2016;375:1019-32.

ACIP Recommendations for Zoster Vaccine

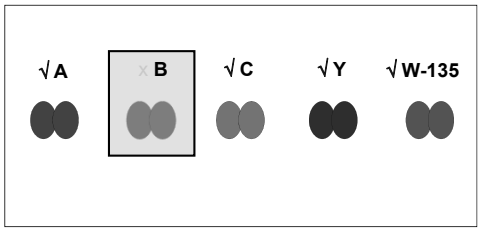
- ZVL is no longer available
- RZV is preferred over ZVL
- Healthy adults ≥ 50 years
  - Regardless of prior h/o HZ
  - No need to wait any specific period of time after HZ to give RZV (just not during acute episode)
- 2 doses, 2-6 months apart
- Wait a minimum of 8 weeks after giving ZVL to give RZV
- ACIP - no recommendation for use in immunocompromised persons (except low-dose immunosuppression)

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

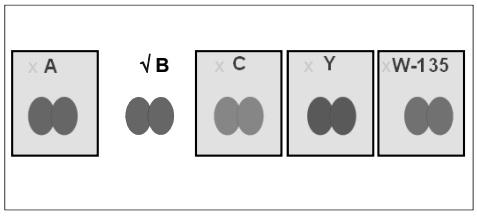
Meningococcal Quadrivalent Vaccines
Serogroups Included in Vaccine: A, C, Y, W-135



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

Meningococcus returns to OSU: Student being treated for disease

BENNETT HALL Corvallis Gazette-Times Oct 27, 2017 0

CDC. MMWR. 2015;64:1171-6.

Eculizumab

- Soliris (eculizumab) 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: 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: 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

36 – Immunizations: Domestic, Travel, and Occupational

Speaker: Shireesha Dhanireddy, MD

Yellow Fever Vaccine

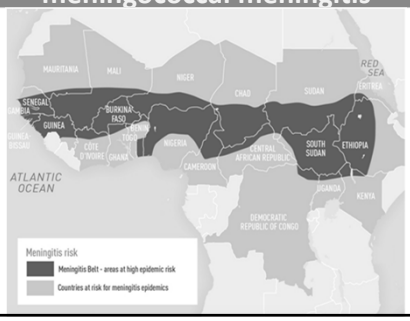
- Recommended for ≥ 9 months traveling to or living in areas of risk or countries requiring vaccine for entry
- In 2014, WHO concluded that single dose fellow fever vaccine provides lifelong protection and no booster needed
  - Exceptions if ongoing risk and the following
    - pregnant when initially vaccinated
    - underwent HSCT after initial vaccine
    - HIV+

Yellow Fever Vaccine

As of April 5, 2021, Yellow Fever Vaccine (YF-VAX®) is available again in US

STAMARIL® (through Expanded Access Program) no longer being shipped to US as of May 6, 2021

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

36 – Immunizations: Domestic, Travel, and Occupational

Speaker: Shireesha Dhanireddy, MD

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

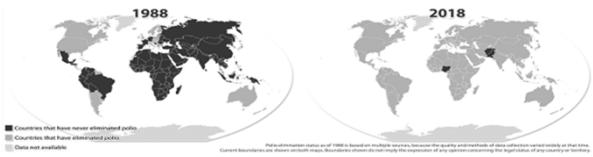
- Vaccine 2 doses, 28 days apart. 2nd dose should be given at least a week prior to travel
- 2 months or older
  - Smaller dose for children under 3
  - ? Booster dose for ≥ 17 years if risk and > 1 year since prior vaccine

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 months)

Polio

- Decreased over 99% since 1988 (350,000 cases)
- 2019: Global cases: 176 wild cases, 368 circulating vaccine-derived
- So far in 2020: 84 wild cases, 208 circulating vaccine-derived
- Pakistan and Afghanistan, as of 2020 Nigeria is not longer on the list



www.polioeradication.org

Polio Vaccine

One dose after age 18 years in addition to the pediatric series of 4 doses if going to area with polio

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 vaccine
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

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*.

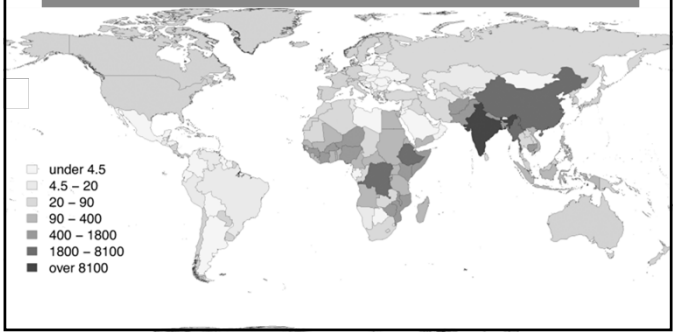
What do you recommend?

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

Human Deaths Attributed to Rabies, 2017



Rabies Vaccine

- Pre-exposure prophylaxis – updated February 2021
  - Vaccination on day 0, 7, ~~and 21 OR 28 days~~

Risk Category	Nature of Risk	Typical Population	Preexposure Recommendations
Continuous	Virus present continuously, often in high concentrations. Specific exposures likely to go unrecognized. Bite, nonbite, or aerosol exposure.	Rabies research laboratory workers; rabies biologics production workers.	Primary course. Serologic testing every 6 months; booster vaccination if antibody titer is below acceptable level.
Frequent	Exposure usually episodic, with source recognized, but exposure also might be unrecognized. Bite, nonbite, or aerosol exposure.	Rabies diagnostic lab workers, spelunkers, veterinarians and staff, and animal-control and wildlife workers in rabies-enzootic areas. All persons who frequently handle bats.	Primary course. Serologic testing every 2 years; booster vaccination if antibody titer is below acceptable level.
Infrequent	Exposure nearly always episodic with source recognized. Bite or nonbite exposure.	Veterinarians and terrestrial animal-control workers in areas where rabies is uncommon to rare. Veterinary students. Travelers visiting areas where rabies is enzootic and immediate access to appropriate medical care including biologics is limited.	Primary course. No serologic testing or booster vaccination.
Rare (population at large)	Exposure always episodic with source recognized. Bite or nonbite exposure.	U.S. population at large, including persons in rabies-epizootic areas.	No vaccination necessary.

May also give booster dose between 21 days and 3 years of completing 2-dose series

Rabies Vaccine

- 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: 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

36 – Immunizations: Domestic, Travel, and Occupational

Speaker: Shireesha Dhanireddy, MD

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)

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

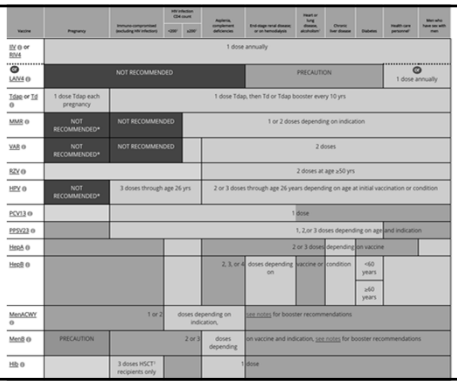
Precautions for use in:

•Individuals with latex allergy

•H/o anthrax

•Immunocompromised individuals

•Moderate to severe illness from anthrax



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

If CD4 count > 200

Inactivated influenza

Tdap

Pneumococcal

Meningococcal

HBV

HPV

MMR

Varicella

If CD4 count < 200

Inactivated influenza

Tdap

Pneumococcal

Meningococcal

HBV

HPV

MMR

Varicella

Speaker: Shireesha Dhanireddy, MD

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 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)

Post-Vaccine HBV serologies

- Serologic testing not necessary after routine vaccination of infants, children, or adults
- Anti-HBs recommended for the following:
  - Infants born to HBsAg–positive or unknown mothers (check HBsAb and sAg)
  - Health care personnel and public safety workers
  - Hemodialysis patients
  - Persons with HIV
  - Other immunocompromised persons (e.g., hematopoietic stem-cell transplant recipients or persons receiving chemotherapy)
  - Sex partners of HBsAg-positive persons

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

37

Acute Hepatitis

Dr. David L. Thomas

37 – Acute Hepatitis

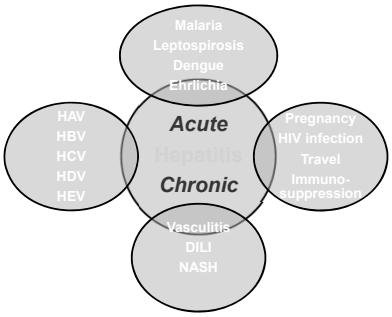
Speaker: David Thomas, MD

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

- Data and Safety Monitoring Board: Merck
- Advisory Board: Merck



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
- PMH – ETOH, IDU
- SH – homeless
- Baltimore for 20 years, previously Missouri

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

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. SARS-CoV-2

Leptospirosis

1. **Exposure to fresh water (eg rafting in Hawaii or Costa Rico) OR rats (Baltimore)**

Leptospirosis

2. **Systemic findings** (conjunctival suffusion, kidney, skin, muscle, lungs, liver)

ddx: liver and muscle: flu, adeno, EBV, HIV, malaria, Rickettsia/Ehrlichiosis, tularemia, TSS, coxsackie

Leptospirosis

3. **Bilirubin fold change > ALT**

Acute Hepatitis in Uganda

- 42 year old female has malaise and RUQ pain; she just returned from 2 months working 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; Hb 13.4 g/dl; TB 3.2 mg/dl; WBC 3.2k nl differential.

Acute hepatitis in Uganda

Which test result is most likely positive?

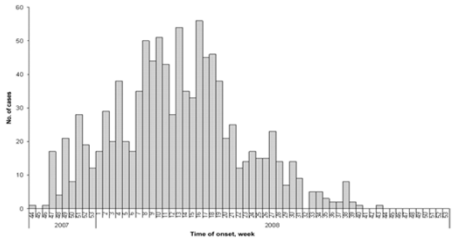
A. Ebola PCR
B. IgM anti-HEV
C. IgM anti-HAV
D. Schistosomiasis "liver" antigen
E. 16S RNA for Rickettsial organism

1. Vaccination works vs immune globulin to prevent hepatitis A *up to 14d 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

2. There are HEV outbreaks, eg. North-Ugandan IDP Camp



Teshale CID 2010

3. Hepatitis E: Epidemiologic Clues

- –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

4. Hepatitis E: Clinical Clues

- –Fatalities in pregnant women
- –Can be chronic in transplant (rarely in HIV)
- –GBS and neurologic manifestations (vs other hep viruses); pancreatitis
- –Diagnosis: RNA PCR; IgM anti-HEV
- –Treatment: ribavirin for chronic

Acute Hepatitis at ID Week

- 42 year old homeless male approaches a group of ID fellows while attending ID Week in San Diego.
- One fellow noticed jaundice and suggested he seek medical testing. With what diagnosis was the fellow most concerned?

Acute hepatitis at ID week

Fellow worried about?

A. HAV
B. HBV
C. Delta
D. HCV
E. HEV

1. Hepatitis A: Key Epidemiologic Clues – People, Places and Things (Foods)

Homelessness and Hepatitis A—San Diego County, 2016–2018

Corey M. Peak,[1,2,3] Sarah S. Stous,[2] Jessica M. Healy,[2] Megan G. Hofmeister,[1] Yulin Lin,[1] Sumathi Ramachandran,[1] Monique A. Foster,[1] Annie Kao,[2] and Eric C. McDonald[2]

[1]Epidemic Intelligence Service, Centers for Disease Control and Prevention, Atlanta, Georgia; [2]County of San Diego Health and Human Services Agency, and [3]Division of Global Migration and Quarantine, Centers for Disease Control and Prevention, San Diego, California; and Divisions of [4]Foodborne, Waterborne, and Environmental Diseases, and [5]Viral Hepatitis, Centers for Disease Control and Prevention, Atlanta, Georgia

Morbidity and Mortality Weekly Report (*MMWR*)

CDC • MMWR

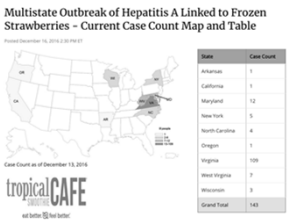
Notes from the Field: Increase in Reported Hepatitis A Infections Among Men Who Have Sex with Men — New York City, January–August 2017

Weekly / September 22, 2017 / 66(37);999–1000

37 – Acute Hepatitis

Speaker: David Thomas, MD

1. Hepatitis A: Key Epidemiologic Clues – People, Places and Foods



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

2. Hepatitis A: Key Clinical Clues

- 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

3. Vaccination to Prevent Hepatitis A

- ***Pre-exposure:*** **vaccinate**
  - **HOW: Inactivated vaccines USA (HAVRIX,VAQTA)(TWINRIX)**
  - **WHOM: 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'**
  - **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

Vaccination works vs immune globulin to prevent hepatitis A up to 14d *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)
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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

Acute Viral Hepatitis B Clues

- **Most linked to sex, drugs, nosocomial**
  - –**Nosocomial (fingerstick devices, etc)**
  - –**Most transmissible (HBV>HCV>HIV)**
- **Clinical**
  - –**Acute immune complex disease possible**
  - –**Diagnose: IgM anti-core, HBsAg and HBV DNA**
  - –**New infection vs reactivation (both can be IgM pos)**

Acute Viral Hepatitis Delta will be with HBV

- **HDV**
  - –**HBV coinfection**
    - **Fulminant with acute HBV**
  - –**HBV superinfection**
    - **Acute hepatitis in someone with chronic HBV**
  - –**Test for HDV RNA**

Acute Viral Hepatitis C clues

- **HCV**
  - –IDU link (hepatitis in Appalachia)
  - –HIV pos MSM
  - –Acute RNA pos but AB neg or pos
  - –60-80% persist: more in men, HIV pos, African ancestry, INFL4 gene intact

Cox CID 2005

Hepatitis in a pilot

- 70 y/o pilot presents with 1 week of fever, diarrhea and sweats, then "collapses"
- 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, 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)

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 with liver, lung, renal, skin, CNS disease but tend to be cholestatic vs Rickettsia/Ehrlichia

37 – Acute Hepatitis

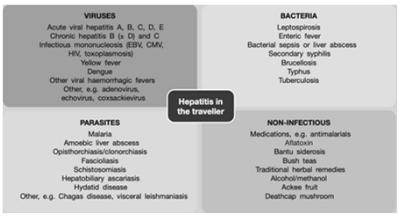
Speaker: David Thomas, MD

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

Especially 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 in Pregnancy

- **25yo G1P1 34 wks gestation with 1wk fever, chills, abd pain. 1 wk earlier cephalexin for GpB Strep.**
- **T 102; other vitals and exam as expected**
- **Plt 143K; Hb 8.6; WBC 6.4K 20% bands; glucose, creat and INR WNL; ALT 279; AST 643; TB 0.8.**
- **Hosp day 4:PLT 83K; PT 16; PTT 44; AST 2,240; ALT 980; BR nl; Fibrinogen NL;**

Allen OB GYN 2005

Hepatitis in pregnancy

What is the best diagnosis?

A. HELLP
B. Acute fatty liver of pregnancy
C. Atypical DRESS from cefelexin
D. HSV infection
E. HEV

Hepatitis in pregnancy

1. Rule out HSV

~50% have muco-cutaneous lesions

High mortality without acyclovir

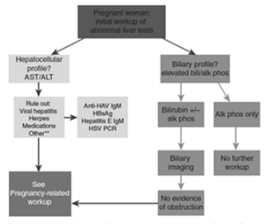


Figure 1. Workup of abnormal liver test in pregnant woman. **Other differential diagnosis to consider if clinically appropriate: AIH, Wilson disease.

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)

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.**

Fulminant Hepatitis

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

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

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

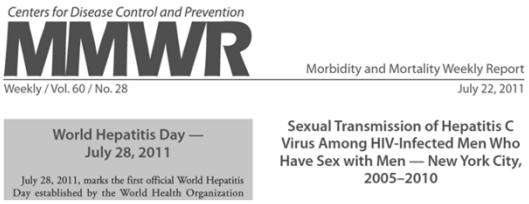
Which of the following is the most likely cause of hepatitis:

A. toxicity from the RAL
B. acute HCV infection
C. IRIS
D. resistant HBV
E. HDV

37 – Acute Hepatitis

Speaker: David Thomas, MD

Recognize acute HCV in HIV POS MSM


Centers for Disease Control and Prevention
MMWR
Morbidity and Mortality Weekly Report
Weekly / Vol. 60 / No. 28
July 22, 2011

World Hepatitis Day — July 28, 2011

July 28, 2011, marks the first official World Hepatitis Day established by the World Health Organization

Sexual Transmission of Hepatitis C Virus Among HIV-Infected Men Who Have Sex with Men — New York City, 2005–2010

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)

Thanks and good luck on the test!

Questions:

Dave Thomas

–dthomas@jhmi.edu

BREAK

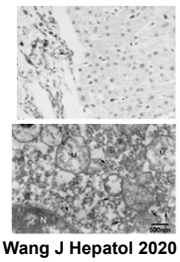
SLIDES BEYOND THIS ARE FOR THE PRESENTER'S RECORDS; NOT TO BE DISTRIBUTED OR SHOWN

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)
$\geq 0.8 \times 10^9$/L	654 (83.0)
$<0.8 \times 10^9$/L	134 (17.0)
Platelets, $\times 10^9$/L	181 (147-221)
$\geq 100 \times 10^9$/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

Case 6. Hepatitis in Pregnancy

- 24yo 33 wks gestation with nausea and vomiting and RUQ pain. Taking acetaminophen 1gm q6; 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.

Case 4: Tired and jaundiced

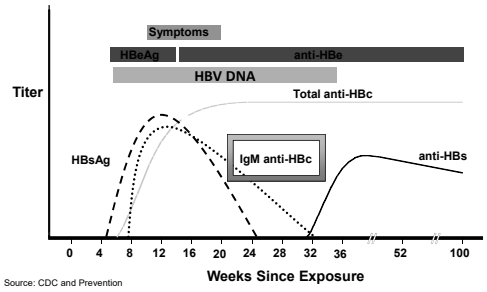
- 27 year old male presents with fatigue and dark urine. Hx recent sexual exposures with other men.
- No fever, vitals normal. Mild icteric. ALT 1945 IU/ml; AST 1239 IU/ml; TB 4.2 mg/dl; WBC 3.2k nl diff.
- Total HAV pos; HAV IgM neg; HCV RNA neg; IgM anti-HBc pos; HBsAg pos; RPR neg; HIV 4th gen neg
- Ptr was tested and is HBsAg and anti-HBs neg

Question #4

Which is easiest to justify medically?

A. Repeat HBsAg and anti-HBs testing for partner
B. HBIG and HBV vaccine for partner
C. HBV vaccine for partner
D. Entecavir 0.5 mg/d for patient
E. TAF for partner

Diagnose acute HBV infection with IgM anti-HBc



2. No treatment indicated for acute HBV (unless fulminant)

3. Prevention by vaccine +/ HBIG

- HBsAg and anti-HBs screening of partners
- Tools: HBIG and/or HBV vaccine (USA)
  - Engerix, Recombivax, Heplisav-B, Pediarix, Twinrix
- Post-exposure:
  - Vaccinated and anti-HBs >10 ever, done*
  - No hx vaccine and/or anti-HBs >10, HBIG and vaccinate

*may be exception for patients with immunosuppression like HIV or dialysis

Schillie MMWR 2018

3. Prevention by vaccine +/ HBIG con't

- Pre-exposure:
  - no vaccine hx – vaccinate
  - Vaccine hx no testing – test for anti-HBs, boost or revaccinate if neg, retest anti-HBs

MMWR 2018

38

Viral and Bacterial Meningitis

Dr. Allan Tunkel

38 –Viral and Bacterial Meningitis

Speaker: Allan Tunkel, MD

Viral and Bacterial Meningitis

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

- 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 99.8°F 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

38 –Viral and Bacterial Meningitis

Speaker: Allan Tunkel, MD

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

13

- Now rarely reported as an etiologic agent
- Transmitted to humans by contact with rodents (hamsters, rats, mice) or their excreta
- As estimated 5% of house mice in the US are infected; infection more common in winter when mice are indoors
- 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

14

- 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

15

- Presented 1 month later with headache, meningismus and altered mental status, and a temperature of T 39^{o}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

16

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

17

- 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

18

- Children and young adults; mortality 3-13%
- Serogroups A, B, C, W, and Y
- Serogroup B disease in recent outbreaks
- Predisposition in those with congenital deficiencies in terminal complement components (C5-C8, and perhaps C9) and properdin deficiencies
- Increased risk: MSM, HIV infection, use of complement inhibitors that block C5 (eculizumab, ravulizumab), microbiologists exposed to isolates, travel to epidemic or hyperendemic areas, outbreak-related, college students

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, and from patients with CSF shunts or drains
- 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

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

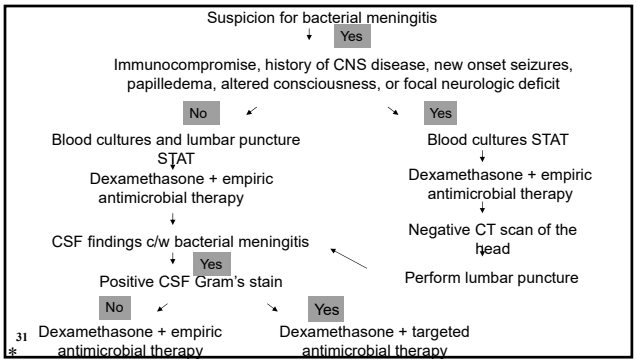
- A 35-year-old woman presents to the hospital with a 2-day history of fever, chills, headache, and mild confusion. She had head trauma several weeks earlier, associated with clear fluid draining out of her nose
- T 40.5°C, P 140, RR 32, BP 90/60 mmHg
- Obtunded, stiff neck
- WBC 30,000/mm^3 (40% bands), platelets 20,000/mm^3
- Lumbar puncture revealed an opening pressure of 400 mm H_2O, WBC 2500/mm^3 (99% segs), glucose 20 mg/dL, and protein 400 mg/dL

Question #3

27

Which of the following empiric antimicrobial regimens should be initiated?

A. Ampicillin
B. Ceftriaxone
C. Vancomycin + ampicillin
D. Vancomycin + ceftriaxone
E. Vancomycin + trimethoprim-sulfamethoxazole



EMPIRIC ANTIMICROBIAL THERAPY OF PURULENT MENINGITIS

29

Age	Antimicrobial Therapy
<1 month	Ampicillin + gentamicin + either cefotaxime (if available) or 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

30

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

31

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

32

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

33

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

34

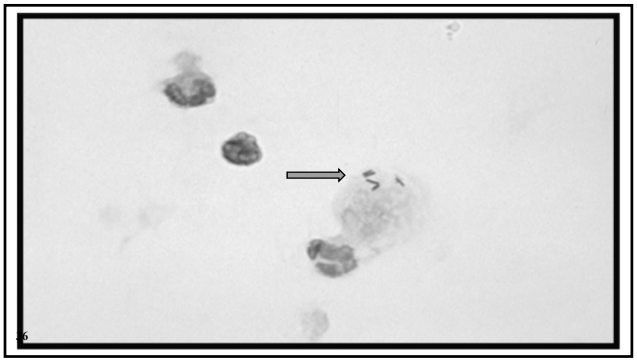
Organism	Antimicrobial Therapy
Pseudomonas aeruginosa	Ceftazidime or cefepime or meropenem
Acinetobacter baumannii	Meropenem or colistin (formulated as colistimethate sodium)[a] or polymyxin B[a]
Streptococcus agalactiae	Ampicillin or penicillin G
Listeria monocytogenes	Ampicillin or penicillin G[b]
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

35

- 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 102ºF, 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



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Question #4

37

Which of the following antimicrobial regimens should be initiated?

A. Vancomycin
B. Trimethoprim-sulfamethoxazole
C. Chloramphenicol
D. Moxifloxacin
E. Daptomycin

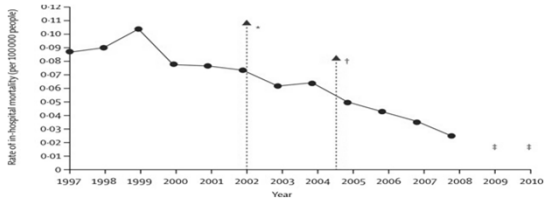
ADJUNCTIVE DEXAMETHASONE IN BACTERIAL MENINGITIS

38

- 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

IN-HOSPITAL MORTALITY FOR PNEUMOCOCCAL MENINGITIS

39



Castelblanco et al. Lancet ID 2014;14:813

40

QUESTIONS

Allan R. Tunkel, MD, PhD, MACP
Email: allan_tunkel@brown.edu

39

Chronic Hepatitis

Dr. David Thomas

39 – Chronic Hepatitis

Speaker: David Thomas, MD

Chronic Hepatitis and Liver Disease

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

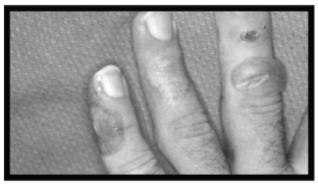
- Data and Safety Monitoring Board: Merck
- Advisory Board: Merck

Chronic Hepatitis and Liver Disease

- HCV
- HBV (and delta)
- Other forms
- HIV coinfection

Case: 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

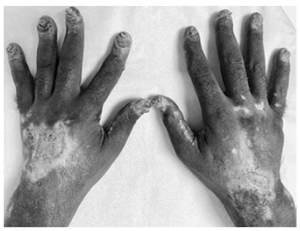
Question: HCV with a rash

The most likely dx is:

A. Cirrhosis due to HCV and alcohol
B. Necrolytic acral erythema
C. Porphyria cutanea tarda
D. Essential mixed cryoglobulinemia
E. Yersinia infection

Porphyria Cutanea Tarda Associated with Hepatitis C

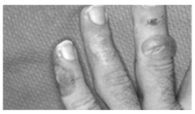
Tejesh S. Patel, M.D., and Evgeniya Teterina Mohammed, M.D.



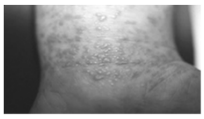
June 10, 2021
N Engl J Med 2021; 384:e86

Compare

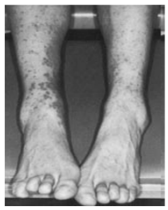
Porphyria cutanea tarda



Lichen planus



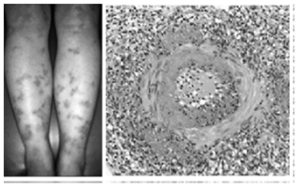
Cryoglobulin vasculitis



blogspot.com; OConnor Mayo Clin Proc 1998

Case: HBV and rash

46 year old woman HBsAg pos, anti-HCV neg



Chen Rheum 2014

Question: 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**

Question: 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 with new exposure after 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.

Case: 54 y/o with HCV antibodies and RNA

54 year old 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; creatinine 1.2 mg/dl; HBsAg pos; anti-HBc pos. HIV neg

Question: 54 y/o with HCV antibodies and RNA

Which of the following is the next appropriate step:

A. **Treat with oral regimen for 8-12 weeks**
B. **Check HCV 1a resistance test**
C. **Elastography**
D. **Confirm HCV antibody test**

HCV NS5 RAS testing is uncommonly recommended

Treatment naive

- **Genotype 1a and elbasvir/grazoprevir**
- **Genotype 3 AND cirrhosis for sofosbuvir/velpatasvir**

Treatment experienced

- **1a and ledipasvir/sofosbuvir 'considered'**
- **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

Accepted staging methods

1. **Liver biopsy**
2. **Blood markers**
3. **Elastography**
4. **Combinations of 1-3**

Not for routine staging

1. **Viral load**
2. **HCV genotype**
3. **Ultrasound**
4. **CT scan or MRI**

Hcvguidelines.org

$$\text{FIB 4} = \frac{\text{Age (yrs) x AST (U/L)}}{\text{Platelet count } (10^9/\text{L}) \text{ x ALT (U/L)}^{1/2}}$$

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

Of imperfect tests elastography is most sensitive for detection of 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

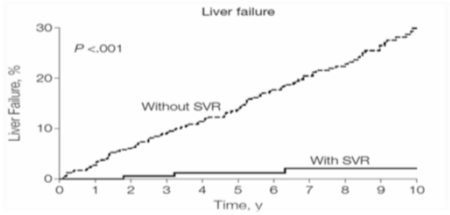
Singh Gastro 2017; Chou Ann Intern Med 2013; Castera Gastro 2012

Case con't: 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. He wants to know why. Which can you NOT say is true of successful treatment?

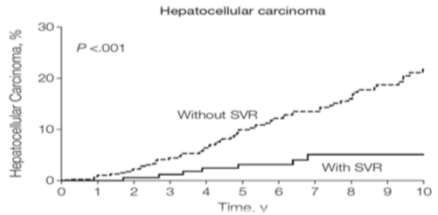
A. **reduces risk of reinfection**
B. **reduces risk of death**
C. **reduces risk of HCC**
D. **reduces risk of liver failure**

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



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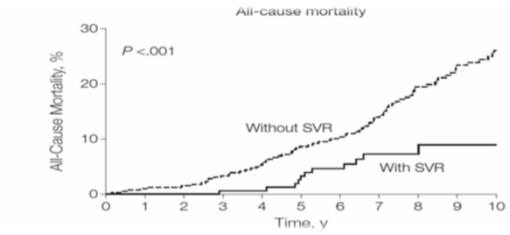
SVR reduces clinical outcomes



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AASLD AMERICAN ASSOCIATION FOR THE STUDY OF LIVER DISEASES

HCV Guidance: Recommendations for Testing, Managing, and Treating Hepatitis C

IDSA Infectious Diseases Society of America

Test, Evaluate, Monitor | Treatment-Naive | Treatment-Experienced | Unique & Key Populations

Simplified: No Cirrhosis

Simplified: Comp. Cirrhosis

the Guidance

Recommended regimens listed by evidence level and alphabetically for:

Treatment-Naive Genotype 1a Patients With Compensated Cirrhosis[a]

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 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
Daily fixed-dose combination of glecaprevir (300 mg)/pibrentasvir (120 mg)[c]	8 weeks	I, B

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. HCV IRIS T cell marker
D. HBV DNA
E. Liver biopsy with EM

U.S. Food and Drug Administration Protecting and Promoting Your Health — **Drug Safety Communications**

FDA Drug Safety Communication: FDA warns about the risk of hepatitis B reactivating in some patients treated with direct-acting antivirals for hepatitis C

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

Which is NOT a pangenotypic regimen?

A. Glecaprevir and pibrentasvir
B. Sofosbuvir and velpatasvir
C. Sofosbuvir and ledipasvir

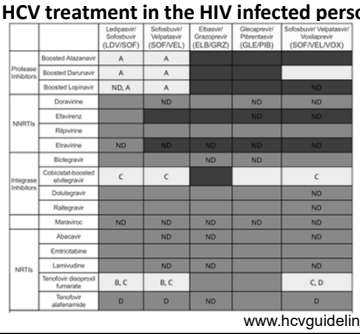
Which regimen is approved for ESRD?

A. Glecaprevir and pibrentasvir
B. Sofosbuvir and velpatasvir
C. Sofosbuvir and ledipasvir
D. Elbasvir and grazoprevir
E. All of the above

Which regimen is worst with darunavir?

A. Glecaprevir and pibrentasvir
B. Sofosbuvir and velpatasvir
C. Sofosbuvir and ledipasvir

HCV treatment in the HIV infected person



		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	
	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

Slide 28 of 44

www.hcvguidelines.com

HCV treatment summary 2021

- Test, stage, and treat
- Two pangenotypic regimens: SOF/VEL and GP
- Watch for HBV relapse at week 8
- No change for HIV (avoid drug interactions), renal insufficiency, acute infection, cirrhosis

Case of 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.

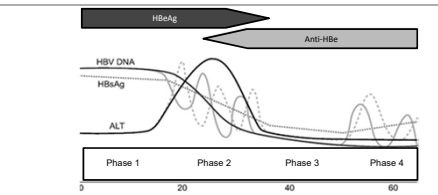
Which of the following tests is NOT recommended?

A. HIV test
B. HBV resistance
C. HBV genotype
D. Hepatitis Delta testing
E. Quantitative HBV DNA level

The essential evaluation of persons with CHB

- HBeAg, HIV, HBV DNA, delta, genotype
- Stage (liver enzymes and/or elastography or biopsy)
- Renal status
- US to r/o HCC
  - Asian: male 40; female 50
  - African: 25-30

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

Use testing to define disease phase

- The natural history of chronic HBV infection has been schematically divided into five phases

Chronic HBV infection	HBeAg positive		HBeAg negative		
	Phase 1	Phase 2	Phase 3	Phase 4	Phase 5
	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 disease phase to determine whom to treat

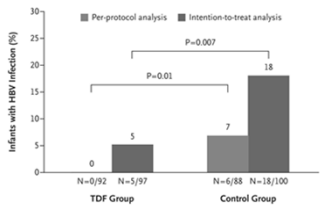
Chronic HBV infection	HBeAg positive		HBeAg negative	
	Phase 1	Phase 2	Phase 3	Phase 4
	Chronic HBV infection	Chronic hepatitis B	Chronic HBV infection	Chronic hepatitis B
HBV DNA	$>10^7$ IU/mL	10^4–10^7 IU/mL	<2,000 IU/mL*	>2,000 IU/mL
ALT	Normal	Elevated	Normal	Elevated†

Treat with both high DNA and ALT

*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

Test pregnant women for HBsAg and, if pos, for HBV DNA* and treat if > 200,000 IU/ml

Rec for all pregnant women to have quantitative HBV DNA TEST



*test in 3rd trimester

Terrault Hepatology 2015; Pan NEJM 2016

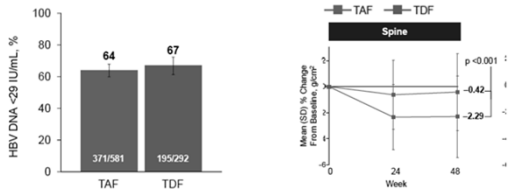
Four preferred treatments for chronic hepatitis B

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

Treatment of HBV changes with renal insufficiency

- **GFR 30-60 mL/min/1.73 m²** : TAF 25 mg preferred
- **GFR <30-10:** TAF 25mg OR entecavir 0.5 mg q 3d
- **GFR <10 no dialysis:** entecavir 0.5 mg
- **Dialysis:** TDF 300mg/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

- **<u>All</u> are treated and tested for both**
- **HBV-active ART**
- **Entecavir less effective if LAM exposure**
- **Watch switch from TAF- or 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**

HBV Reactivation with immunosuppression

Rituximab, high dose corticosteroids, and BMT 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**

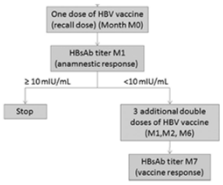
AASLD Terrault Hepatology 2018

Isolated anti-core antibodies usually reflect occult hepatitis B in high risk groups

- **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

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

Thanks and good luck on the test!

Questions:

Dave Thomas
–dthomas@jhmi.edu

BONUS CASE

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. Hunts wild boar in Texas

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.

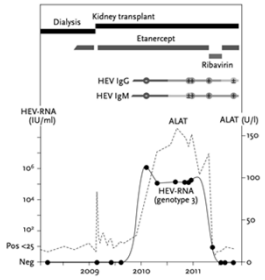
Barrague Medicine 2017

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

40

Brain Abscess, Cavernous Sinus Thrombosis, and Subdural and Epidural Empyema

Dr. Allan Tunkel

40 – Brain Abscess, Cavernous Sinus Thrombosis, and Subdural and Epidural Empyema

Speaker: Allan Tunkel, MD

Brain Abscess, Cavernous Sinus Thrombosis, and Subdural and Epidural Empyema

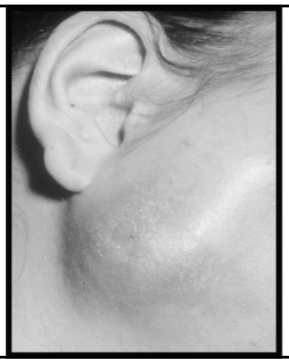
Allan R. Tunkel, MD, PhD, MACP
Senior Associate Dean for Medical Education
Professor of Medicine and Medical Science
The Warren Alpert Medical School of Brown University

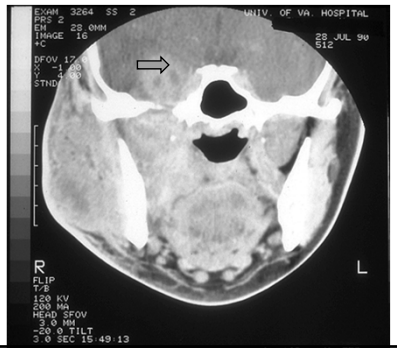
Disclosures of Financial Relationships with Relevant Commercial Interests

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

40 – Brain Abscess, Cavernous Sinus Thrombosis, and Subdural and Epidural Empyema

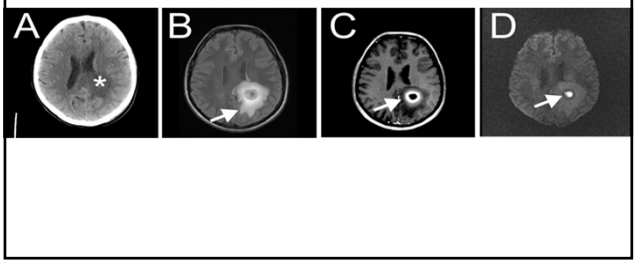
Speaker: Allan Tunkel, MD

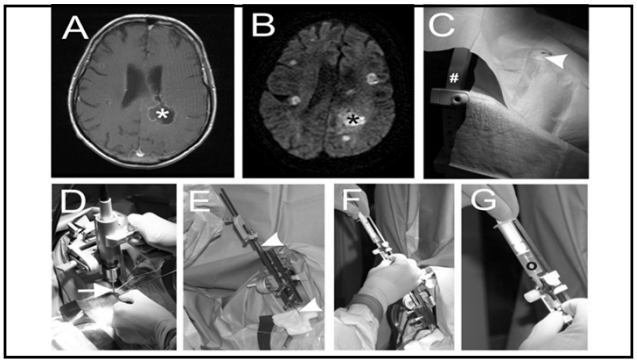
PREDISPOSING CONDITIONS FOR BRAIN ABSCESS

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]cefotaxime or ceftriaxone
[b]additional agents may be used based on other likely microbial etiologies

EMPIRIC ANTIMICROBIAL THERAPY OF BRAIN ABSCESS

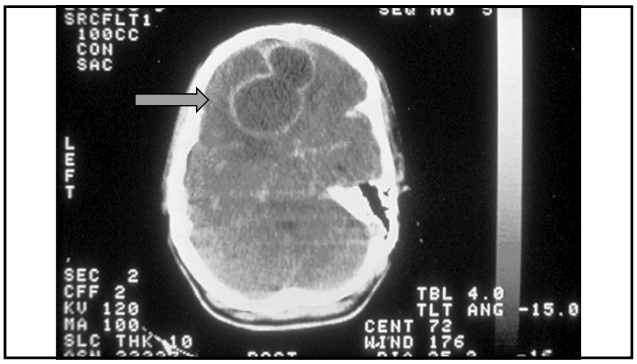
Predisposing Condition	Antimicrobial Regimen
Unknown	Vancomycin + metronidazole + a third or fourth generation cephalosporin
Transplant recipients	Add voriconazole, plus trimethoprim-sulfamethoxazole or sulfadiazine
HIV-infected patients	Add pyrimethamine + sulfadiazine; consider isoniazid, rifampin, pyrazinamide, and ethambutol for possible tuberculosis

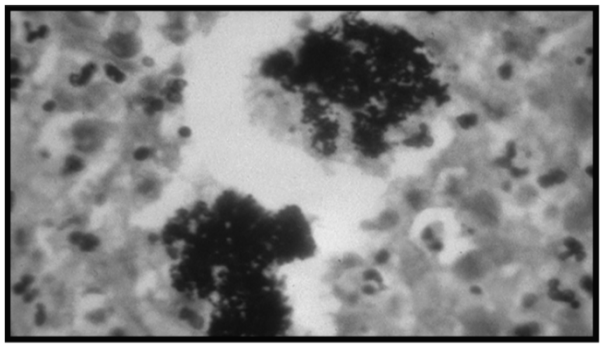
40 – Brain Abscess, Cavernous Sinus Thrombosis, and Subdural and Epidural Empyema

Speaker: Allan Tunkel, MD

CASE #2

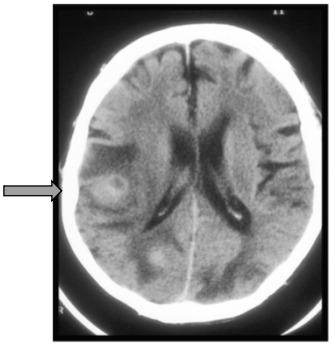
- 21-year-old member of a motorcycle gang thrown from his bike, and suffered a depressed skull fracture
- In the OR, a large subdural hematoma was evacuated
- Discharged in 5 days
- Returned by mother 5 days later because of bizarre behavior
- No headache, afebrile

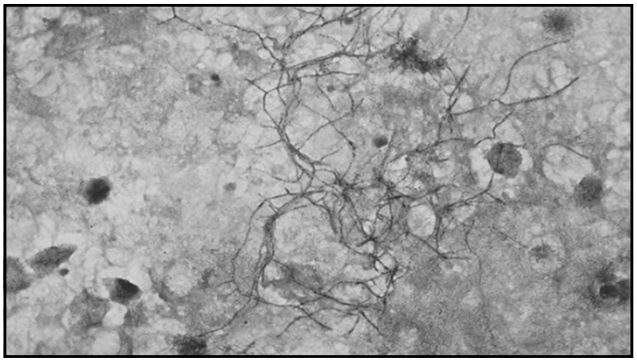




CASE #3

- 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





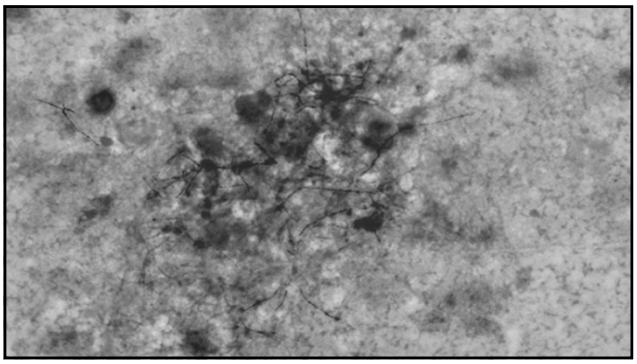
40 – Brain Abscess, Cavernous Sinus Thrombosis, and Subdural and Epidural Empyema

Speaker: Allan Tunkel, MD

Question #2 (Case #3)

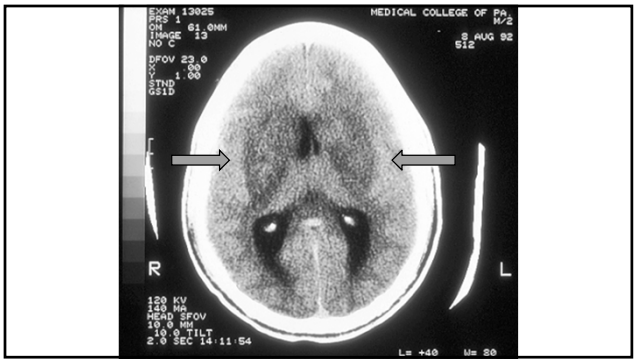
Which of the following antimicrobial regimens should be initiated?

A. Penicillin + metronidazole
B. Trimethoprim-sulfamethoxazole
C. Daptomycin
D. Liposomal amphotericin B + 5-FC
E. Voriconazole



CASE #4

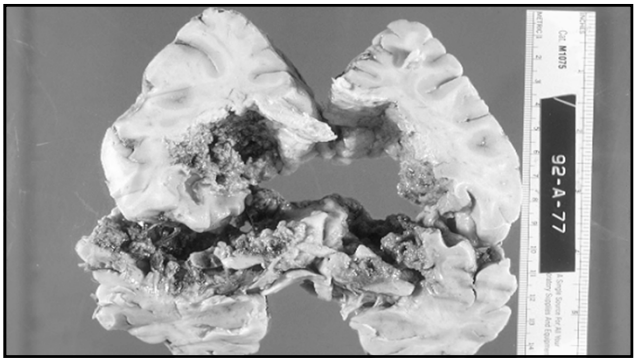
- 24-year-old injection drug user who, while injecting intravenous drugs with his girlfriend, fell out of the second story window of his apartment. When he did not return for 48 hours, she found him unresponsive on the ground and called fire rescue
- T 103ºF, P 150, RR 32, BP 110/76 mmHg
- On exam, he was comatose without evidence of head trauma
- WBC 13,000/mm^3, profound metabolic acidosis



Question #3 (CASE #4)

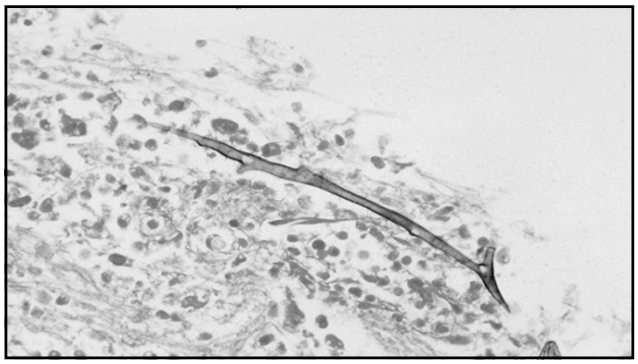
The most likely etiologic agent of the patient's CNS lesions is which of the following?

A. Staphylococcus aureus
B. Pseudomonas aeruginosa
C. Nocardia asteroides
D. Candida albicans
E. Rhizopus arrhizus



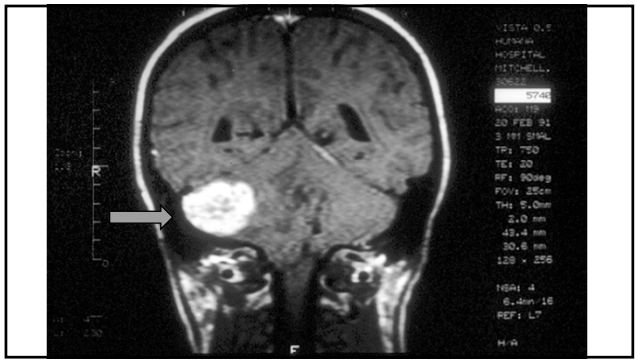
40 – Brain Abscess, Cavernous Sinus Thrombosis, and Subdural and Epidural Empyema

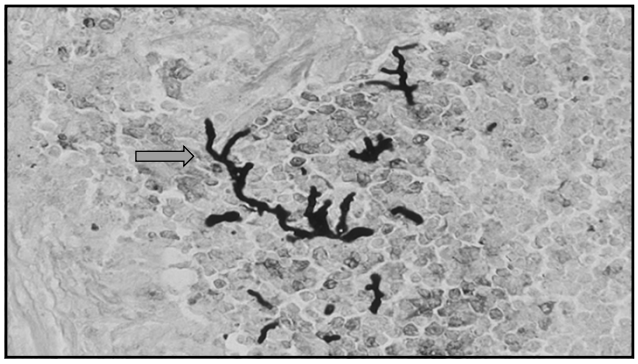
Speaker: Allan Tunkel, MD



CASE #5

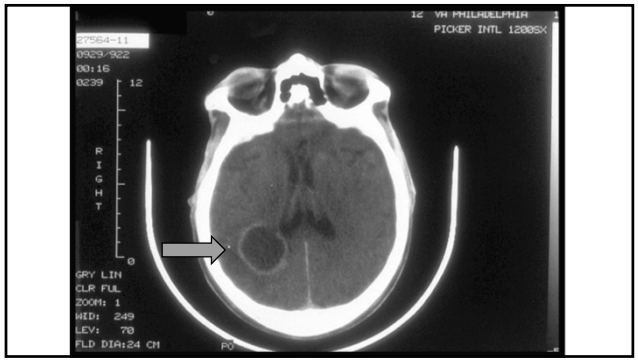
- 11-year-old boy with chronic granulomatous disease on chronic TMP-SMX therapy noted the onset of a mild headache which lasted 10 minutes.
- Two weeks later at a routine physician visit, the patient had no complaints and denied recurrence of the headache
- On examination, the patient had normal vital signs and a normal neurologic examination
- The physician ordered an MR imaging of the head





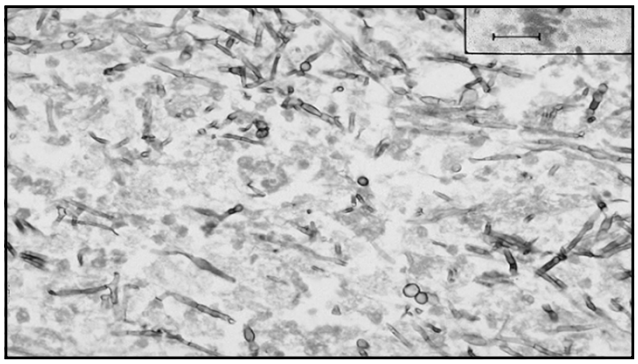
CASE #6

- 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 liposomal 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



40 – 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

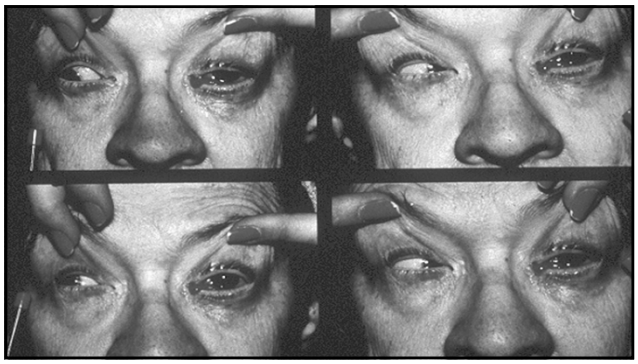
[a]Addition of 5-flucytosine should be considered

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

40 – Brain Abscess, Cavernous Sinus Thrombosis, and Subdural and Epidural Empyema

Speaker: Allan Tunkel, MD



Question #4 (CASE #7)

Which of the following studies should be performed to establish the diagnosis?

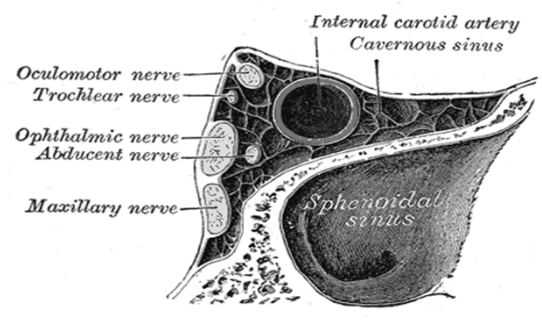
A. CT scan of the head and sinuses with contrast
B. MR imaging with MR venography
C. Cerebral angiography
D. Positron emission tomography of the head
E. Lumbar puncture

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.

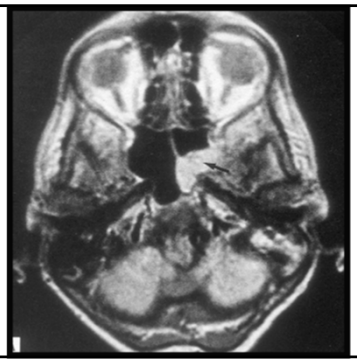
RADIOLOGIC FINDINGS IN SEPTIC CAVERNOUS SINUS THROMBOSIS

MR imaging

- Noninvasive diagnostic procedure of choice
- MRA and MRV can directly visualize cerebral vasculature
- Fullness in cavernous sinus region
- Paranasal sinus fluid

40 – Brain Abscess, Cavernous Sinus Thrombosis, and Subdural and Epidural Empyema

Speaker: Allan Tunkel, MD

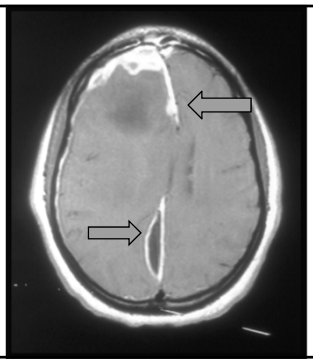


MANAGEMENT OF SEPTIC CAVERNOUS SINUS THROMBOSIS

- 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 102º 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

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%)

40 – Brain Abscess, Cavernous Sinus Thrombosis, and Subdural and Epidural Empyema

Speaker: Allan Tunkel, MD

CRANIAL SUBDURAL EMPYEMA AND CRANIAL EPIDURAL ABSCESS

Subdural Empyema (acute course)	Epidural Abscess (indolent course)
□ Fever	□ Headache
□ Headache	□ Fever
□ Depressed consciousness	□ Seizures
□ Hemiparesis	□ Focal neurologic signs
□ Seizures	□ Altered mental state
□ Nuchal rigidity	
□ Gaze palsies/ataxia	

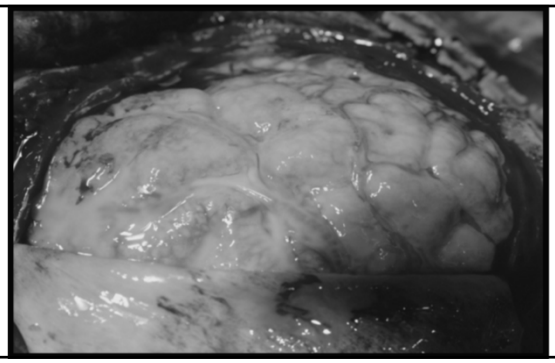
PRINCIPLES OF MANAGEMENT OF CRANIAL SUBDURAL EMPYEMA

- 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

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

40 – Brain Abscess, Cavernous Sinus Thrombosis, and Subdural and Epidural Empyema

Speaker: Allan Tunkel, MD

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

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QUESTIONS

Allan R. Tunkel, MD, PhD, MACP
Email: allan_tunkel@brown.edu

Tuesday, August 24, 2021

AM Moderator: Gulick
PM Moderator: Masur

#	Start		End	Presentation	Speaker
41	9:30 AM	-	10:00 AM	**Daily Question Preview Day 4**	*Roy Gulick, MD (Moderator)*
42	10:00 AM	-	10:30 AM	**Gastrointestinal Disease: Clinical Syndromes**	*Herbert Dupont, MD*
43	10:30 AM	-	11:15 AM	**Clinical Manifestations of Human Retroviral Diseases and Slow Viruses**	*Frank Maldarelli, MD*
44	11:15 AM	-	11:45 AM	**Gastrointestinal Disease: Etiologic Agents**	*Herbert Dupont, MD*
	11:45 AM	-	12:15 PM	***BREAK with FACULTY CHAT***	
45	12:15 PM	-	12:30 PM	**HIV Diagnosis**	*Frank Maldarelli, MD*
46	12:30 PM	-	1:15 PM	**Antiretroviral Therapy**	*Roy Gulick, MD*
47	1:15 PM	-	1:30 PM	**HIV Drug Resistance**	*Michael Saag, MD*
48	1:30 PM	-	2:00 PM	**Antiretroviral Therapy for Special Populations**	*Roy Gulick, MD*
	2:00 PM	-	2:30 PM	***BREAK with FACULTY CHAT***	
49	2:30 PM	-	3:15 PM	**Board Review Session 4**	*Drs. Gulick (Moderator), Bloch, Dorman, Dupont, Maldarelli, Saag, and Weinstein*
50	3:15 PM	-	4:00 PM	**Syndromes that Masquerade as Infections**	*Karen Bloch MD*
51	4:00 PM	-	4:45 PM	**Tuberculosis in Immunocompetent and Immunosuppressed Hosts**	*Susan Dorman, MD*
	4:45 PM	-	5:15 PM	***BREAK with FACULTY CHAT***	
52	5:15 PM	-	6:00 PM	**Non AIDS-Defining Complications of HIV/AIDS**	*Michael Saag, MD*
53	6:00 PM	-	7:00 PM	**Hospital Epidemiology**	*Robert Weinstein, MD*
54	7:00 PM	-	7:15 PM	**Pharyngitis Syndromes including Group A Strep Pharyngitis**	*Karen Bloch, MD*
	7:15 PM	-	7:45 PM	***END OF THE DAY FACULTY CHAT***	

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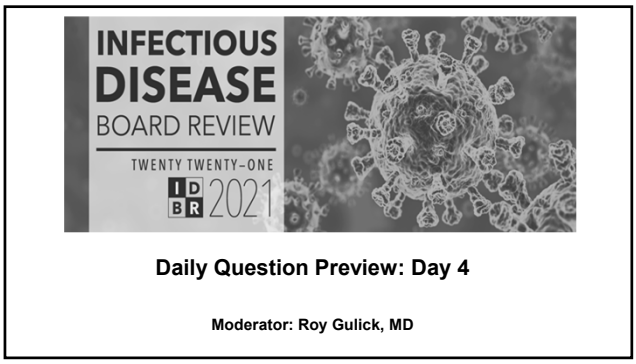
Daily Question Preview 4

Dr. Roy Gulick (Moderator)

41 – Daily Question Preview: Day 4

Moderator: Roy Gulick, MD



Daily Question Preview: Day 4

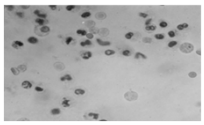
Moderator: Roy Gulick, MD

PREVIEW QUESTION

4.1

A 35-year old woman develops diarrhea, cramps and is passing bloody stools with fever while snorkeling with her family in Cozumel, Mexico

Grossly bloody stool



Many leukocytes of stool microscopically indicate diffuse colonic inflammation

PREVIEW QUESTION

4.1 **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

PREVIEW QUESTION

4.2 **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

PREVIEW QUESTION

4.3 **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**

PREVIEW QUESTION

4.3 **What is the likely cause of the outbreak?**

A) Norovirus

B) Shigella sonnei

C) Enterotoxin from Staphylococus aureus

D) Clostridium perfringens

E) Bacillus cereus

41 – Daily Question Preview: Day 4

Moderator: Roy Gulick, MD

PREVIEW QUESTION

4.4 A 49-year-old woman from Guinea-Bissau has a reactive HIV-1/2 ELISA and a HIV Geenius positive for HIV-2 and negative for HIV-1.

CD4 cell count is 350 cells/µl.

PREVIEW QUESTION

4.4 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

PREVIEW QUESTION

4.5 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

PREVIEW QUESTION

4.6 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.

PREVIEW QUESTION

4.6 The most likely explanation for these results is

A) This person HIV-infected and is an elite 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

PREVIEW QUESTION

4.7 A 65-year-old 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 never been on antiretroviral therapy and has no history of travel outside the US.

41 – Daily Question Preview: Day 4

Moderator: Roy Gulick, MD

PREVIEW QUESTION

4.7 **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 viral load too low to be detected because he is a long term non progressor.

C) The patient is not infected with HIV-1 or -2, all tests are false positive.

D) The patient is infected with non-B subtype of HIV-1

PREVIEW QUESTION

4.8 **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-progressor 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 cells/uL.

PREVIEW QUESTION

4.9 **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) raltegravir + darunavir (boosted)

B) tenofovir alafenamide/emtricitabine/rilpivirine

C) abacavir/lamivudine + efavirenz

D) lamivudine/dolutegravir

E) tenofovir alafenamide/emtricitabine/bictegravir

PREVIEW QUESTION

4.10 **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 98 cps/ml and CD4 352.

PREVIEW QUESTION

4.10 **What do you recommend?**

A) Obtain genotype.

B) Obtain genotype and phenotype.

C) Repeat HIV RNA at next visit.

D) Change regimen to TAF/emtricitabine/bictegravir to improve adherence

PREVIEW QUESTION

4.11 **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.

41 – Daily Question Preview: Day 4

Moderator: Roy Gulick, MD

PREVIEW QUESTION

4.11 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.

PREVIEW QUESTION

4.12 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

4.13 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.

PREVIEW QUESTION

4.14 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.

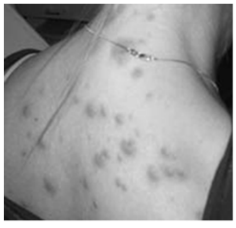
The day of admit she developed fever without localizing symptoms. CBC showed a white blood cell count of 12,250 with 20% bands.

Exam: T 101.4; P 98, Otherwise unremarkable.
Blood cultures were sent, and she was started on broad spectrum empiric antibiotics.

PREVIEW QUESTION

4.14

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.

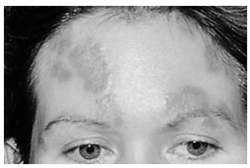


PREVIEW QUESTION

4.14

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

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



41 – Daily Question Preview: Day 4

Moderator: Roy Gulick, MD

PREVIEW QUESTION

4.14 Which is the most likely diagnosis?

A) Ecthyma gangrenosum

B) Pyoderma gangrenosum

C) DRESS

D) Leukemic infiltrates

E) Sweet syndrome

PREVIEW QUESTION

4.15 38-year-old male 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.

PREVIEW QUESTION

4.15 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

PREVIEW QUESTION

4.16 24-year-old 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.

PREVIEW QUESTION

4.16 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

PREVIEW QUESTION

4.17 24-year-old U.S. born male whose wife (with whom he lives) was recently diagnosed with smear-positive pulmonary TB.

During a contact investigation, the 24-year-old male 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.

41 – Daily Question Preview: Day 4

Moderator: Roy Gulick, MD

PREVIEW QUESTION

4.17 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

PREVIEW QUESTION

4.18 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

PREVIEW QUESTION

4.18 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)

42

Gastrointestinal Disease: Clinical Syndromes

Dr. Herbert L. DuPont

42 – Gastrointestinal Disease: Clinical Syndromes

Speaker: Herbert DuPont, MD

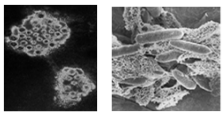
Gastrointestinal Disease: Clinical Syndromes

Herbert L. DuPont, MD
Professor, Infectious Diseases, Epidemiology
The University of Texas McGovern Medical School
School of Public Health
Clinical Professor, Infectious Diseases
Baylor College of Medicine and MD Anderson Cancer

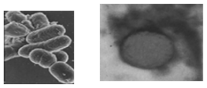
Disclosures of Financial Relationships with Relevant Commercial Interests

- **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

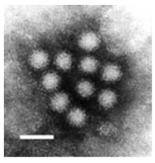
EVALUATION OF CASES OF DIARRHEA
KEYS CLINICAL FEATURES SPECIAL SETTINGS

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%

42 – Gastrointestinal Disease: Clinical Syndromes

Speaker: Herbert DuPont, MD

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%

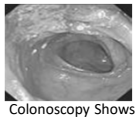
https://www.cdc.gov/norovirus/trends-outbreaks/responding.html

INDIVIDUAL CASES KEYS TO ESTABLISH CAUSE

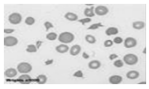
CLINICAL FEATURES
SETTING (EPIDEMIOLOGY)
LABORATORY TESTING

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"

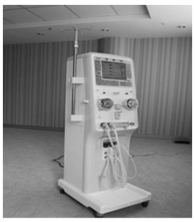


Peripheral Smear Shows Red Cell Fragments

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

42 – Gastrointestinal Disease: Clinical Syndromes

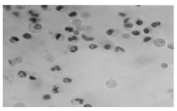
Speaker: Herbert DuPont, MD

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

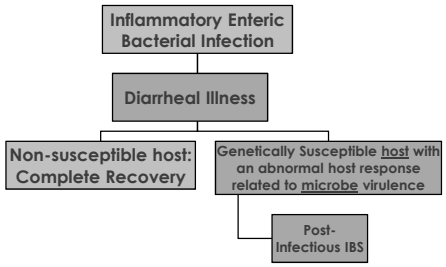
POST-ENTERIC INFECTION DISORDER

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



POST-ENTERIC INFECTION DISORDER 2

QUESTION 7

Which one of the following represents an antibody-Mediated post- enteric autoimmune complication?

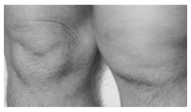
A. CROHN'S DISEASE
B. FUNCTIONAL CONSTIPATION
C. REACTIVE ARTHRITIS
D. CELIAC DISEASE
E. WHIPPLE'S DISEASE

42 – Gastrointestinal Disease: Clinical Syndromes

Speaker: Herbert DuPont, MD

Post-Enteric Infection Disorder 2

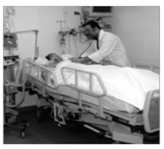
- Reactive arthritis after infection by *Salmonella*, *Shigella* or *Yersinia* due to autoimmune responses targeting epitopes common to pathogen and joint tissues



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?

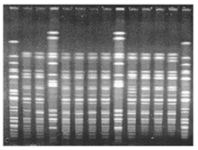
A. Norovirus
B. *Shigella sonnei*
C. Enterotoxin from *Staphylococus aureus*
D. *Clostridium perfringens*
E. *Bacillus cereus*

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*

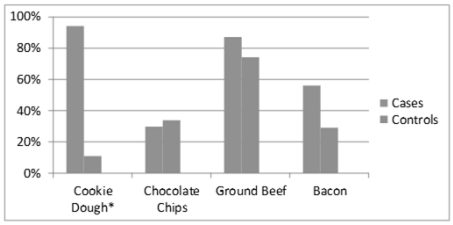
A CASE CONTROL STUDY WAS PERFORMED TO IDENTIFY THE SOURCE

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

43

Clinical Manifestations of Human Retroviral Diseases and Slow Viruses

Dr. Frank Maldarelli

43 – Clinical Manifestations of Human Retroviral Diseases and Slow Viruses

Speaker: Frank Maldarelli, MD

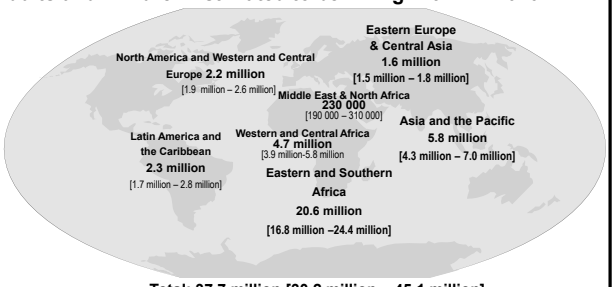
Clinical Manifestations of Human Retroviral Diseases and Slow Viruses

Frank Maldarelli, MD
Bethesda, MD

Disclosures of Financial Relationships with Relevant Commercial Interests

- **None**

Adults and Children Estimated to be Living with HIV 2020

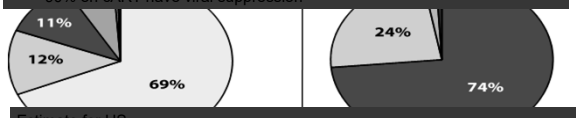


Total: 37.7 million [30.2 million – 45.1 million]
27.7 million accessing antiretroviral therapy

UNAIDS

HIV Prevalence:
Adults and Adolescents United States and 6 Dependent Areas

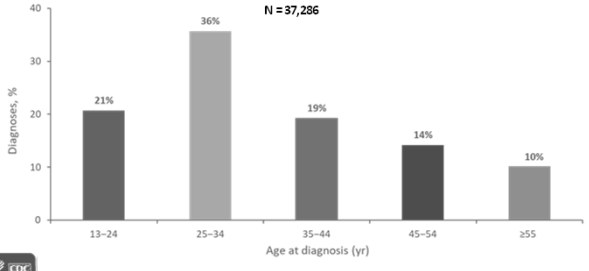
2020 Goal
90% infected know their diagnosis
90% diagnosed on cART
90% on cART have viral suppression



Estimate for US
86% infected know their diagnosis
74% of those diagnosed on cART
67% of those on cART have viral suppression

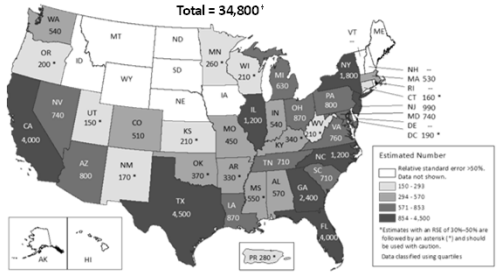
Source: 2018 CDC

Trends in the US Epidemic: Age at Diagnosis

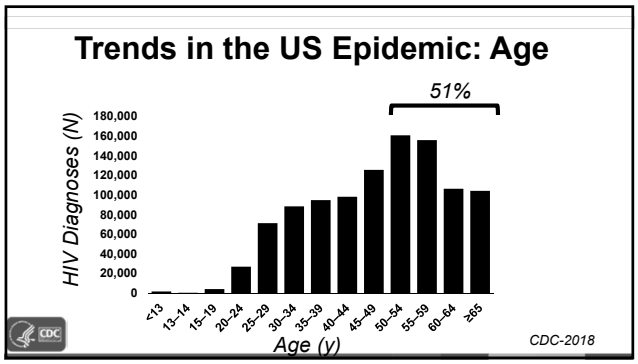


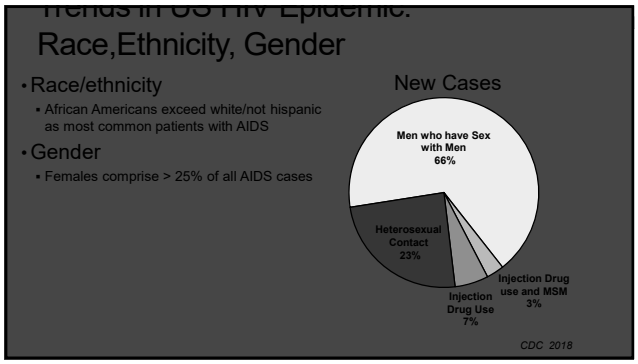
Note. Data for the year 2018 are considered preliminary and based on 6 months reporting delay.

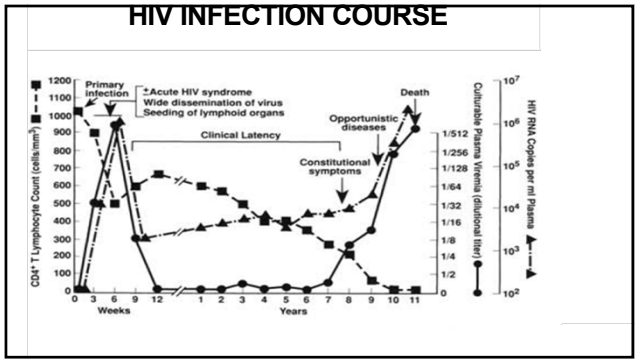
Trends in the US Epidemic: Geography



Note. Estimates were derived from a CD4 depletion model using HIV surveillance data. Estimates rounded to the nearest 100 for estimates >1,000 and to the nearest 10 for estimates ≤1,000 to reflect model uncertainty.
†Total estimate for the United States does not include data for Puerto Rico.





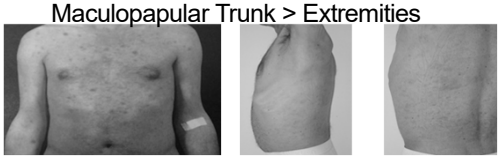


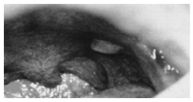
Acute HIV Syndrome

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	12-27
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	2	nd	nd
Too ill to work	nd	44	58

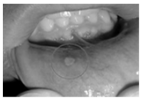
Primary HIV-1 Infection Syndrome

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 supplemental 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 explanation for the absence of positive results with the supplementary HIV test:

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 results with the supplementary 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 remain negative
- HIV-1 DNA PCR has been useful in documenting infection

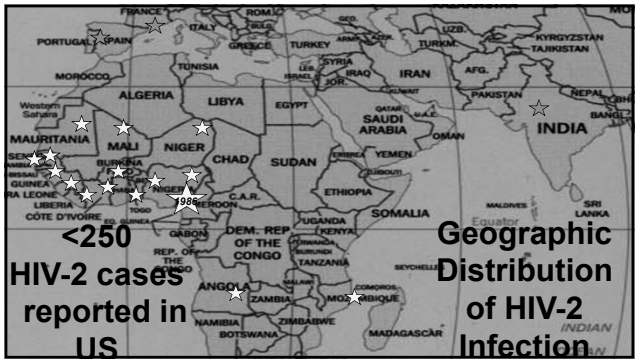
HIV Clinical Presentation: Question #2

A 49 year old woman from Guinea-Bissau has a reactive HIV-1/2 ELISA and a HIV Geenius 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

Characteristic	HIV-2	HIV-1
Epidemiology		
Geography	West /Central 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 **NOT** NNRTI **NOT** Fusion	NRTI, PI, NNRTI 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 the hematology technician remarks that some of the lymphocytes are "flower cells". Which of the following is most correct in explaining the hematology findings:

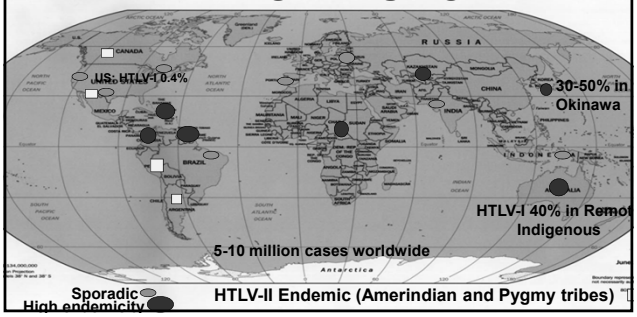
A. The patient has HIV and B cell lymphoma
B. The patient has HIV infection and the elevated CD4 count is due to steroids used in the treatment of the *Pneumocystis* pneumonia
C. The patient has HTLV-1 infection only the HIV test is a false positive
D. The patient has both HIV infection and HTLV-1 infection

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 DISTRIBUTION

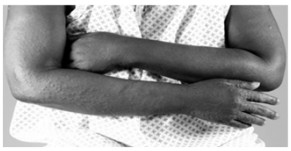


HTLV-I Transmission

- 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 South America
- 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

- Corticosteroids
  - May slow progression and reduce disability
- Mogamulizumab
- 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

Pearls

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**

Thanks to Tamara Nawar, Ying Taur, Anna Kaltsas (SKMC, NYC)

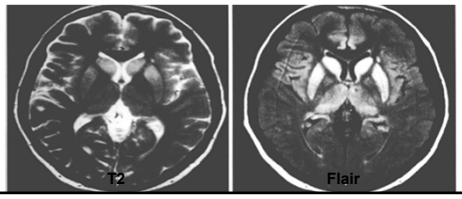
SLOW VIRUSES

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

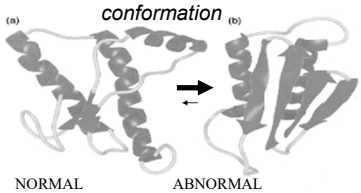


Prion Diseases: Transmissible Spongiform Encephalopathies

- **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



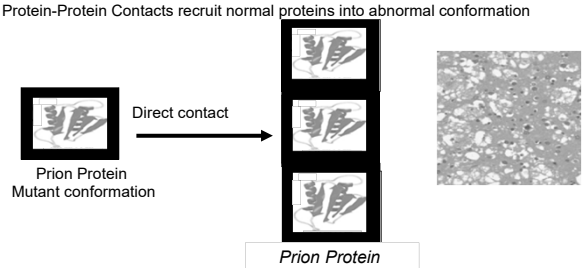
NORMAL ABNORMAL

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



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

43 – Clinical Manifestations of Human Retroviral Diseases and Slow Viruses

Speaker: Frank Maldarelli, MD

Dementia Comparison

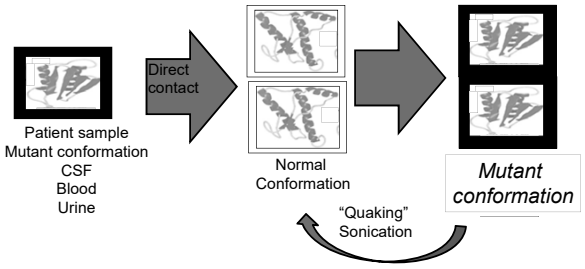
Type	Protein	Clinical	Course	Path	MRI
sCJD	Prion	Myoclonus	<2y	Spongif. Degen.	Caudate Striatum Thalamus
Alzheimer	Apo E4, Tau	Memory Language	>4y	Neurofib. tangles	Hippocampus White matter
Lewy Body	α- Synuclein	Parkinsonian Visual hallucin.	>4y	Lewy Bodies	Less common
Multi-infarct	Atheroma	Focal	Incremental	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)

Abnormal Prion Detection RT-QuIC



Sensitivity 92% Specificity >99%

Spontaneous Creutzfeldt-Jacob Disease

Typical Clinical Presentation

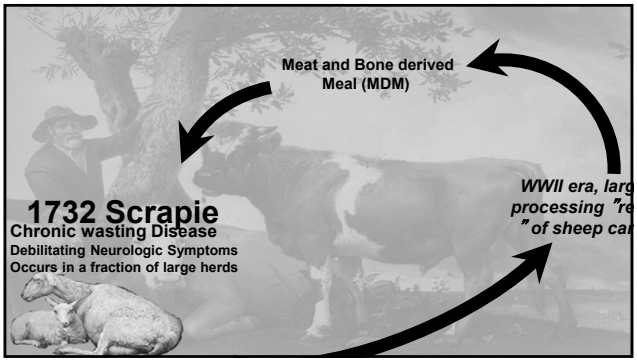
- Rapid progression
- Classic Clinical Triad
  - Dementia
  - Myoclonus
  - EEG: periodic sharp waves
- RT-QuIC elevated abnormal prion protein
- 14-3-3 not specific for CJD

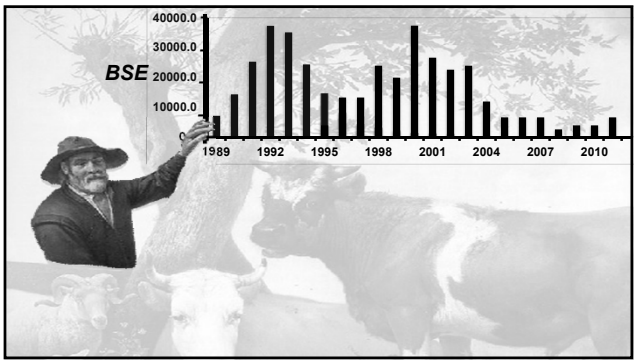
Prion Disease Question #2

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





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

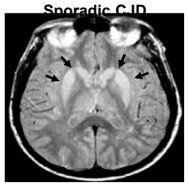
- United Kingdom: 178
- France: 28
- Spain: 5
- **US: 4**
  - **(ALL infections acquired OUTSIDE of US)**
- Ireland: 4
- Netherlands, Italy: 3
- Portugal, Canada: 2 each
- Saudi Arabia, Japan, Taiwan: 1 each

(Nat'l CJD Res. Surv. Unit, U. Edinburgh, www.cjd.ed.ac.uk 2019)

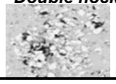
vCJD vs. sCJD

	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"

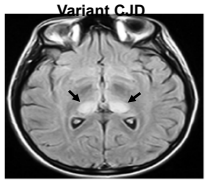
sCJD ***vCJD***



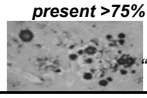
T2 axial proton weighted
Putamen and caudate head
"Double hockey stick sign"



"Abnormal Prion accumulation"



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

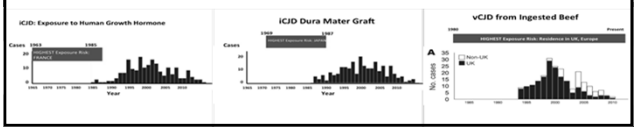
- **Pituitary extracts**
  - **Human Growth Hormone**
  - **Gonadotrophin**
  - **Delay may be >30 y**
  - **(Role in AD as well?)**
- **Dura mater grafts**
  - **Mostly Lyodura brand**
- **Transplants**
  - **Corneal**
  - **Pericardium**
  - **Liver**
- **Instrumentation**
  - **Implantable Neurosurgical-EEG, 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 121° 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**
- fmaldarelli3@gmail.com

44

Gastrointestinal Disease: Etiologic Agents

Dr. Herbert L. DuPont

44 – Gastrointestinal Disease: Etiologic Agents

Speaker: Herbert DuPont, MD

Gastrointestinal Disease: Causative Agents

Herbert L. DuPont, MD
Professor, Infectious Diseases, Epidemiology
The University of Texas McGovern Medical School
School of Public Health
Clinical Professor, Infectious Diseases
Baylor College of Medicine and MD Anderson Cancer

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

44 – Gastrointestinal Disease: Etiologic Agents

Speaker: Herbert DuPont, MD

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

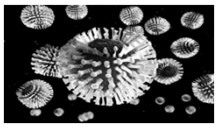
VIRAL GASTROENTERITIS

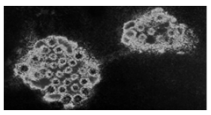
ROTAVIRUS

- 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%)
- INCREASING IN CHILDREN AS ROTAVIRUS DECREASING





SHIGA TOXIN-PRODUCING *E. COLI* INFECTION (~300,000 CASES IN U.S.)

***E. COLI* O157**

SORBITOL-NON-FERMENTING
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

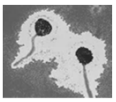
85%
13%

Hemolytic Uremic Syndrome

9%
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 IMPROVE 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

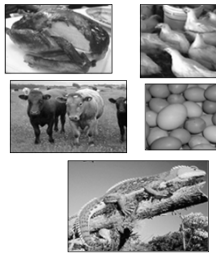
NON-TYPHOID SALMONELLOSIS

- 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%

44 – Gastrointestinal Disease: Etiologic Agents

Speaker: Herbert 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*

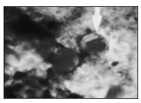
Animals reservoir, water vehicle of transmission

- *E. histolytica* produces liver abscess most importantly in males

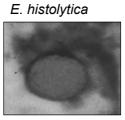
Serology helpful in hepatic abscess as stools often negative

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

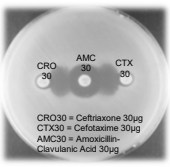
ESBL or MDR Enterobacteriaceae Risk Factors:

- Travel to tropical and semitropical areas, especially Asia (highest for travel to India)
- Diarrhea increases rate and receipt of antibiotics further increases risk

Endogenous Infections* or Spread to Family Duration of Colonization After Returning Home

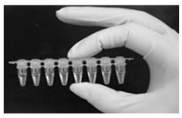
- < 3 months to 12 months
- Shorter than when acquired in a hospital
- Treat only more severe Travelers' diarrhea

Extended spectrum beta lactamase-producing Enterobacteriaceae



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

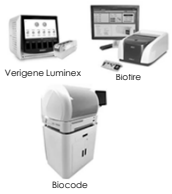
44 – Gastrointestinal Disease: Etiologic Agents

Speaker: Herbert DuPont, MD

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



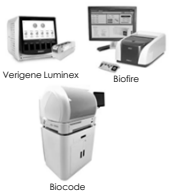
Requires clinical judgement & correlation

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

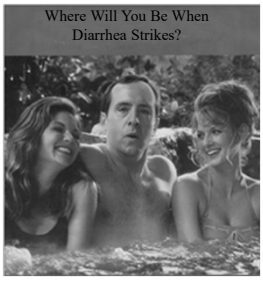
Shane, et. al. CID 2017:65 e45-80

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



45

HIV Diagnosis

Dr. Frank Maldarelli

45 – HIV Diagnosis
Speaker: Frank Maldarelli, MD

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

A. This person HIV-infected and is an elite controller

B. This person is HIV-infected but is in the window period for HIV infection

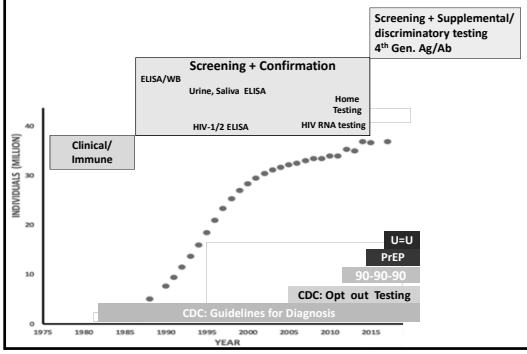
C. This person is infected with an HIV variant that is not detected by the supplemental test

D. This person is not HIV-infected

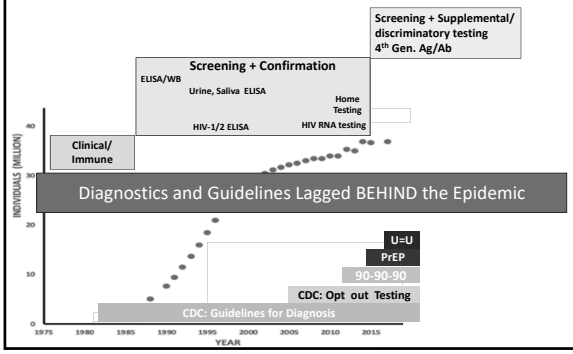
HIV Diagnosis: New Modalities and New Terminology Old Limitations Persist

- 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

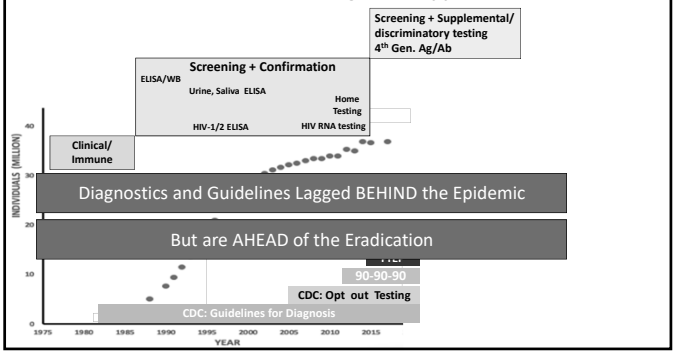


Evolution of the HIV Diagnostic Approach



45 – HIV Diagnosis
Speaker: Frank Maldarelli, MD

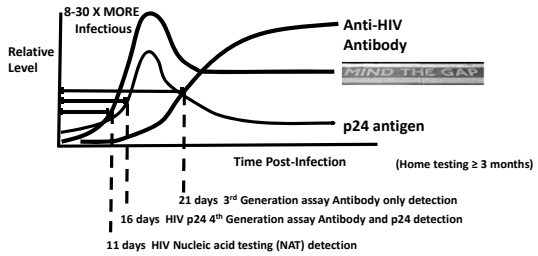
Evolution of the HIV Diagnostic Approach



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



CDC 2014

Detecting HIV Infection TWO STEPS

- **Screening - Highest Sensitivity**
  - **4th gen ELISA for HIV antibody + p24 antigen detection**
  - **Qualitative HIV RNA**
- **Supplemental/Discriminatory - Highest Specificity**
  - **GEENIUS**
    - **Confirms HIV-1 or HIV-2**

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 compared with 4th gen testing**
- **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

A. Obtain the HIV viral RNA test to find out how high the viral load is, and begin antiretroviral therapy immediately
B. Consider laboratory error, repeat the same 4th generation test
C. Perform supplemental testing with third generation discriminatory testing
D. 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 for diagnosis**
    - **Rapid turnaround but low level results are possible**
- **Rapid screening reactive during labor in previously untested**
  - **Initiate therapy**
  - **Do not wait for supplemental results**

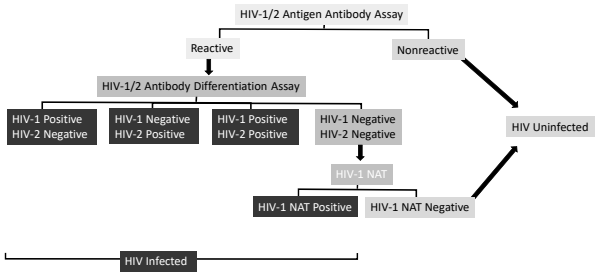
A 65 yo American male has had unprotected sex with men for many years. The HIV-1/2 ELISA is reactive and supplemental testing is positive for HIV-1. Viral RNA level is <50 copies/ml and CD4 count is 700 cells/µl. He has never been on antiretroviral therapy and has no history of travel outside the US. 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 viral load too low to be detected 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. Signed consent in addition to the consent for care required
D. Consent for HIV testing is not required

45 – HIV Diagnosis

Speaker: Frank Maldarelli, MD

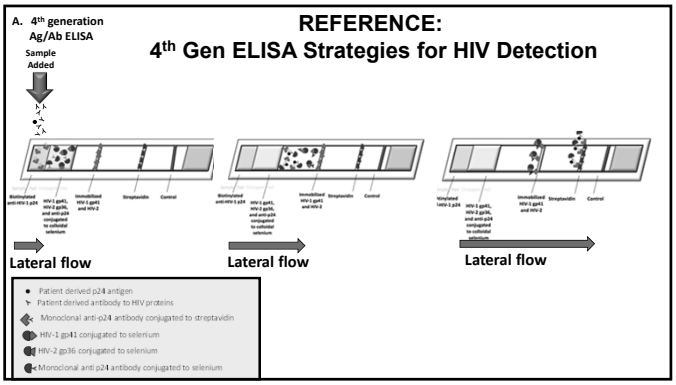
HIV Testing

- 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

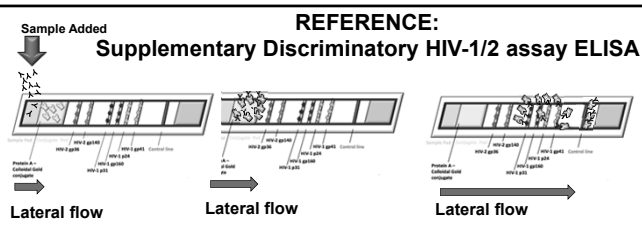
Pearls for Board Exam

- 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
  - Fmaldarelli3@gmail.com
  - Reference slides follow
- No test is perfect
  - 4th Gen less sensitive
    - Acute
    - PEP/PrEP
    - Early Antiretroviral therapy
  - False Positives
    - Pregnancy
  - Mind the gap
    - Long gap for Home testing
- Board exam isn't perfect either
  - So don't overthink it

REFERENCE: 4th Gen ELISA Strategies for HIV Detection



REFERENCE: Supplementary Discriminatory HIV-1/2 assay ELISA



HIV-1
Positive: Any 2 bands of the 4 HIV-1 test lines with at least 1 ENV - gp160 (Band 4) or gp41 (Band 6)
Negative: NO Bands
Indeterminate: 1ENV (Band 4 or 6) 1GAG (Band 5) 1POL (Band 3) 1GAG and 1POL (Bands 5 and 3)
HIV-2:
Positive: 2 HIV-2 bands must be present: gp36 and gp140 (Band 1 and 2)
Negative: No bands

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Antiretroviral Therapies

Dr. Roy Gulick

Antiretroviral Therapy (ART)

Roy M. Gulick, MD, MPH
Rochelle Belfer Professor in Medicine
Chief, Division of Infectious Diseases
Weill Cornell Medicine

Disclosures of Financial Relationships with Relevant Commercial Interests

- **None**

ID Boards – Medical Content: 15% HIV

- Epidemiology (<2%)
  - Transmission
  - Testing and counseling
  - Initial laboratory evaluation
  - Prevention
- Pathogenesis (<2%)
  - Virology
  - Immunopathogenesis
  - Acute HIV infection
- Lab testing (<2%)
  - Diagnostic evaluation
  - Baseline evaluation
- HIV Treatment Regimens (4.5%)
  - ART drug classes
  - Adverse effects of treatment
  - Drug-drug interactions
  - When to start therapy
  - Selection of optimal initial regimen
  - Laboratory monitoring
  - Treatment-experienced patients

ID Boards – Medical Content: 15% HIV

- Opportunistic Infections (5%)
  - Prevention
  - When to start ART with an OI
  - IRIS
  - Bacteria; Mycobacteria; Fungi; Parasites; Viruses
- Malignancies (<2%)
  - Kaposi sarcoma (KS)
  - Lymphoma
  - Cervical cancer
  - Anal cancer
- Other complications of HIV (2%)
  - Heme, endocrine, GI, renal (including HIVAN), cardiac, pulmonary, HEENT, musculoskeletal, neuro, psych, derm
- Related issues (<2%)
  - Substance use
  - Organ transplantation
  - Primary care
  - Misc non-HIV complications
  - Pregnancy

Antiretroviral Therapy (ART)

- Questions
  - When to start?
  - What to start?
  - When to switch?
  - What to switch to?
- Treatment as Prevention
- HIV Drug Resistance / Case Scenarios
- ART for Special Populations

WHEN TO START?

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-progressor 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 cells/uL.

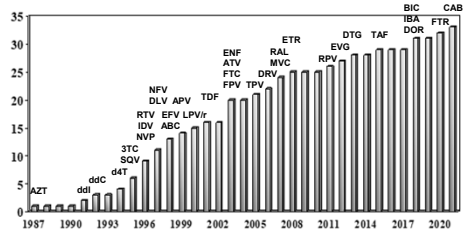
When to Start?: Chronic Infection

	AIDS/ symptoms	Asymptomatic			
		CD4 <200	CD4 200-350	CD4 350-500	CD4 >500
US DHHS 2021 www.clinicalinfo.hiv.gov	recommended				
IAS-USA 2020 Saag JAMA 2020;324:1651-1669	recommended				

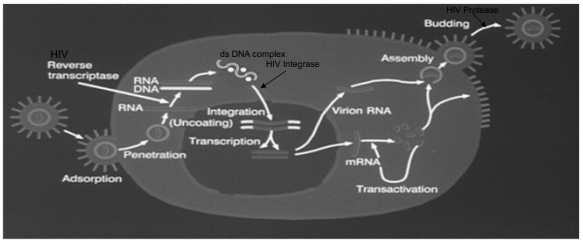
Goal of Antiretroviral Therapy

- 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)

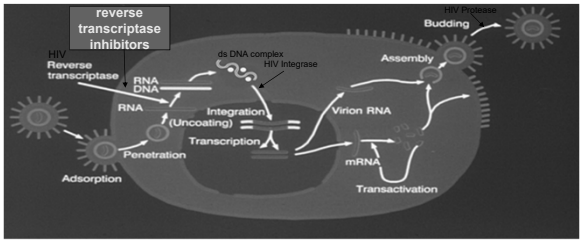
Antiretroviral Drug Approval: 1987 - 2021

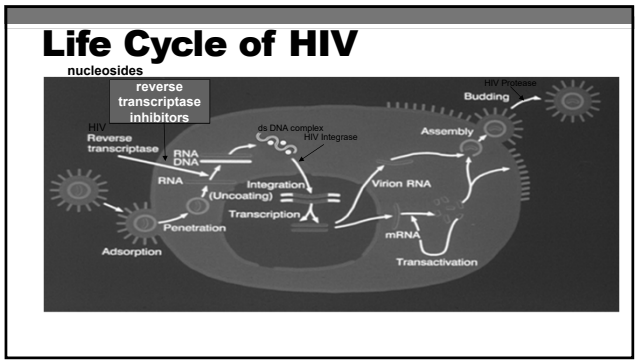


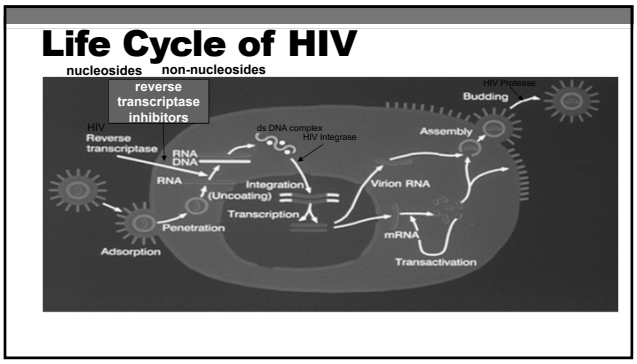
Life Cycle of HIV

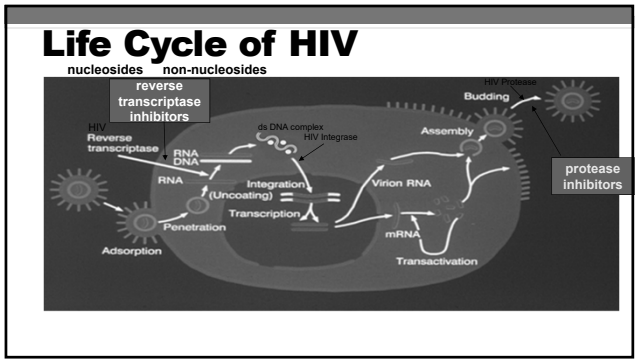


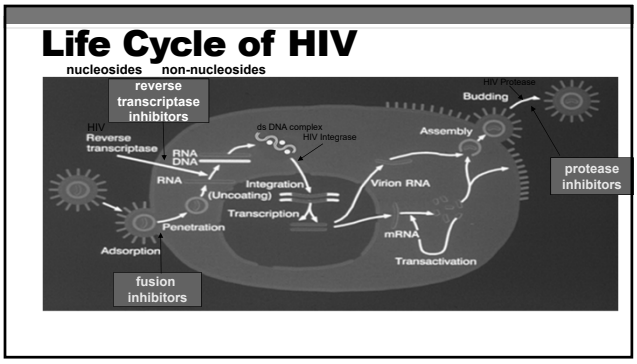
Life Cycle of HIV

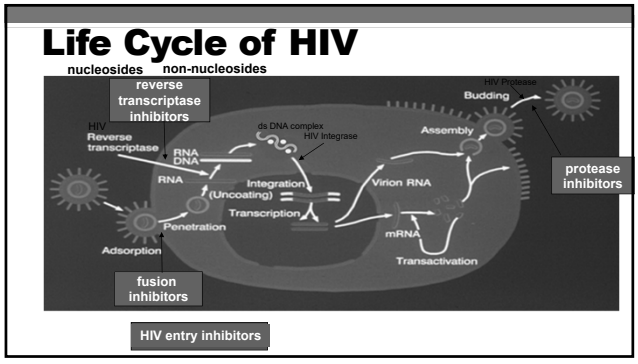


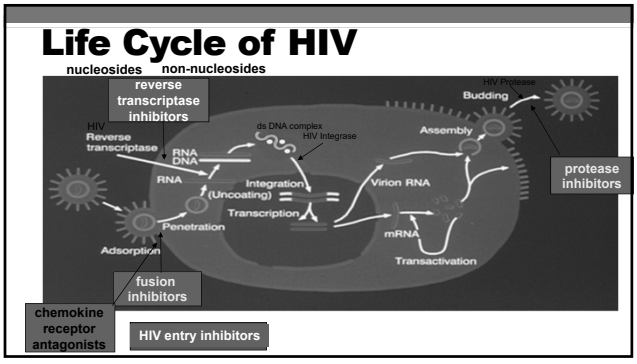




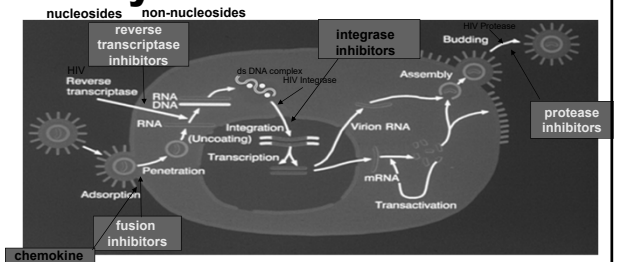




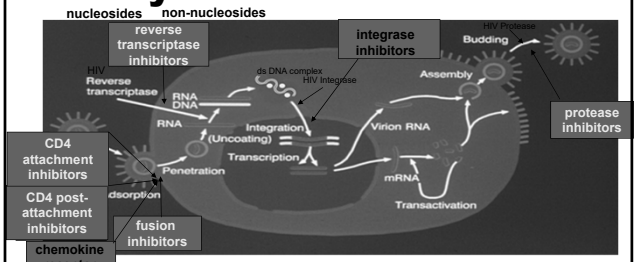




Life Cycle of HIV



Life Cycle of HIV



Approved ART: 2021*

nucleoside/tide RTIs (NRTIs)
- zidovudine (ZDV, AZT)
- lamivudine (3TC)
- abacavir (ABC)
- emtricitabine (FTC)
- tenofovir (TAF, TDF)

NNRTIs
- nevirapine (NVP)
- 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)

*ddI, ddC, d4T, DLV, and APV discontinued from market

entry inhibitors (EIs)
- enfuvirtide (T-20, fusion inhib.)
- maraviroc (MVC, CCR5 antagonist)
- ibalizumab (IBA, CD4 post-attachment inhib.)
- fostemsavir (FTR, CD4 attachment inhib.)

integrase inhibitors (IIs)
- raltegravir (RAL)
- elvitegravir (EVG)
- dolutegravir (DTG)
- bictegravir (BIC)
- cabotegravir (CAB)

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. raltegravir + darunavir (boosted)
B. tenofovir alafenamide/emtricitabine/rilpivirine
C. abacavir/lamivudine + efavirenz
D. lamivudine/dolutegravir
E. tenofovir alafenamide/emtricitabine/bictegravir

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) (1-2 NRTI + integrase inhibitor)

- Integrase inhibitor-based
  - **bictegravir**/tenofovir alafenamide (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)

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Alternative Regimens (Certain Situations) (1)

- Integrase inhibitor-based (INSTI + 2 NRTI)
  - **elvitegravir**/cobicistat/tenofovir (TAF or TDF)/emtricitabine
  - **raltegravir** + tenofovir (TAF or TDF) + (lamivudine or 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)
  - **darunavir**/(ritonavir or cobicistat) + abacavir*/lamivudine
  - **atazanavir**/(ritonavir or cobicistat) + tenofovir (TDF or TAF) + (lamivudine or emtricitabine)

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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 600 + TAF/emtricitabine
    - efavirenz 400/TDF/lamivudine
  - **rilpivirine** + tenofovir (TAF or TDF)/emtricitabine (if VL <100,000 cps/ml and CD4 >200)

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Alternative Regimens (Certain Situations) (3)

- Options 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 + lamivudine
  - **darunavir**/ritonavir + raltegravir BID (if HIV RNA <100,000 cps/ml and CD4 >200)

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Choice of NRTIs

Combination	DHHS GL	Dosing	Toxicities	Considerations
tenofovir (TAF or TDF)/ **emtricitabine** (FTC)	recommended	1 tab qd	renal, bone (with TDF); ↓ toxicity with TAF	1-pill, once-daily formulations available
abacavir/ lamivudine (ABC/3TC)	recommended (with dolutegravir only) / alternative	1 tab qd	HSR (5-8%) (do HLA-B*5701 test)	ABC/3TC/DTG available; less effective with VL >100K; ??↑MI
zidovudine/ lamivudine (ZDV/3TC)	not recommended	1 tab bid	GI, anemia, lipoatrophy	toxicity

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Choice of NNRTIs

Drug	DHHS GL	Dose	Toxicities	Considerations
doravirine (DOR)	alternative	qd	↓ CNS toxicity than EFV; ↓ lipids	TDF/FTC/DOR (1 pill, once-daily)
efavirenz (EFV)	alternative	qd (600 or 400 mg)	CNS toxicity (50%), rash (10%), suicidality (rare)	TDF/FTC/EFV (1 pill, once-daily)
rilpivirine (RPV)	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 (NVP)	not recommended	qd or bid	hepatotoxicity, hypersensitivity	toxicity

DHHS Guidelines 6/3/21

Choice of PIs

Drug	DHHS GL	Dose	Toxicities	Considerations
darunavir /(ritonavir or cobicistat) (DRV/r or c)	alternative; in general, preferred over ATV	qd (if no prior PI resistance) or bid	skin rash (rare);	active against PI-resistant viral strains
atazanavir /(ritonavir or cobicistat) (ATV/r or c)	alternative	qd	↑ indirect bilirubin, GI	avoid PPI; kidney stones (uncommon)
lopinavir/ ritonavir (LPV/r)	not recommended	bid or qd	diarrhea, ↑lipids	co-formulated

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Choice of Integrase Inhibitors (II)

Drug	DHHS GL	Dosing	Toxicities	Considerations
bictegravir (BIC)	recommended with TAF/FTC	1 coform-ulated pill	few, ↑creat, wt gain	TAF/FTC/BIC (1 pill, qd); ↑ barrier to resistance
dolutegravir (DTG)	recommended with (TAF or TDF)/(FTC or 3TC) or ABC/3TC	50 mg qd (bid with II resistance)	few, ↑creat, CNS, neural tube defects (rare), wt gain	ABC/3TC/DTG (1 pill, qd); ↑ barrier to resistance
elvitegravir (EVG)	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 (RAL)	alternative with (TAF or TDF)/FTC	400 mg bid; 600 mg X 2 qd	few	twice-daily dosing; no co-formulations

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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

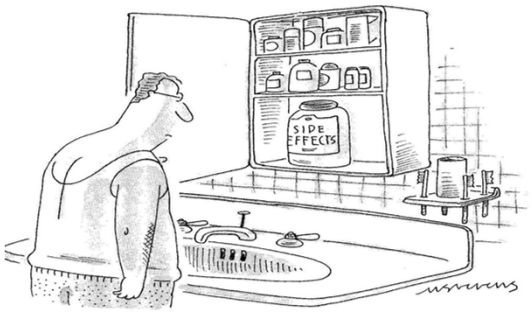
Selected Drug Interactions (2)

- Cytochrome P450 3A4 effects
- PIs are inhibitors; ritonavir is the most potent inhibitor ever described; cobicistat is a potent 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 (e.g. zidovudine)
- Non-nucleosides (NNRTI)
  - older drugs (e.g. nevirapine)
  - etravirine
- Protease Inhibitors (PI)
  - unboosted PIs
  - older drugs (fosamprenavir, indinavir, lopinavir, nelfinavir, ritonavir [except as a booster], saquinavir tipranavir)
- Entry inhibitors (EI) all
- Some 2-drug regimens
  - CAB + RPV or DTG + RPV

Based on DHHS Guidelines 6/3/21



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
  - Stevens-Johnson syndrome (nevirapine, etravirine)
  - teratogenicity*
    - efavirenz = pregnancy category D
    - dolutegravir during conception/very early pregnancy → neural tube defects -- RARE

ART Side Effects (2)

- **Acute/early**
  - gastrointestinal (zidovudine, 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)
  - morphologic –
    - fat loss – lipoatrophy (stavudine, zidovudine)
    - fat gain – lipohypertrophy (older PIs)
  - peripheral neuropathy (stavudine, zalcitabine, didanosine)
  - proximal renal tubular dysfunction (TDF)
  - weight gain (bictegravir, dolutegravir, TAF)

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); IM CAB + RPV
  - Not recommended: monotherapy, boosted ATV + RAL, MVC-based
- Consideration: concomitant HBV infection

DHHS Guidelines 6/3/21

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 98 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 TAF/emtricitabine/bictegravir to improve adherence

When to change therapy?

Virologic failure

- VL undetectable – drug resistance unlikely
- VL <200 cps/ml (low-level viremia) – risk of resistance believed to be relatively low
- 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 6/3/21

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 fully active agents (one with a high barrier to resistance: boosted darunavir, dolutegravir, [bictegravir])

DHHS Guidelines 6/3/21

TREATMENT = PREVENTION

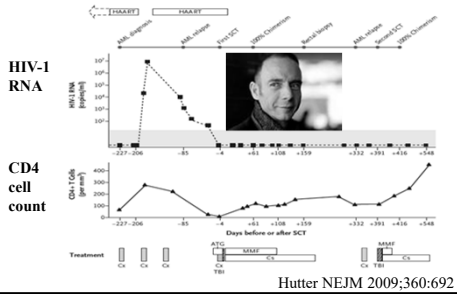
Treatment = Prevention

- HIV+ pregnant women *Fowler NEJM 2016;375:1726*
  - 3-drug ART ↓ transmission risk to child to 0.5%
- HIV+ men and women *Cohen NEJM 2016;375:830*
  - Suppressive ART ↓ transmission to sexual partners by 93%
- HIV- post-exposure prophylaxis (PEP) *CDC Guidelines*
  - 3-drug integrase inhibitor-based ART recommended for 4 weeks
- At-risk HIV- men and women

  Molina NEJM 2015, McCormack Lancet 2016; Choopanya Lancet 2013
  - PrEP ↓ HIV acquisition by sex >75-85% (TDF ♂ + ♀; TAF ♂ only)
  - PrEP ↓ HIV acquisition by injection drug use ~50%

CURE

HIV Cure (N=2)



Hutter NEJM 2009;360:692

Cure #2 Gupta Nature 2019;568: 244-248.

ART Controversies: Conclusions

- **When to start?** Any viral load or CD4 count and "when the patient is ready."
- **What to start?** Excellent options; integrase inhibitor-based regimens; individualization is key.
- **When to change?** Evaluate virologic response; try to prevent emergence of resistance.
- **What to change to?** Use treatment history and drug resistance testing to design new regimen with 2 active drugs (1 with ↑ barrier to resistance).
- **Treatment = Prevention** Treat HIV+, offer PEP and PrEP

Acknowledgements

- **Cornell HIV Clinical Trials Unit (CCTU)**
- Division of Infectious Diseases
- Weill Cornell Medicine
- AIDS Clinical Trials Group
- HIV Prevention Trials Network
- Division of AIDS/NIAID/NIH
- The patient volunteers!

47

HIV Drug Resistance

Dr. Michael Saag

47 – HIV Drug Resistance

Speaker: Michael Saag, MD

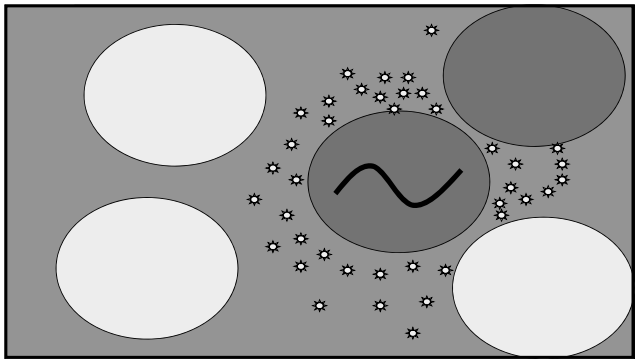
HIV Drug Resistance

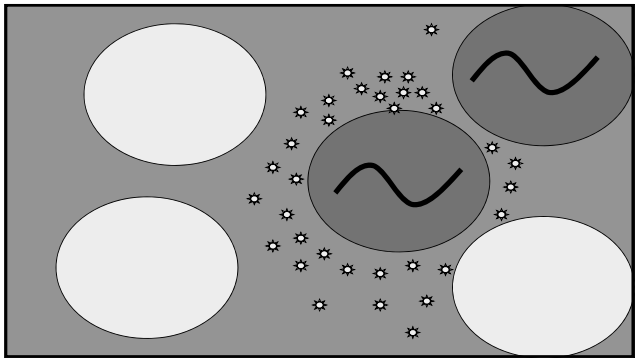
Michael S. Saag, MD
Director, Center for AIDS Research, University of Alabama at Birmingham
Professor of Medicine, Director of UAB CFAR, Jim Straley Chair in AIDS Research, University of Alabama at Birmingham

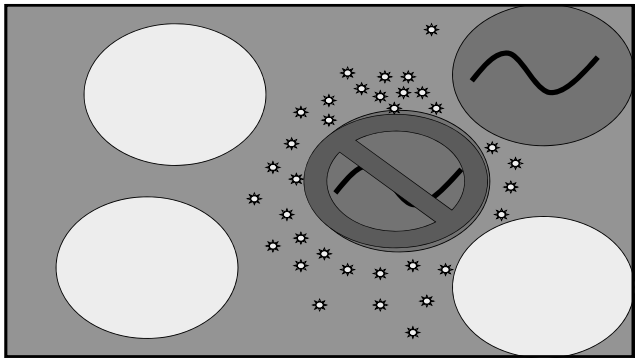
Disclosures of Financial Relationships with Relevant Commercial Interests

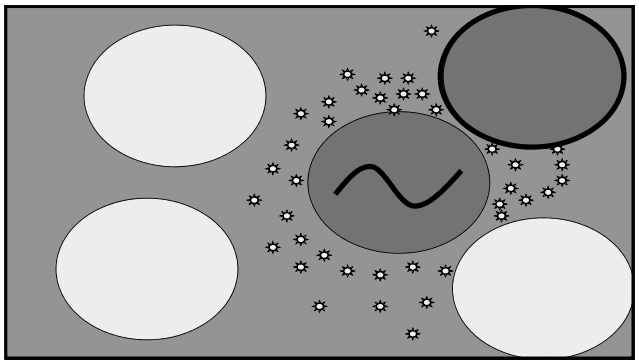
- **None**

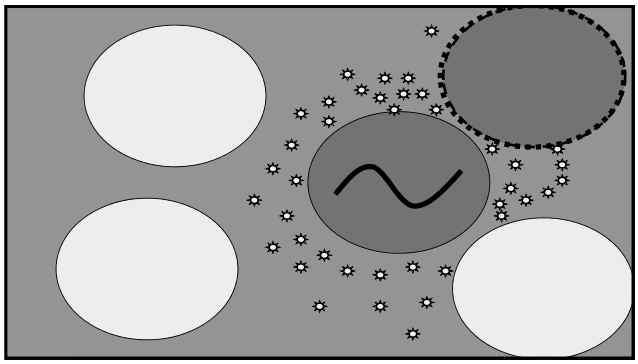
How does resistance happen?

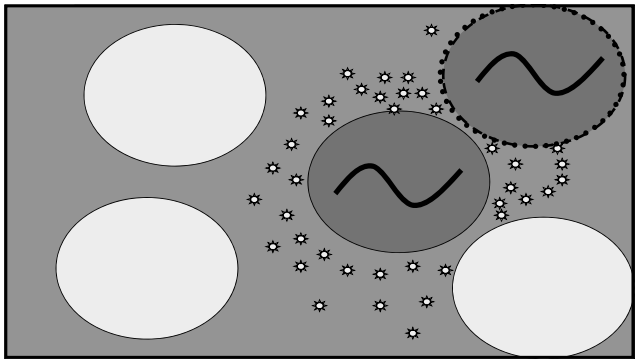












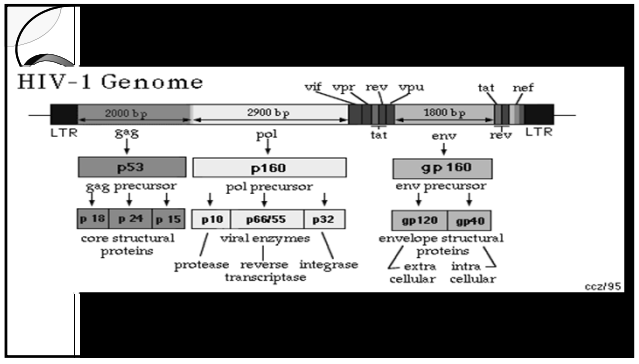


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Table 1. Amino acids and their abbreviations.

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
Tryosine	Y

Mu[redacted]

Nonnucleoside Analogue Reverse Transcriptase Inhibitors (NNRTIs)[1,11]

Drug	Mutations
Doravirine[12]	V106 A, I, M, T; Y188 C, L, H; G190 E; P225 H; F227 C, L, R; M230 L; L234 I
Efavirenz	L100 I; K101 P; K103 N, S; V106 M; V108 I; Y181 C, I; Y188 L; G190 S, A; P225 H; M230 L
Etravirine[13]	V90 I; A98 G; L100 I; K101 E, H, P; V106 I; E138 A, G, K, Q; V179 D, F, T; Y181 C, I, V; G190 S, A; M230 L
Nevirapine	L100 I; K101 P; K103 N, S; V106 A, M; V108 I; Y181 C, I; Y188 C, L, H; G190 A; M230 L
Rilpivirine[14]	L100 I; K101 E, P; E138 A, G, K, Q, R; V179 L; Y181 C, I, V; Y188 L; H221 Y; F227 C; M230 I, L

[redacted]

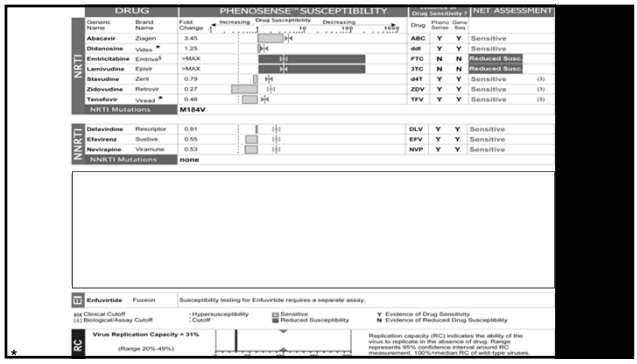
Everything You Need to Know About Nucleoside Analog Resistance in One Slide!

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)

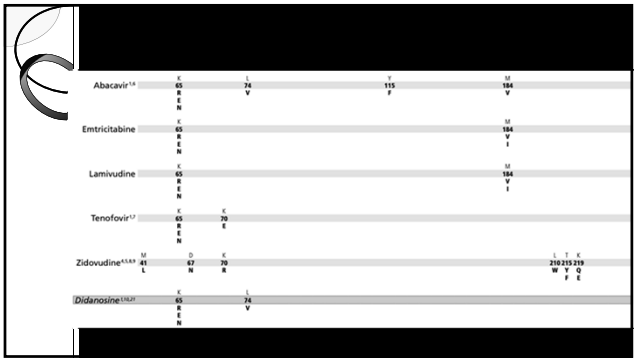
[redacted]

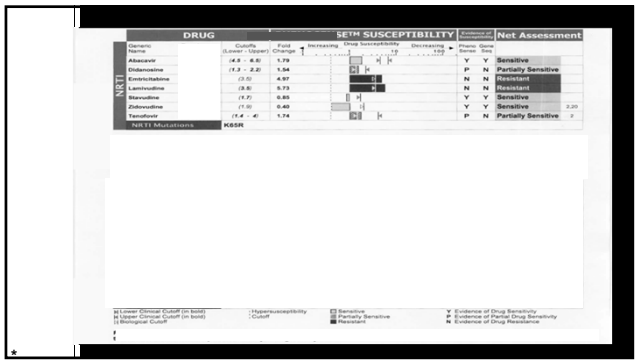
Question #1

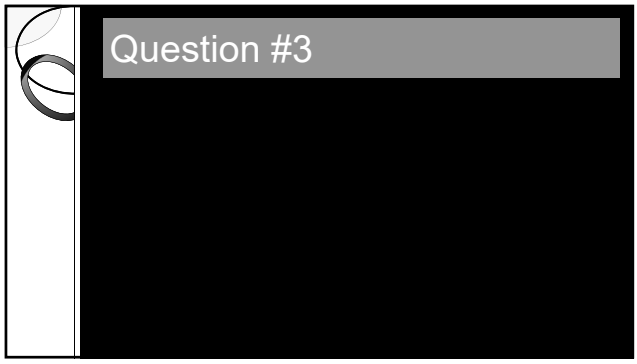
Answer #1



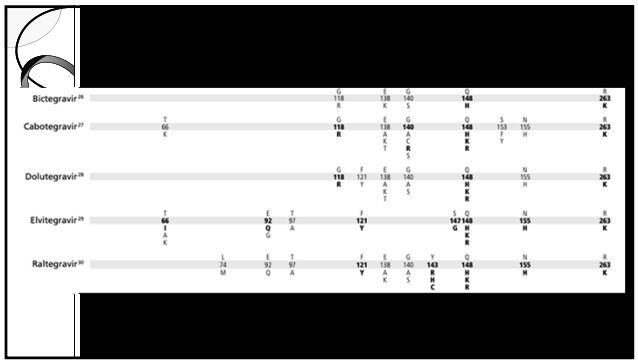
Question #2





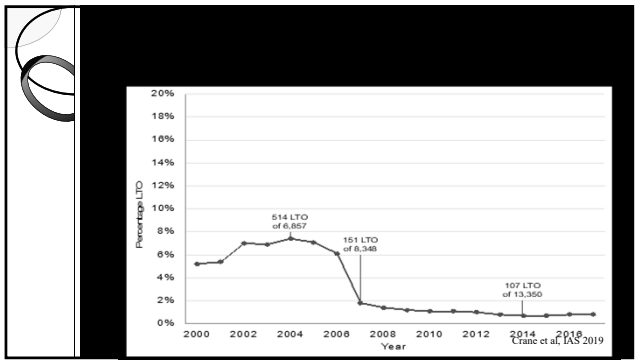


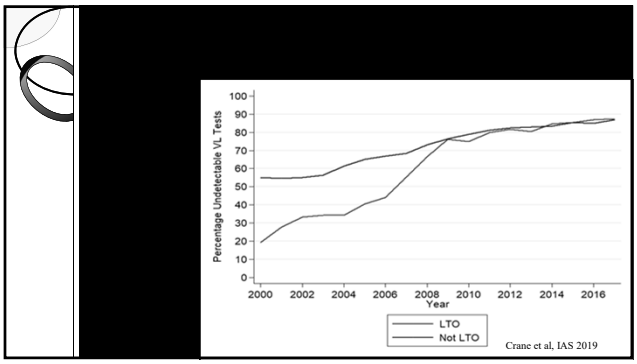
Question #4



Question #5

Question #6





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

- **msaag@uabmc.edu**

48

Antiretroviral Therapy for Special Populations

Dr. Roy Gulick

Antiretroviral Therapy (ART) for Special Populations

Roy M. Gulick, MD, MPH
Rochelle Belfer Professor in Medicine
Chief, Division of Infectious Diseases
Weill Cornell Medicine

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.

Disclosures of Financial Relationships with Relevant Commercial Interests

- **None**

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, dolutegravir,** or **boosted darunavir,** together with tenofovir (TAF or TDF) + emtricitabine.
- Can modify regimen, if needed, when testing results return.

DHHS Guidelines 6/3/21

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 #2

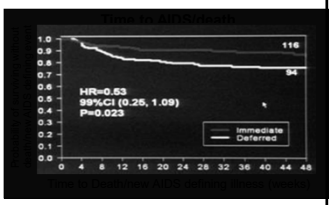
A 52-year-old woman is admitted for progressive SOB, is intubated, undergoes BAL and is found to have PCP. HIV Ab test is positive, CD4 103, HIV RNA 135,000 copies/ml. She is day 4 of IV trimethoprim-sulfa and corticosteroids and still intubated.

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

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. TDF/emtricitabine/efavirenz
B. TAF/emtricitabine + atazanavir (boosted)
C. TDF/emtricitabine + atazanavir (unboosted)
D. TAF/emtricitabine + darunavir (boosted)

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 (2)

- Include a rifamycin in the regimen.
  - rifampin
    - significantly ↓ **TAF** – current FDA label: not recommended
    - significantly ↓ ALL **PIs** – cannot use together
    - ↓ **Dolutegravir (DTG)** concentrations (need to ↑ DTG to 50 mg bid)
    - ↓ NNRTI concentrations: **Efavirenz** (**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 6/3/21

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 6/3/21

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 (can select M184V) *McMahon NEJM 2007;356:2614*
- If treatment started, treat both optimally
  - 2 active agents for HBV
  - + 3rd drug for HIV (preferred = BIC or DTG)

DHHS Guidelines 6/3/21

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 as early as possible:
    - 2 NRTIs + 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 2/10/21 <www.clinicalinfo.hiv.gov>

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 (including assessing liver fibrosis stage).
  - Also evaluate for HBV co-infection.
- HCV direct-acting antiviral regimens → high cure rates

DHHS Guidelines 6/3/21

ART in Pregnancy: NRTI

- Preferred:
  - abacavir/lamivudine
  - tenofovir (TDF)/(emtricitabine or lamivudine)
- Alternative:
  - tenofovir alafenamide (TAF)/emtricitabine
  - zidovudine/lamivudine
- Not recommended:
  - zidovudine/lamivudine/abacavir (3 NRTIs) (insufficient virologic activity)
- IV zidovudine recommended close to delivery if HIV RNA >1000

DHHS Perinatal Guidelines 2/10/21 <www.clinicalinfo.hiv.gov>

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.

ART in Pregnancy: NNRTI

- Alternative:
  - efavirenz (birth defects reported in primate studies, NO evidence in human studies and extensive experience; screen for depression)
  - rilpivirine (NOT with baseline VL >100K or CD4 <200 or PPIs)
- Insufficient data: doravirine
- Not recommended:
  - etravirine (not for treatment-naïve)
  - nevirapine (toxicity, need for lead-in dosing, low barrier to resistance)

DHHS Perinatal Guidelines 2/10/21 <www.clinicalinfo.hiv.gov>

ART in Pregnancy: PI

- Preferred:
  - atazanavir/ritonavir
  - darunavir/ritonavir (use bid)
- Not recommended:
  - cobicistat (↓ drug concentrations, limited experience)
  - lopinavir/ritonavir (side effects)

DHHS Perinatal Guidelines 2/10/21 <www.clinicalinfo.hiv.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

ART in Pregnancy: II

- Preferred:
  - dolutegravir (small, but statistically significant, risk of neural tube defects)
  - raltegravir
- Insufficient data: bictegravir
- Not recommended:
  - elvitegravir/cobicistat (↓ drug concentrations)

DHHS Perinatal Guidelines 2/10/21 <www.clinicalinfo.hiv.gov>

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

ART in Pregnancy: Other

- Not recommended:
  - 2-drug regimens (e.g. dolutegravir/lamivudine, dolutegravir/rilpivirine)
  - enfuvirtide (not for treatment-naïve)
  - maraviroc (tropism testing; not recommended in treatment-naïve)
- Insufficient data: ibalizumab

DHHS Perinatal Guidelines 2/10/21 <www.clinicalinfo.hiv.gov>

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 or 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.clinicalinfo.hiv.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.

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!

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
- 2019 FDA approved TAF/FTC for PrEP for ♂ (NOT ♀), based on DISCOVER

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) – TDF/FTC (♂+♀), TAF/FTC (♂)

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Board Review Session 4

Drs. Gulick (Moderator), Bloch, Dorman, Dupont, Maldarelli, Saag, and Weinstein

49 – Board Review Day 4

Speaker: Drs. Gulick (Moderator), Bloch, Dorman, Dupont, Maldarelli, Saag, and Weinstein

Board Review: Day 4

Moderator: Dr. Gulick
Faculty: Drs. Bloch, Dorman, Dupont, Maldarelli, Saag, Weinstein

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BOARD REVIEW DAY 4

#46 **An 88-year-old man who lives in a nursing home in a large U.S. city develops diarrhea and vomiting.**

He has not recently taken antibiotics and is not on a proton pump inhibitor.

He develops diarrhea and is taken to a hospital where he is found to have advanced renal failure and ventricular arrhythmia and despite fluid therapy and cardiovascular drugs he dies 12 hours after admission.

BOARD REVIEW DAY 4

#46 **Which of the following is the most likely cause of his enteric syndrome and death?**

A) Norovirus

B) *Aeromonas*

C) *Listeria monocytogenes*

D) *Shigella*

E) *Campylobacter*

BOARD REVIEW DAY 4

#47 **A 40-year-old healthy traveler to Nepal develops diarrhea consisting of passage of 2 soft stools/d with mild cramps. This has persisted for 9 days.**

She is able to do what she came to do but needs to know where bathrooms are located at all times.

BOARD REVIEW DAY 4

#47 **What would you recommend she do about her enteric syndrome?**

A) Ciprofloxacin 500 mg bid for 3 days

B) Azithromycin 1,000 mg single dose

C) Rifaximin 200 mg tid for 3 days

D) Fluids (soups, broth, non-carbonated drinks) only with or without loperamide she has with her

E) No therapy

BOARD REVIEW DAY 4

#48 **A 44-year-old man recently diagnosed with HIV is concerned about drug side effects and wants to start an ART regimen with the "lowest number of drugs possible."**

49 – Board Review Day 4

Speaker: Drs. Gulick (Moderator), Bloch, Dorman, Dupont, Maldarelli, Saag, and Weinstein

BOARD REVIEW DAY 4

#48 **Which of the following initial regimens is optimal for his initial therapy?**

A) bictegravir monotherapy

B) boosted darunavir + lamivudine

C) dolutegravir/lamivudine

D) dolutegravir/rilpivirine

BOARD REVIEW DAY 4

#49 **A 36-year-old female is referred to ID clinic from the Gynecology Department, where she had presented with 6 months of abdominal discomfort and swelling, accompanied by 12 lb weight loss and fevers.**

She was originally from Brazil and had moved to the US four months prior.

She has severe, poorly controlled asthma and has received several steroid tapers over the past year. Evaluation by the Gynecology team had included CA-125, which was elevated at 608 U/ml (normal range <35 U/ml).

BOARD REVIEW DAY 4

#49 **CT imaging of the abdomen and pelvis showed ascites and omental caking.**

Laparoscopy was performed and on visual inspection there was diffuse studding of intraperitoneal surfaces with 2-3 mm tan nodules.

A biopsy of affected material was obtained and showed non-caseating granulomas without evidence of malignancy; cultures were set up and are in progress.

BOARD REVIEW DAY 4

#49 **What is the most likely mode of transmission of the infection?**

A) Bite of a triatomine (kissing bug) insect

B) Bite of a sand fly

C) Inhalation of airborne bacteria

D) Sexual transmission of a spirochete

BOARD REVIEW DAY 4

#50 **An 18-year-old male is referred to you for evaluation and management of a positive QuantiFERON-TB Gold test. He was born in India and is in the U.S. as a high school exchange student. He reports no significant past medical history, and he feels entirely well without cough, fevers, or weight loss.**

To his knowledge he has never been in contact with anyone with pulmonary TB.

Records from the referring provider document a negative HIV test, normal CBC and liver chemistries, and a normal chest X-ray, all performed 2 weeks ago.

BOARD REVIEW DAY 4

#50 **What is the best next step?**

A) Recommend treatment for latent TB infection with 2 months of rifampin and pyrazinamide

B) Recommend treatment for latent TB infection with 12 weeks of once weekly isoniazid and rifapentine

C) Perform a tuberculin skin test to make sure that this is not a false-positive QuantiFERON-TB Gold test

D) Initiate TB treatment with rifampin, isoniazid, pyrazinamide, ethambutol

E) No further action needed since the positive QuantiFERON-TB Gold test most likely represents immunological cross-reactivity to neonatal vaccination with Bacille Calmette-Guerin (BCG)

49 – Board Review Day 4

Speaker: Drs. Gulick (Moderator), Bloch, Dorman, Dupont, Maldarelli, Saag, and Weinstein

BOARD REVIEW DAY 4

#51 **A 71 y/o man with HIV disease transfers care to you with a history of taking and failing "nearly all HIV medications including T20 (enfuvirtide)".**

He currently takes tenofovir alafenamide (TAF)/emtricitabine (FTC) + etravirine + darunavir + ritonavir with a CD4 15 and HIV RNA 233,140 copies/ml.

You send an HIV genotype, phenotype, and tropism test. The tropism test returns "dual/mixed virus".

BOARD REVIEW DAY 4

#51 **In addition to optimizing his antiretroviral regimen, you recommend:**

A) Adding maraviroc

B) Adding double-dose maraviroc

C) Adding enfuvirtide

D) Adding ibalizumab

BOARD REVIEW DAY 4

#52 **A 22 y/o man is found HIV+ with a CD4 344 and HIV RNA 16,000 copies/ml and starts abacavir (ABC)/lamivudine (3TC)/dolutegravir(DTG) at an outside clinic.**

After several days, he develops a rash, nausea and vomiting for which he does not seek medical attention. He discontinues his medications and feels much better.

Three months later, after urging from his mother, he presents to you now to restart HIV therapy.

He is asymptomatic, has a normal physical exam, CD4 322, and HIV RNA 15,000 copies/ml.

BOARD REVIEW DAY 4

#52 **What do you advise regarding ART?**

A) Repeat CD4 and HIV RNA

B) Check G6PD before restarting ART

C) Check HLA-B*5701 before restarting ART

D) Restart ABC/3TC/DTG with instructions to call clinic for any symptoms

BOARD REVIEW DAY 4

#53 **Over a 3-week period, 5 patients in a 12-bed ICU have infections with a carbapenem-resistant *Klebsiella pneumoniae* (KPC): Two have symptomatic urinary tract infections, 2 have ventilator-associated pneumonia, and 1 has a line-related bacteremia. These are the only KPC infections recognized in this ICU in the past 6 months.**

Whole genome sequence (WGS) analysis of the isolates shows that four are nearly identical and one probably genetically unrelated.

BOARD REVIEW DAY 4

#53 **The most likely epidemiologic explanation for these infections is that this cluster represents which of the following:**

A) Is a pseudoepidemic

B) Results from lapses in infection control

C) Results from common source medication contamination

D) Represents a water-borne outbreak

E) Represents a food-borne outbreak

49 – Board Review Day 4

Speaker: Drs. Gulick (Moderator), Bloch, Dorman, Dupont, Maldarelli, Saag, and Weinstein

BOARD REVIEW DAY 4

#54 A 56-year-old female presents c/o sore throat. She was in her usual state of health until 1 day prior to admission when she noted pain on swallowing and myalgias.

A rapid strep test at a walk-in clinic was negative and she was given a presumptive diagnosis of viral pharyngitis. That evening the pain progressed and she presented for ER evaluation.

She lives in rural Idaho and has well water. She raises chickens and has a pet goat.

She has not travelled outside of the region in the last year. She notes exposure to her 2-year-old grandson who had a fever the previous week.

BOARD REVIEW DAY 4

#54 On presentation she is afebrile and vitals signs are stable. She is breathing comfortably on room air without stridor however she is spitting into a cup next to the bed because it hurts to swallow.

Oropharyngeal exam shows good dentition, normal mucosa and no tonsillar enlargement or inflammation. There is no cervical swelling or lymphadenopathy.

White blood cell count is 15.9, other labs are unremarkable.

BOARD REVIEW DAY 4

#54 Which of the following is the most likely diagnosis in this patient?

A) Ludwig's angina

B) Streptococcal pharyngitis

C) Diphtheria

D) Pharyngeal tularemia

E) Epiglottitis

BOARD REVIEW DAY 4

#55 A previously healthy 29yo female presents with 1 week of fevers, chills, and headache. She decided to seek medical care after she noted dark discoloration of her urine.

She lives in Connecticut and has a vacation home on Martha's Vineyard.

She is an avid hiker and notes many tick and mosquito bites in the last month.

She has traveled extensively for work, including a trip to South Africa 1 year previously where she visited a game preserve.

BOARD REVIEW DAY 4

#55 On physical exam, her temperature is 102.8 F, heart rate is 118 bpm, and BP is 125/68. Otherwise, exam is unremarkable, with no rash, photophobia, or nuchal rigidity.

Laboratory studies include:

- WBC=5.8
- H/H=7.4/22
- Platelets=97
- AST/ALT=127/119
- Alk phos=384
- Total Bilirubin=1.7
- Haptoglobin <8
- LDH 784
- A lumbar puncture was done, with 1 WBC

BOARD REVIEW DAY 4

#55 A Giemsa stain of a thin blood smear is below:

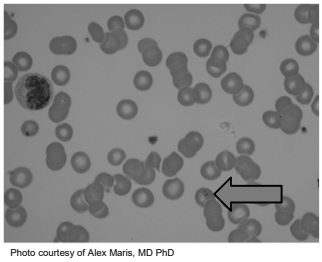


Photo courtesy of Alex Maris, MD PhD

49 – Board Review Day 4

Speaker: Drs. Gulick (Moderator), Bloch, Dorman, Dupont, Maldarelli, Saag, and Weinstein

BOARD REVIEW DAY 4

#55 **Which of the following pathogens is the most likely cause of her illness?**

A) Plasmodium falciparum

B) Powassan virus

C) Babesia microti

D) Anaplasma phagocytophilum

E) Plasmodium knowlesi

BOARD REVIEW DAY 4

#56 **A 28 y/o HIV negative woman with an HIV+ male sexual partner asks about taking HIV pre-exposure prophylaxis (PrEP).**

BOARD REVIEW DAY 4

#56 **Which do you recommend?**

A) None, PrEP not indicated

B) Daily tenofovir disoproxil fumarate (TDF)/emtricitabine

C) Episodic TDF/emtricitabine

D) Daily tenofovir alafenamide (TAF)/emtricitabine

E) Episodic TAF/emtricitabine

BOARD REVIEW DAY 4

#57 **26-year-old HIV+ man on his first ART regimen, tenofovir (TDF)/emtricitabine + raltegravir, for 2 years.**

HIV RNA originally 203,000 copies/ml, then decreased to <50 copies/ml by 4 months.

On his most recent routine lab tests, HIV RNA was 13,900 copies/ml, repeated 2 weeks later after adherence counseling at 11,400 copies/ml.

BOARD REVIEW DAY 4

#57 **What lab test(s) would you now order?**

A) Drug level testing

B) Genotype testing (reverse transcriptase/protease and integrase)

C) Phenotype testing (reverse transcriptase/protease and integrase)

D) Genotype and phenotype testing (reverse transcriptase/protease and integrase)

E) CCR5 tropism testing

BOARD REVIEW DAY 4

#58 **A 23 y/o man presents to the emergency room asking for "HIV PEP" (post-exposure prophylaxis).**

He states that he had receptive anal intercourse 2 hours ago with a male partner with unknown HIV status and that "the condom broke."

He is in good health and a rapid HIV antigen/antibody test is negative.

49 – Board Review Day 4

Speaker: Drs. Gulick (Moderator), Bloch, Dorman, Dupont, Maldarelli, Saag, and Weinstein

BOARD REVIEW DAY 4

#58 Which do you recommend?

A) No PEP – low-risk exposure

B) Start PEP when HIV drug-resistance testing results available

C) Start PEP now with zidovudine/lamivudine + lopinavir/ritonavir

D) Start PEP now with tenofovir (TDF)/lamivudine + dolutegravir

E) Start PEP now with single-dose nevirapine

BOARD REVIEW DAY 4

#59 A 32-year-old man returns for routine follow up in the HIV clinic and is found to have new elevations in his liver function tests.

He has no complaints and his physical exam is normal.

BOARD REVIEW DAY 4

#59 Lab evaluation from this visit reveals:

- Normal electrolytes
  - AST 130 u/ml (35 u/ml last visit)
  - ALT 180 u/ml. (25 u/ml last visit)
  - Bilirubin 0.8 mg/dl
  - Alk phos 110 mg/dl
- RPR non-reactive
- Urine / rectal NATs negative for GC and Chlamydia

BOARD REVIEW DAY 4

#59 He has been on BIC / FTC / TAF (Biktarvy-bictegravir, emtricitabine & tenofovir alafenamide) for the last 2 years with undetectable virus.

His last CD4 count 1 year ago was 855 cells /ul.

Three years ago he was diagnosed with HCV (no evidence of cirrhosis on fibroscan at that time) and he received treatment with sofosbuvir and ledipasvir for 12 weeks, achieving an undetectable HCV RNA at month 4 post-treatment.

BOARD REVIEW DAY 4

#59 At the time of his HCV treatment he was vaccinated for Hepatitis A and Hepatitis B.

His post vaccine hepatitis B surface antibody (anti-HBs) titer was >10 milli-international units/mL.

He reports frequent sexual activity with same sex partners; at least 4 – 6 different partners per month over the last 5 months.

BOARD REVIEW DAY 4

#59 Which of the following is most likely responsible for his increased liver enzymes:

A) Hepatitis A infection

B) Hepatitis B infection

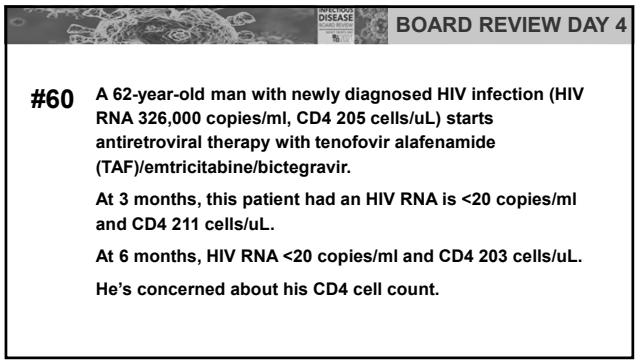
C) Hepatitis C infection

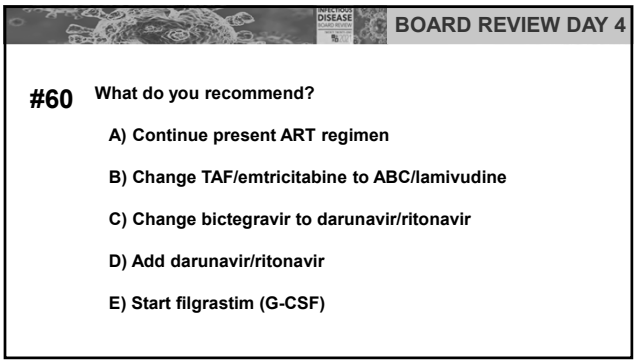
D) Drug induced liver injury (DILI)

E) Cirrhosis

49 – Board Review Day 4

Speaker: Drs. Gulick (Moderator), Bloch, Dorman, Dupont, Maldarelli, Saag, and Weinstein





50

Syndromes that Masquerade as Infections

Dr. Karen Bloch

50 – Syndromes that Masquerade as Infections

Speaker: Karen Bloch, MD

Syndromes that Masquerade as Infections

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

Disclosures of Financial Relationships with Relevant Commercial Interests

- **None**

With Special Thanks to Dr. Bennett Lorber!

Mimics

- Many conditions masquerade as infections.
  - Often with fever
  - Sometimes focal abnormality
    - Cellulitis vs stasis dermatitis
    - Viral vs Organizing Pneumonia
    - Lymphadenitis vs Lymphoma

VS

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”

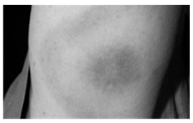
You say…..

YERSINIA

Test taking tip

I say ”Bull’s-eye rash”

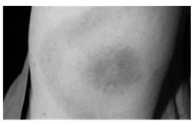
You say…..



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

Examples

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

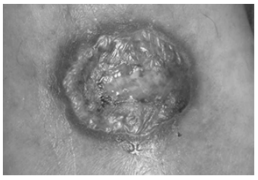
Sweet Syndrome is *most* likely to occur in a patient with which of the following illnesses?

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 lesion 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



But this being boards…..

Case 4

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

Case 4

- Exam:
  - Vitals:
    - T=38.4ºC, HR=118 bpm
  - No cervical 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. CMV PCR
  - D. Soluble IL-2 receptor level
  - E. Toxoplasma titer

Hemophagocytic Lymphohistiocytosis

- Immune activation syndrome
  - Primary: Familial due to genetic mutation
  - Secondary:
    - Infections (EBV or other herpes group viruses, HIV, histoplasmosis, *Ehrlichia*, COVID-19 etc)
    - Malignancy (lymphoma, leukemia)

HLH: Diagnostic Criteria

- At least 5 of the following:
  - Fever
  - Splenomegaly
  - Cytopenias (any line)
  - Hypertriglyceridemia (>3mmol/L)
  - Ferritin >500 mcg/mL
  - Elevated soluble IL-2 receptor (aka CD25)
  - Low NK cell activity
  - Hemophagocytosis on pathology

HLH Clues

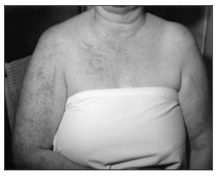
- EBV or other infection with progressive symptoms
- Massively elevated ferritin
- Cytopenia with negative ID evaluation

Case 5

- 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.

Physical Exam

- T=104.2º F.
- Tender cervical LAN appreciated.
- 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.



- 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.

Question 5

- The most likely diagnosis is?
  - A. Lymphoma
  - B. Adult Still's Disease
  - C. Acute Rheumatic Fever
  - D. Cryoglobulinemia
  - E. Kikuchi Disease

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

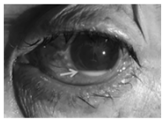
- Buzz words and associations:
  evanescent, **salmon-colored** rash

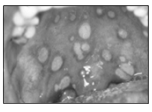
- Other clues:
  - Elevated ferritin
  - Pharyngitis
  - Koebner phenomenon = rash elicited by stroking skin or areas of pressure.

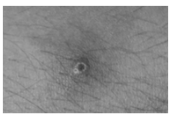
Case 6

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

- 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 where they drew blood yesterday in the ED.







Question 6

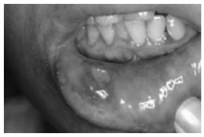
- The most likely diagnosis is?
  - A. Syphilis
  - B. Behçet's disease
  - C. Herpes simplex virus infection
  - D. Sarcoidosis
  - E. Cytomegalovirus infection

Behçet's disease

- Pleomorphic vasculitis diagnosised clinically
  Recurrent oral ulcers (≥3 per year) PLUS 2 of the following
  1) recurrent genital ulcers
  2) eye (uveitis, retinitis, hypopyon)
  3) skin lesions (EN, papules) including pathergy (red papule 24-48 hours after needlestick)
- "Silk road" ancestry (Asia->Mediterranean)
- Less common manifestations
  - GI disease (abdo. Pain, bloody diarrhea)
  - CNS disease (aseptic meningitis)
  - Arterial and venous thrombosis

Behçet's disease

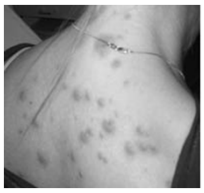
- Buzz words and associations:
  Mucosal ulcers on mouth and/or genitals PLUS….
  GI symptoms (vs CMV)
  Aseptic meningitis (vs HSV)
  Ocular findings
  Pathergy (needle or IV site)
  Asian or Mediterranean ancestry



Case 7

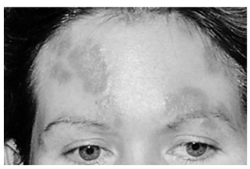
- A 38-year-old woman with AML is admitted with fever. She underwent induction chemotherapy 2 weeks prior, complicated by neutropenic fever. Following marrow recovery, she was d/c to home. The day of admit she developed fever without localizing symptoms. CBC showed a white blood cell count of 12,250 with 20% bands.
- Exam: T 101.4; P 98, Otherwise unremarkable.
- Blood cultures were sent, and she was 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: skin biopsy: dense perivascular infiltrates of neutrophils without evidence of vasculitis; stains for organisms negative.



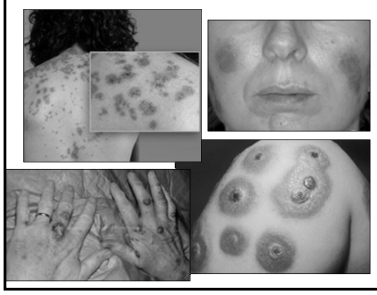
Question 7

- Which 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, antibiotics
- Fever and Rash 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

Skin Lesions in 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

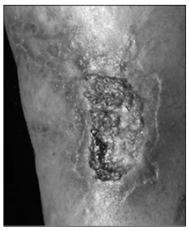
Be suspicious in patients with malignancy (esp AML, past or present), IBD, recent URI, vaccination, pregnancy, or colony stimulating factor use in preceding 2 weeks

Case 8

- 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
- There has been no response to oral antibiotics.
- For the past year he has been troubled by an "upset stomach". On further probing, he describes intermittent abdominal cramps, frequent diarrhea; and, on 2 occasions, blood in the stool.

- 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
  - 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?

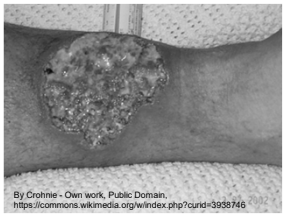
A. Ulcerative colitis
B. Cutaneous leishmaniasis
C. Amebic colitis
D. Necrotizing fasciitis
E. Squamous cell cancer

Pyoderma gangrenosum

- *Another* neutrophilic dermatosis
  - Indolent, fever rare (vs Sweet)
- Papule starts at site of often trivial trauma, progressing to a **painful** ulcer with violaceous border and necrotic base
- >50% of cases occur with systemic illness (but may precede dx, or occur independent of flares)
  - IBD (Ulcerative colitis>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**
  - Associated with IBD, arthritis, neoplasm



By Crohnie - Own work, Public Domain, https://commons.wikimedia.org/w/index.php?curid=3938746

Case 9

- A 79-year-old woman is seen for 3 weeks of fever and fatigue.
- One week earlier she developed jaw discomfort when chewing food and had a brief episode of double vision.
- One month ago, she attended a luau and ate roast suckling pork prepared over an open fire.

- Exam:
  T 102.2, P 104, BP 124/84
  Slight tenderness over left scalp
  mitral regurgitant murmur
  rest of exam normal
- Labs:
  Hb 9.8; WBC 9800, normal diff
  UA normal
  basic metabolic panel normal
  sedimentation rate 147

Question 9

Which of the following is most likely to be diagnostic?

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)= Arteritis of extracranial branches of the carotid.
- A disease of the older adult: Almost all >50 years old
- Clinical findings:
  - Fever (think of this with FUO in elderly)
  - HA, scalp or TA tenderness, jaw claudication
  - amaurosis fugax or sudden vision loss
- 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:

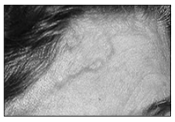
Age >50 years; fever (FUO) and:

scalp or TA tenderness

diplopia or transient visual loss

jaw or tongue fatigue or pain while chewing

high sedimentation rate



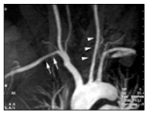
Polymyalgia Rheumatica (PMR)

Buzz words and associations:

- Half of all patients with GCA have concomitant PMR
- Up to 1/3 of patients with PMR have 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, carotids 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 10

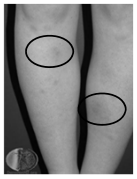
- A 37-year-old female presents with fever and joint pain. She is a long-distance runner and in excellent health.
- Three weeks prior she noted R knee pain after a long run. She was treated with a steroid injection with transient improvement, but subsequently developed bilateral ankle pain and redness. 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

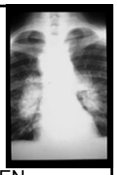
RF <15, CCP negative

Question 10

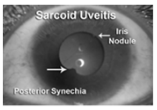
Which of the following is most likely to be diagnostic?

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

Sarcoidosis

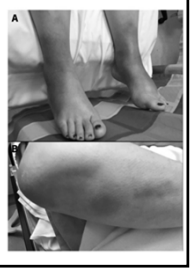


- A common mimicker
- Extra-pulmonary disease in ~1/3 of cases
- Lofgren Syndrome
  - Clinical diagnosis: Triad of hilar LAN, acute arthritis, EN
  - Women, ankles (>90%), fevers common
- BUZZ WORDS
  - Hilar LAN, EN, parotid enlargement, uveitis
  - Aseptic meningitis with basilar enhancement
  - Non-caseating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



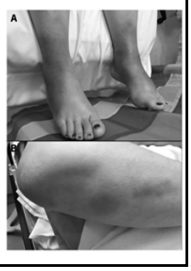
Erythema nodosum

- No cause >50% of cases
- Drugs: sulfonamides, penicillins
- Oral contraceptives
- Sarcoid (Lofgren's syndrome)
- Ulcerative colitis (or Crohn's)
- 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 11

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

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

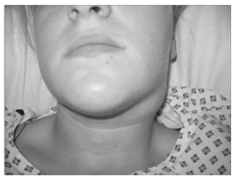
A. Hereditary angioneurotic edema
B. Familial Mediterranean fever
C. Systemic lupus erythematosus
D. Crohn's disease
E. Acute intermittent porphyria

Familial Mediterranean Fever

- Auto-inflammatory dz, causing hereditary periodic fevers
  - Others: PFAPA, TRAPS, hyperimmunoglobulin D
- Sporadic, recurrent attacks of fever & serositis (peritonitis, pleuritis, arthritis) manifesting as pain.
- Variably erysipeloid rash LE
- Dx: Genetic testing
- Buzz words and associations:
  - Periodic episodes (fever PLUS…)
  - Serositis
  - Mediterranean ancestry

Case 12

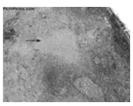
- A 26-year-old medical student presents with fever and cervical adenopathy.
- She was completely well until 9 days ago when she had the acute onset of fever and vague neck discomfort. She had no sore throat and no dental or scalp problems.



- 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 IgG positive, IgM negative
  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

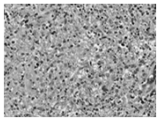
Which one of the following is the most likely diagnosis?

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 Disease

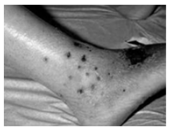


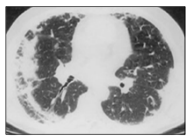
- Diagnosis by pathology:
  - necrotizing histiocytic infiltrate (not neutrophils) and fragments of nuclear debris.
- Buzz words and associations:
  - Acute onset fever and cervical adenopathy in young woman
  - Atypical lymphocytes (mono-like syndrome)
  - Path: necrotizing adenitis with histiocytosis

Case 13

- 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 infiltrate in setting of difficult to control asthma
- Tapering of steroids often "unmasks" EGPA
- May be p-ANCA positive.

Churg-Strauss Syndrome

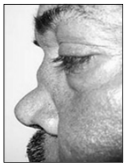
- Buzz words and associations:
  - Longstanding asthma
  - New infiltrates and eosinophilia (>10%) as steroids tapered.
  - Rash (tender nodules on extensor surfaces, purpura, ecchymosis, necrosis)
  - Fever UNCOMMON (until late)

Case 14

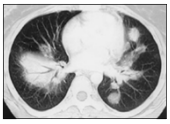
- A 38-year-old man is seen for a 6-week history of cough, intermittent fever and night sweats.
- He has had nasal stuffiness for 4-5 months with occasional epistaxis.
- He lives in Philadelphia, and 6 months ago traveled to Cincinnati, OH on business.
- He has no pets and takes only an OTC decongestant;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

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 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) (~~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: Positive ANCA (~85% sensitivity)
  IFA: c-ANCA.
  ELISA: anti-proteinase 3 (PR3-ANCA)
  Diagnostic: Biopsy

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

Case 15

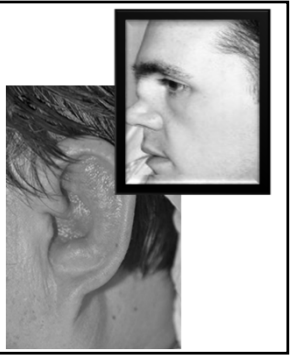
- A 42-year-old man is seen for his third episode of cellulitis of the external ear.
- Two previous episodes involving the same ear, 2 and 5 months ago, responded very slowly to antibiotics.
- He has a several year history of chronic nasal stuffiness and had an episode of knee arthritis in the past year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

Case 15

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

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

Labs: CBC normal



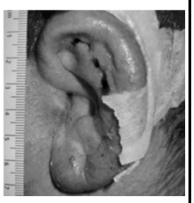
Question 15

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.

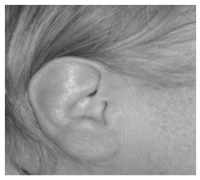


Saddle-nose Deformity

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

51

Tuberculosis in Immunocompetent and Immunosuppressed Hosts

Dr. Susan Dorman

51 – Tuberculosis in Immunocompetent and Immunosuppressed Hosts

Speaker: Susan Dorman, MD

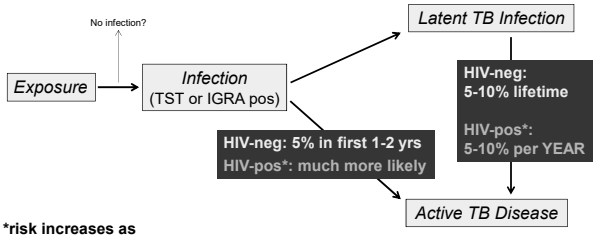
Tuberculosis in Normal and Compromised Hosts

Susan E. Dorman, MD
Professor of Medicine
Medical University of South Carolina

Disclosures of Financial Relationships with Relevant Commercial Interests

- **None**

Overview of TB Epidemiology

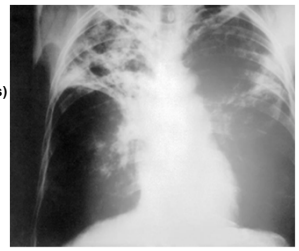


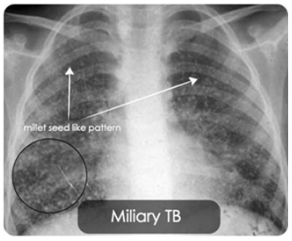
***risk increases as immunosuppression increases**

Epi risk factors for TB INFECTION	Medical 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





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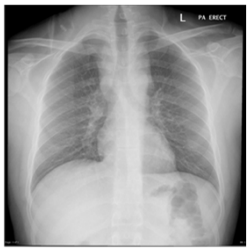


Tuberculous mediastinal lymphadenopathy

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/PCR, 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, other tissue specimens

Active TB disease: diagnosis

Smear microscopy	current nucleic acid amplification tests	culture
		
LOD: 10,000 cfu/ml	100 cfu/ml	1-10 cfu/ml
Sensitivity: LOW	MEDIUM	HIGH

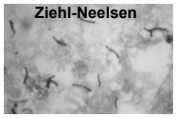
ADJUNCTIVE:
IGRA, TST: do not distinguish latent from active; NEG test does not rule out active TB
Chest X-ray, other radiology: can be suggestive of active TB; not specific
Histopathology: can be suggestive of active TB; not specific

Active TB disease: diagnosis

Smear microscopy for acid fast bacilli

* ***NEGATIVE SMEARS DO NOT EXCLUDE A DIAGNOSIS 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 obtained
- Not specific for M.tb (most mycobacteria look alike)
- Good PPV in TB endemic settings



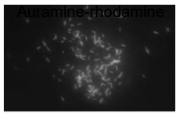


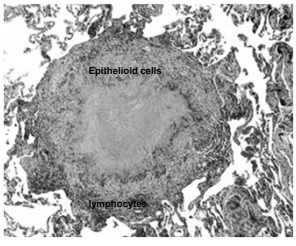
Image credits:
1. CDC/Dr. George P. Kubica
2. https://laboratoryinfo.com/auramine-rhodamine-staining-for-afb-principle-procedure-reporting-and-limitations/

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 amplification inhibitors

Active TB disease: diagnosis

Mycobacterial Culture
- The **most sensitive method** but SLOW (3-6 weeks)
- Once growth observed, the lab performs additional tests:
  - Species identification
  - Growth-based DST
- Considered the gold standard, but not 100% sensitive
  - Pulmonary TB around 90-95% sensitive
  - Extrapulmonary TB much less sensitive



Caseating granuloma

Image credit: 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

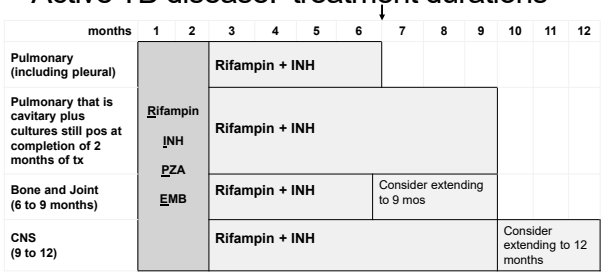
Extend continuation phase therapy for

- 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



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 (acuity, color vision)**
- Arthralgias: PZA

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

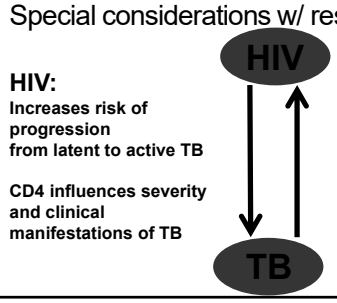
- Risk factors for:
  - Contact with drug-resistant TB case
  - Prior h/o TB treatment, esp if non-adherent with tx
- **MDR=resistance to isoniazid plus rifampin**
- **XDR=MDR plus resistance to fluoroquinolones plus at least one of the injectable 2nd line drugs (amikacin, kanamycin, capreomycin)**
- 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



HIV:
Increases risk of progression from latent to active TB

CD4 influences severity and clinical manifestations of TB

TB:
Can increase HIV viral load

Associated with more rapid progression of 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
  - Extrapulmonary TB (with or WITHOUT pulmonary involvement)
  - 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=20, viral load >1 million 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 treatment initiated

UNMASKING of 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 TB contact CXR with fibrotic changes Transplantation Prednisone ≥ 15 mg/d x 1 month or more TNF-α antagonists	Recent arrival (w/in 5 years) from TB high prevalence area Injection drug use Residents & employees of high-risk settings (HWC, corrections, homeless shelters) Mycobacteriology lab staff Children < 5 years old Medical conditions: diabetes, silicosis, end-stage renal dz, gastrectomy or small bowel resection, CA head & neck	Persons with no known risk factors for TB infx or progression

Latent TB infection (LTBI): diagnosis

Interferon gamma release assays (IGRAs)

- 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]

52

Non AIDS-Defining Complications of HIV/AIDS

Dr. Michael S. Saag

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

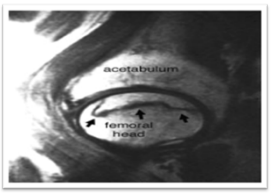
- 55 year old man presents with R hip pain
- H/o COPD requiring steroids frequently
- HIV diagnosed 17 years ago
- On TDF / FTC / EFV for 10 years; originally on IND / AZT / 3TC
- Initial HIV RNA 340,000; CD4 43 cells/ul
  - Now HIV RNA < 50 c/ml; CD4 385 cells/ul
- Electrolytes NL; Creat 1.3; Phos 3.5 Ca 8.5
- Mg 2.1, alk phos 130; U/A neg
- R Hip film unremarkable

QUESTION #1

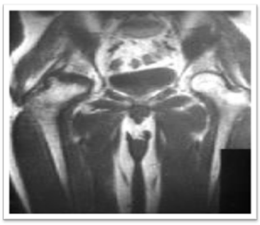
Which if the following is the most likely underlying cause of his hip pain?

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.
- Nl 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

CASE 3

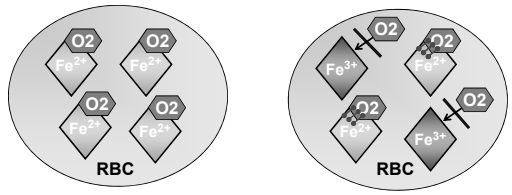
- 35 year old man presents with complaints of increasing fatigue, headache, SOB / DOE
- HIV diagnosed 4 mos ago with PCP; intolerant to TMP/SMX
- Now on TAF / FTC / BIC + PCP Prophylaxis with Dapsone
- Claims adherence to all meds;
  "Doesn't miss a dose!"
- Normal PE
- Pulse Ox 85%; CXR no abnormalities
- 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



CASE 4

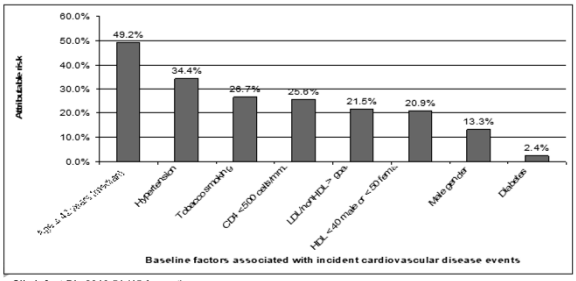
- 55 year old man presents with complaints of crushing chest pain
- HIV diagnosed 10 years ago
- Initial HIV RNA 340,000; CD4 43 cells/ul
  - Now HIV RNA < 50 c/ml; CD4 385 cells/ul
- Initally Rx with ZDV/3TC / EFV;
  now on ABC/3TC/ EFV
- On no other medications / smoker
- ECG shows acute myocardial 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)

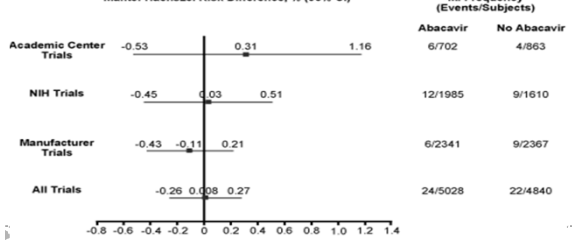
Abacavir and Risk for Myocardial Infarction- Analysis of NA-ACCORD

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

FDA meta-analysis

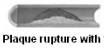
26 randomized, controlled ART trials of abacavir. 16 GSK studies, 5 NIH, 5 academic centers. 5032 received ABV and 4842 non-ABV (CROI 2011)



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

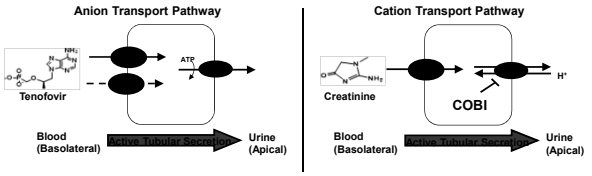
- 45 year old recently diagnosed with HIV
- HIV RNA 140,000; CD4= 230 cells/ul
- Baseline labs:
- Hb 11.2 gm/dl; AST 310 / ALT 120
  140|101 | 5 Gluc 100
  4.2 | 28 |1.1 eGFR = 65 ml/min
- Started on TAF/FTC+ Dolutegravir; No other medications
- Returns 4 weeks later, labs unchanged except creatinine 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

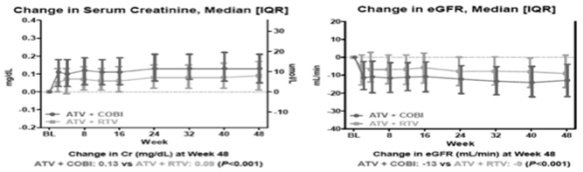


The active tubular secretion of tenofovir and the effect of COBI on creatinine are mediated by distinct transport pathways in renal proximal tubules

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

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

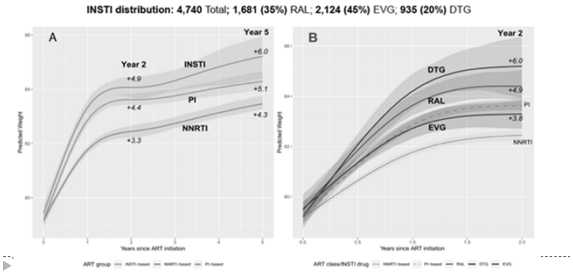
Which of the following will most likely be present on his 3 month visit from use of dolutegravir:

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

INSTI distribution: 4,740 Total; **1,681 (35%)** RAL; **2,124 (45%)** EVG; **935 (20%)** DTG



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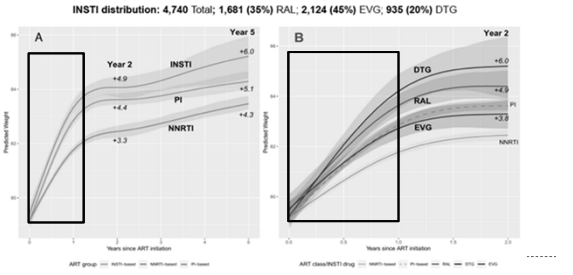

Change in Weight Overtime – NA-ACCORD

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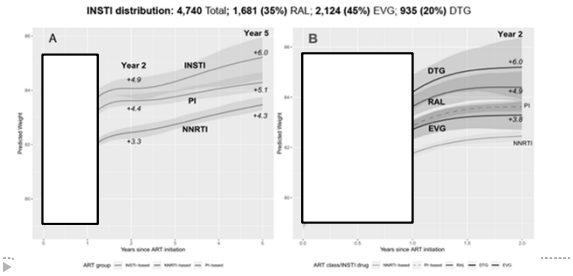


CASE 10

- 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:

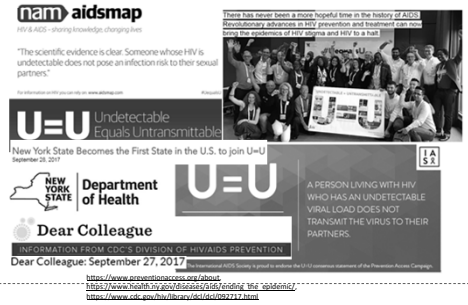
A. Virtually zero risk (< 0.2%)
B. Very low risk (< 2%)
C. Possible (<10 %)
D. It depends on which ARV regimen he's on

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

U=U: Undetectable=Untransmittable



https://www.preventionaccess.org/about
https://www.health.ny.gov/diseases/aids/ending_the_epidemic/
https://www.cdc.gov/hiv/library/dcl/dcl092717.html

CASE 11

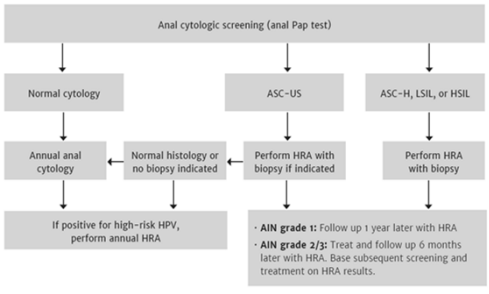
- 58 yo MSM Male presents for routine evaluation
- On ARV Rx:
- **HIV RNA < 20 c/ml; CD4 590 cells/ul**
- **He is sexually active with 3 to 4 different partners / year**
- **Receptive and insertive anal intercourse**
- **A routine annual anal PAP is collected and shows LSIL**

QUESTION # 11

Which of the following should be performed?

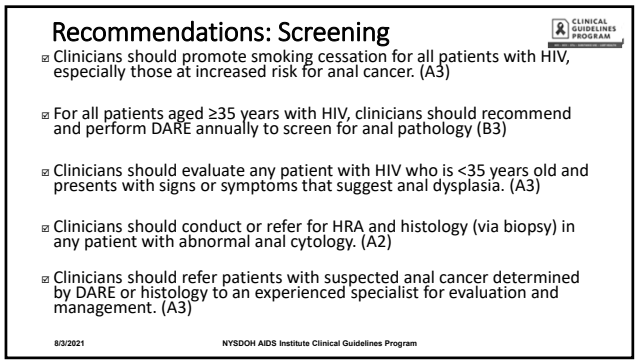
A. High Resolution Anoscopy with Biopsy
B. Digital Rectal Exam; if negative monitor for 1 yr
C. Sigmoidoscopy
D. Colonoscopy
E. Monitor only; repeat anal PAP in 6 months

Figure 1. Follow-up of Anal Cytologic Screening Results



52 – Non AIDS-Defining Complications of HIV/AIDS

Speaker: Michael Saag, MD



53

Hospital Epidemiology

Dr. Robert Weinstein

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

TOPIC 1: PATHOGENS

Question #1

A 50 y.o. previously healthy woman developed a urinary tract infection after a 3-month trip to India. Symptoms persisted despite empiric antibiotic therapy. 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

Disclosures of Financial Relationships with Relevant Commercial Interests

- **None**

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)

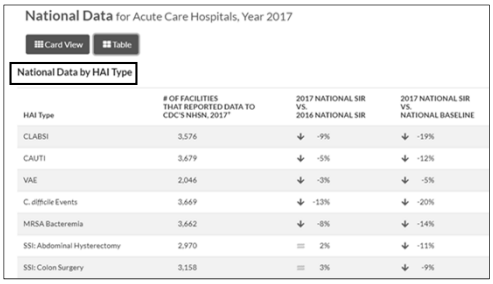
MDR U.S. Case #s 2012-17 (hospital and community); % change

• 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

TOPICS

1. Healthcare-associated Infection (HAI) Pathogens
2. Isolation Precautions
3. Device- and Procedure-related Infections
4. Antimicrobial Stewardship
5. Outbreaks
6. Occupational Health



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

A 40 y.o. woman was admitted via the Emergency Room to the trauma service after a motor vehicle accident. Eight days into her admission she developed fever and flu-like symptoms. An NP PCR test was positive for parainfluenza. The most likely source of infection is:

A. Community exposure before admission
B. In-hospital exposure to visitors or personnel
C. Food-borne illness in the community
D. Emergency Department exposure
E. In-hospital exposure to contaminated respiratory therapy equipment

TOPIC 2: ISOLATION PRECAUTIONS

CONTROL & PREVENTION KEYED TO MODES OF TRANSMISSION

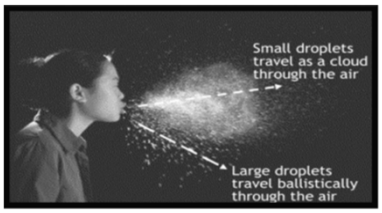
- Contact
  - Direct (body-to-body)
  - Indirect (e.g., fomites/environment, HCWs' hands)
- Droplet (>5 μm; travel 3-6 feet)
- Airborne (droplet nuclei ≤ 5 μm; remain aloft)
- Endogenous (auto-inoculation & device-related)
- Common source (outbreak potential)
- Vectorborne

HCW, healthcare worker

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)

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.

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.

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 #3

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

Question #4

A 55 y.o. homeowner on Martha's Vineyard is admitted with fever and pneumonia. He recalls lawn mowing over a dead rabbit a few days ago. Blood cultures – patient's, not rabbit's – grow gram-negative coccobacilli aerobically. The appropriate patient placement and specimen lab containment 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

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)

CDC Category A Bioterrorism Agent Infection Control

Disease	Patient Isolation	Laboratory Containment
Smallpox	All & CP	Y
Plague	All or DP	Y
Viral Hemorrhagic Fever	All & CP	Y
Anthrax	SP*	N
Botulism	SP	N
Tularemia	SP	Y

All = Airborne Infection Isolation, CP = Contact Precautions, DP = Droplet Precautions, SP = Standard Precautions

*Exception: CP if cutaneous anthrax has uncontained drainage

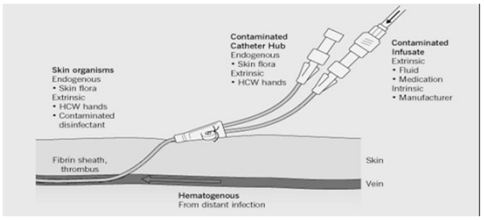
TABLE
Two Perspectives on Occupational Infections

	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	Hierarchy of controls
	Behaviors	Engineering
	Barrier precautions	Work practices
		Personal protective gear

Gerberding JL, *Infect Control Hosp Epidemiol* 1993; 14:686-8.

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 #5

Which one of the following measures does not reduce the risk of CVC infections?

A. Maximum barrier precautions for CVC insertion
B. Removal of idle CVCs
C. Avoiding guidewire-facilitated replacement of CVCs for infection control
D. Preference for chlorhexidine for CVC site preparation
E. Preference for placement of CVCs in operating rooms

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.

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

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.

Question #6

Which of the following patient care measures is least likely to be effective for preventing ventilator-associated pneumonias?

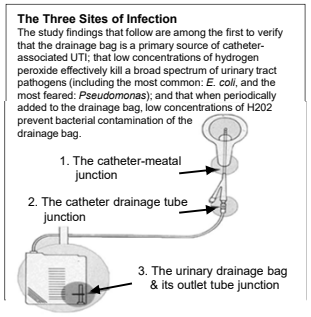
A. Subglottic suction ports on ET tube
B. Elevation of the heads of beds to 30-45 degrees
C. Regularly scheduled changes of the ventilator tubing
D. Assessing extubation readiness daily
E. Non-invasive ventilation

Ventilator Complication Prevention Bundle – Update

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.

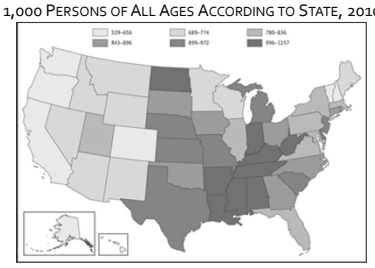


REDUCE cUTIs

- Avoid use of catheters (Key role for bladder ultrasound)
- Don't open or irrigate system
- Aseptic drainage of bag
- Bag below bladder

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.

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.

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

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 5: OUTBREAKS

Question #7

During a 1 week period, 5 of 15 ICU patients developed fulminant sepsis. Blood cultures from each grew *Serratia marcescens*; cultures of respiratory secretions and urine were normal flora and negative, respectively. No Serratia infections had 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

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Speaker: Robert Weinstein, MD

Steps In *This* Outbreak Investigation

1. Establish existence of outbreak: *Easily ID'd bacteria; unexpected change*
2. Verify diagnosis: *Serratia "primary (i.e., no apparent source) bacteremia"*
3. Case count: *5*
4. Orient data into time, place, person: *1 week, ICU, ICU patients*
5. Determine size of population at risk: *15 patients in ICU (5/15 = 33% AR)*
6. Develop hypothesis regarding source & mode of spread, e.g., indirect person-to-person, common source, personnel carrier: *Primary bacteremia – possible contaminated IV medications/infusions; high AR = common item?*
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: *Assess IV exposures of infected and uninfected patients*

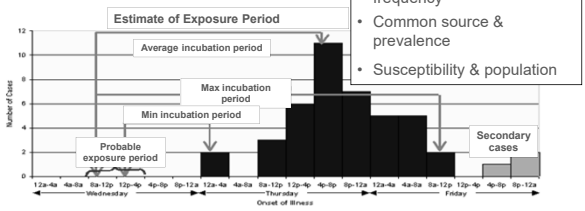
Key Emerging Outbreak Pathogens

- ***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

Interpreting Epidemic Curves

Infer from size, shape, & repetition of curves:

- Person-to-person spread & frequency
- Common source & prevalence
- Susceptibility & population



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; SARS-CoV-2 unlikely
Fungi	Aspergillus, Mucor, Rhizopus, *Candida auris*
Mycobacterium	*M. chimera*

Some Outbreak Associations

- Unusual bug (esp. if BSI): Think common-source contamination, e.g., *Pantoea agglomerans,* Pseudomonas spp, Flavobacterium from IV fluids or propofol; product contamination (extrinsic > instrinsic)
- *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

TOPIC 6: Occupational Health

Question #8

Your neighbor in posh Scarsdale asks you about his TB test results. Testing was required so that he could assist in a cooperative nursery school that his 3-year-old daughter attends. He was told that he had 10 mm of induration at 48 hours around his PPD skin test and a "blood test" was indeterminant. His chest x-ray had 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.

EMPLOYEE HEALTH – COMMON QUESTION
CLASSIFICATION OF THE TUBERCULIN REACTION
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 ≥ 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

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

Question #9

A health care worker who is planning international travel as the COVID-19 pandemic wanes 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

CLASSIFICATION OF THE TUBERCULIN REACTION (CONTINUED)
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

Question #10

A hospital policeman was stabbed with a used IV needle by a combative patient. The patient was in the hospital for treatment of secondary syphilis (RPR 1:128); the patient also had positive tests for HIV antibody, HCV antibody, and HBs Ag. MRI of the patient's brain showed extensive white matter disease without edema. The policeman was a new hire; his recent serologic tests for HBV and HCV were negative.

Question #11

The pathogen most likely to be transmitted by this blood exposure is:

A. JC Virus
B. HBV
C. HIV
D. HCV
E. Treponema pallidum

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)

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)

Thank You

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)

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Pharyngitis Syndromes and Group A Strep

Dr. Karen Bloch

54 – Pharyngitis Syndromes and Group A Strep

Speaker: Karen Bloch, MD

Pharyngitis Syndromes Including Group A Strep Pharyngitis

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

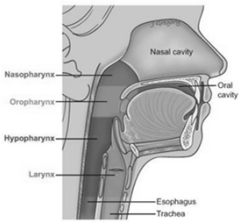
Think Like A Realtor

Disclosures of Financial Relationships with Relevant Commercial Interests

- **None**

With Special Thanks to Dr. Bennett Lorber!

Pharyngitis



- Small square footage
- Micro-neighborhoods
- Regional differences

Think Like a Realtor

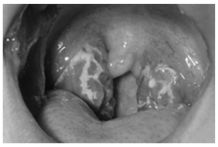
Case 1

38yo 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 test negative

54 – Pharyngitis Syndromes and Group A Strep

Speaker: Karen Bloch, MD

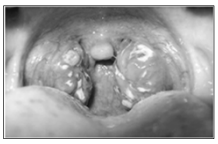
Question 1

What is the most appropriate antimicrobial treatment?

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

Differentiating Pharyngitis

GAS **Viral pharyngitis**



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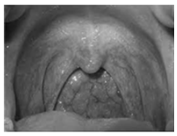
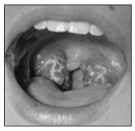


Group A streptococcus



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

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.

Differentiating Pharyngitis

GAS

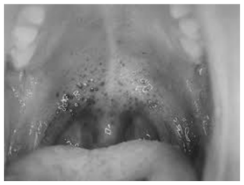
- Sudden onset
- Fever
- Onset in winter and early spring
- Lymphadenopathy
- Exposure to close contact with streptococcal pharyngitis

Viral pharyngitis

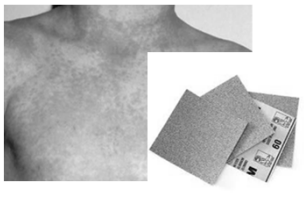
- The 3 C's
  - Conjunctivitis
  - Coryza
  - Cough
- Hoarseness
- Diarrhea
- Ulcerative stomatitis
- Tonsils red, but rarely enlarged or purulent

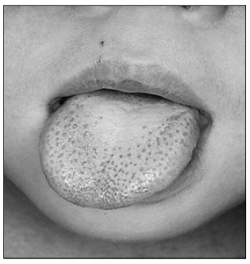
Streptococcal Clues

- Palatal petechia



- Scarletina



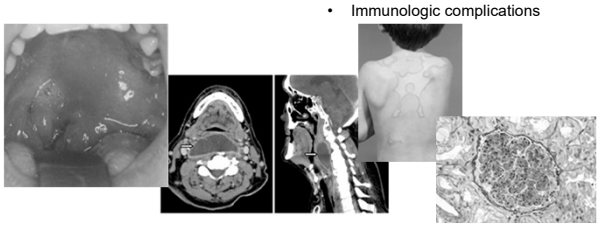


Strawberry tongue

- Group A strep
- Staph toxic shock
- Kawasaki disease

Secondary Complications

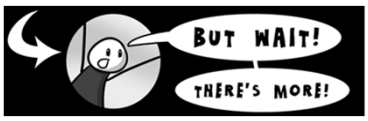
- Infectious complications
- Immunologic complications



Laboratory Diagnosis

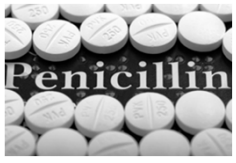
- Adults:
  - RADT screen, if negative, culture optional
- ASO titer or Anti-DNAse B antibodies
  - helpful in diagnosis of rheumatic fever and post-streptococcal glomerulonephritis, but not for strep pharyngitis.

Pharyngitis and….



Treatment for GAS Pharyngitis

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

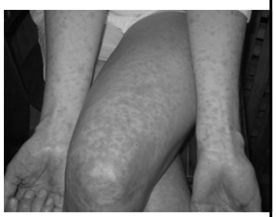


PCN Allergic:

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

Pharyngitis & Rash

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



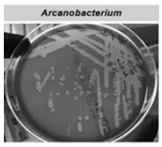
Arcanobacterium haemolyticum

54 – Pharyngitis Syndromes and Group A Strep

Speaker: Karen Bloch, MD

Arcanobacterium haemolyticum

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



Pharyngitis & Conjunctivitis

- 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 & Rash

- Acute HIV

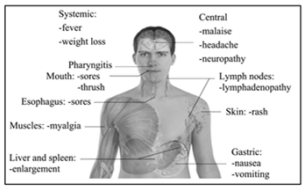
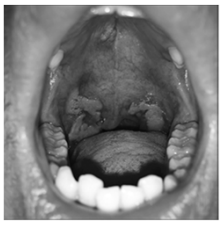


Figure 1 Main symptoms of acute HIV infection

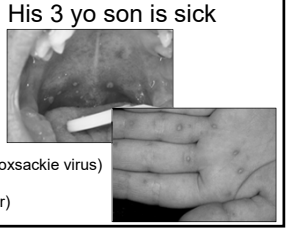
- Secondary syphilis



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)

Pharyngitis after Receptive Oral Intercourse

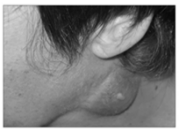
Neisseria gonorrhoeae	Herpes simplex virus
• Highest risk MSM • Most asymptomatic • Nonspecific presentation • Diagnose by nucleic acid amplification test of pharyngeal swab	• HSV 1 or 2 • Usually with acute infection • Nonspecific presentation • Labial or genital ulcers variably present

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.
- His cat recently had kittens

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

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

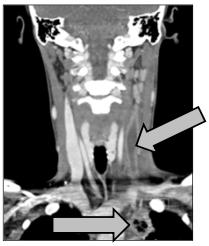
- Septic phlebitis of internal jugular vein
- Often follows Streptococcal pharyngitis or mononucleosis
- Classic cause is *Fusobacterium necrophorum*
- Anaerobic gram-negative rod
- Causes septic pulmonary emboli

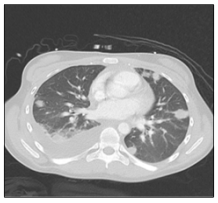
Question 2

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)

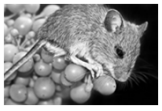
Lemierre Syndrome





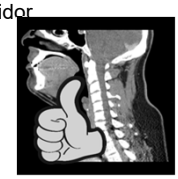
Oropharyngeal Tularemia

- 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 or quinolone



Extra-Tonsillar Infections: 1

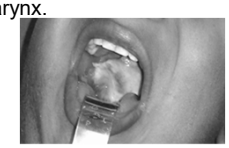
- Epiglottitis
  - Fever, sore throat
  - Hoarseness, drooling, muffled voice, stridor
  - Examine with care!
  - Lateral neck x-ray: Thumb sign
  - *H. influenzae* type B, pneumococcus



Extra-Tonsillar Infections: 2

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

- 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.

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)

Question 3

The most likely diagnosis is?

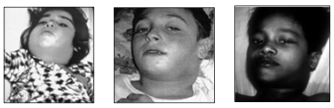
A. Streptococcal pharyngitis
B. Kawasaki disease
C. Vincent angina
D. Diphtheria
E. Lemierre syndrome

Case 3

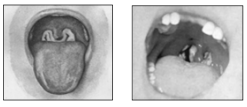
- A 42-year-old, previously healthy woman is seen for a bad “sore throat” that began 4 days earlier while attending her sister’s wedding in southern Ukraine.
- She c/o malaise, odynophagia, and a low-grade fever. Today, she noted a choking sensation, prompting medical evaluation.

Buzz words and Visual Associations

Bull neck:

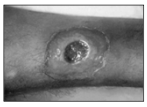


Grey pseudomembrane: extends onto palate or uvula; bleeds when scraped



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



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

Noninfectious Mimics

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

Karen.bloch@vumc.org

Wednesday, August 25, 2021

AM Moderator: Marr
PM Moderator: Auwaerter

#	Start		End	Presentation	Speaker
55	9:30 AM	-	10:00 AM	**Daily Question Preview Day 5**	*Kieren Marr, MD (Moderator)*
56	10:00 AM	-	11:15 AM	**Infections in the Neutropenic Cancer Patient and Hematopoietic Stem Cell Recipients**	*Kieren Marr, MD*
57	11:15 AM	-	12:00 PM	**Fungal Disease in Normal and Abnormal Hosts**	*John Bennett, MD*
	12:00 PM	-	12:30 PM	***BREAK with FACULTY CHAT***	
58	12:30 PM	-	1:30 PM	**Infections in Solid Organ Transplant Recipients**	*Barbara Alexander, MD*
59	1:30 PM	-	2:00 PM	**Pneumonia: Some Cases that Could be on the Exam**	*Paul Auwaerter, MD*
60	2:00 PM	-	2:45 PM	**Board Review Session 5**	*Drs. Auwaerter (moderator), Alexander, Bennett, Marr, and Mitre*
	2:45 PM	-	3:15 PM	***BREAK with FACULTY CHAT***	
61	3:15 PM	-	4:15 PM	**Ticks, Mites, Lice and the Diseases They Transmit**	*Paul Auwaerter, MD*
62	4:15 PM	-	5:15 PM	**Worms and More Worms**	*Edward Mitre, MD*
	5:15 PM	-	5:45 PM	***BREAK with FACULTY CHAT***	
63	5:45 PM	-	6:15 PM	**Lyme Disease**	*Paul Auwaerter, MD*
64	6:15 PM	-	7:15 PM	**Lots of Protozoa**	*Edward Mitre, MD*
	7:15 PM	-	7:45 PM	***FINAL FACULTY CHAT***	

55

Daily Question Preview 5

Dr. Kieren Marr (Moderator)

55 – Daily Question Preview: Day 5

Moderator: Kieren Marr, MD

Daily Question Preview: Day 5

Moderator: Kieren Marr, MD

PREVIEW QUESTION

5.1 **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.

PREVIEW QUESTION

5.1 **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*

PREVIEW QUESTION

5.2 **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. Levofloxacin and fluconazole prophylaxis.

4 days prior to her admission for chemotherapy, she ate Chinese food with fried rice.

PREVIEW QUESTION

5.2 **Which is the most likely etiology?**

A) Norovirus

B) *Clostridioides (Clostridium) difficile*

C) Mixed anaerobic and aerobic bacteria

D) *Candida albicans*

E) *Bacillus cereus*

PREVIEW QUESTION

5.3 **35-year-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.

55 – Daily Question Preview: Day 5

Moderator: Kieren Marr, MD

PREVIEW QUESTION

5.3 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

PREVIEW QUESTION

5.4 40-year-old male. 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.

PREVIEW QUESTION

5.4 The most likely etiology is:

A) Cyclophosphamide

B) CMV

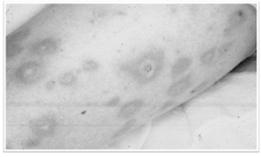
C) EBV

D) BK

E) JC virus

PREVIEW QUESTION

5.5 35-year-old 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.



PREVIEW QUESTION

5.5 The most likely fungus is which of the following:

A) Scedosporium apiospermum (Pseudallescheria boydii)

B) Lomentospora (Scedosporium) prolificans

C) Apophysomyces elegans

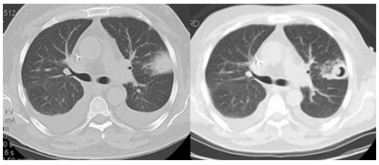
D) Fusarium multiforme

E) Alternaria alternata

PREVIEW QUESTION

5.6 32-year-old male with allogeneic hematopoietic stem cell transplant recipient for AML, developed graft versus host disease, given high dose prednisone, discharged and re-admitted for fever not responding to antibacterial antibiotics.

These two chest CT 's, were taken at admission and a week later while he was responding to voriconazole.



55 – Daily Question Preview: Day 5

Moderator: Kieren Marr, MD

PREVIEW QUESTION

5.6 The most likely source of infection is:

A) Dirt from his garden

B) His oral flora

C) Contaminated food

D) Intravenous catheter

PREVIEW QUESTION

5.7 54-year-old 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.

PREVIEW QUESTION

5.7 The most appropriate treatment for this condition is:

A) Cidofovir

B) Ganciclovir

C) Acyclovir

D) Cyclophosphamide

E) Rituximab

PREVIEW QUESTION

5.8 52-year-old 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.

PREVIEW QUESTION

5.8 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

5.9 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

55 – Daily Question Preview: Day 5

Moderator: Kieren Marr, MD

PREVIEW QUESTION

5.9

- 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

PREVIEW QUESTION

5.9 This presentation is most consistent with:

A) CMV encephalitis

B) HHV6 encephalitis

C) VZV encephalitis

D) Rabies encephalitis

E) Cryptococcal meningitis

PREVIEW QUESTION

5.10

55-year-old male

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

PREVIEW QUESTION

5.10

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

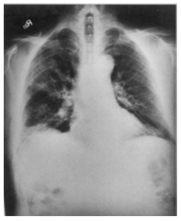
5.10 Which antibiotic will lead to the most rapid improvement?

A) Ceftriaxone

B) Gentamicin

C) Doxycycline

D) Trimethoprim/sulfamethoxazole



PREVIEW QUESTION

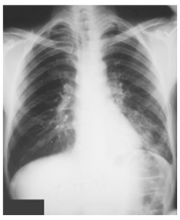
5.11

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



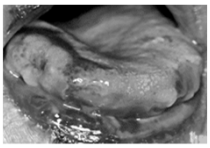
55 – Daily Question Preview: Day 5

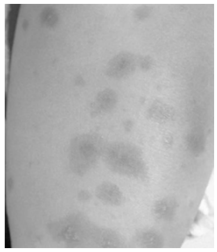
Moderator: Kieren Marr, MD

PREVIEW QUESTION

5.11

- Azithromycin prescribed
- Next day, full body rash and mucosal lesions develop





PREVIEW QUESTION

5.11 What is the most likely etiology?

A) Mycoplasma pneumoniae

B) Enterovirus D68

C) Measles

D) Lyme disease

E) Drug reaction (azithromycin)

PREVIEW QUESTION

5.12 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.

PREVIEW QUESTION

5.12 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

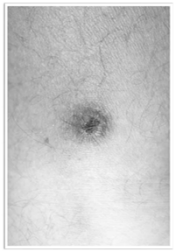
PREVIEW QUESTION

5.13 48-year-old male presents in October with fever and rash

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



PREVIEW QUESTION

5.13 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

55 – Daily Question Preview: Day 5

Moderator: Kieren Marr, MD

PREVIEW QUESTION

5.14 43-year-old 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

PREVIEW QUESTION

5.14 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

PREVIEW QUESTION

5.15 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 an egg with surrounding granulomatous inflammation.

PREVIEW QUESTION

5.15 Most likely diagnosis?

A) Entamoeba histolytica

B) Strongyloides stercoralis

C) Wuchereria bancrofti

D) Schistosoma mansoni

E) Paragonimus westermani

PREVIEW QUESTION

5.16

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.

PREVIEW QUESTION

5.16 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

55 – Daily Question Preview: Day 5

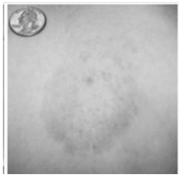
Moderator: Kieren Marr, MD

PREVIEW QUESTION

5.17 A 56-year-old 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)

PREVIEW QUESTION

5.17 Which of the following is the most likely diagnosis?

A) Lyme disease (Borrelia burgdorferi infection)

B) Human Monocytic Ehrlichiosis (Ehrlichia chaffeensis)

C) Borrelia mayonii

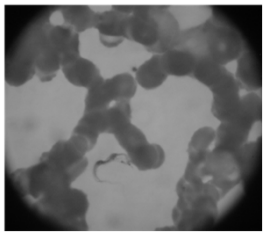
D) Southern tick-associated rash illness (STARI)

E) B. lonestarii infection

PREVIEW QUESTION

5.18 A 41-year-old 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.



PREVIEW QUESTION

5.18 What is the most likely diagnosis?

A) Leishmania donovani

B) Plasmodium vivax

C) Trypanosoma brucei

D) Wuchereria bancrofti

E) Leptospira interrogans

56a

Infections in the Neutropenic Cancer Patient and Hematopoietic Stem Cell Recipients

Dr. Kieren Marr

56a – Infections in the Neutropenic Cancer Patient and Hematopoietic Stem Cell Recipients

Speaker: Kieren Marr, MD

Infections in the Neutropenic Cancer Patient and Hematopoietic Stem Cell 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: Cidara, Merck and Company, Sfunga Therapeutics
- Ownership Interests: MycoMed Technologies

Goals of This Review

- Focus on testable complications specific to the immunocompromised host
  - Types of immune – suppressing drugs and diseases
  - Recognition of specific "neutropenic syndromes"
    - Skin lesions
    - Invasive fungal infections
    - Neutropenic colitis

Fundamentals: Underlying disease 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

Fundamentals: Therapeutic risks

- Recognize risks with cytotoxic therapy (neutropenia)
  - Prolonged (>10 days) and profound (< 500 cells / mm3) leads to high risks for severe bacterial and fungal infections
    - Bacteremia, pneumonia, candidemia, aspergillosis
    - Outcomes tend to be poor – preventative therapies important
- Recognize infectious risks with other biologic therapies that immunosuppress
  - T cell suppressing agents and 'targeted' biologics
    - Viral and fungal infections

Immune modulating anti-cancer drugs

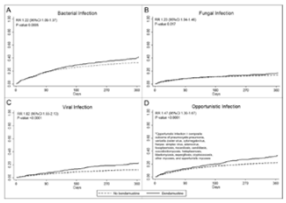
- Drugs that impact neutrophils
  - Many cytotoxic agents
    - Bacterial infections, fungal infections
- Drugs that impact T cells
  - Purine analogs (fludaribine, cladribine, clofarabine) and temozolomide
    - CD4+ T cell dysfunction: Herpes viruses (CMV, VZV), intracellular bacteria, fungi (PJP, Aspergillus)

56a – Infections in the Neutropenic Cancer Patient and Hematopoietic Stem Cell Recipients

Speaker: Kieren Marr, MD

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 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

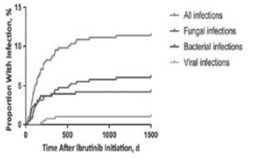
- Common antibodies that impact B and T cells
  - Rituximab (anti-CD20)
    - B cells: CLL, lymphoma
    - Loss of vaccine responses, responses to encapsulated bacteria (pneumonia). Hepatitis B reactivation, PML
  - Alemtuzimab (anti-CD52)
    - T and B cell depletion for a long time (about 6 months): 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)
    - Autoimmune pneumonitis and colitis (infection mimic)
    - Aspergillosis and other IFI

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



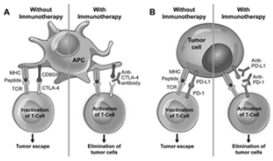
Varughese et al. Clin Infect Dis 2018; 67(5): 687-92
Bercusson A. Blood 2018 132(18): 1985-88
Blez et al. Haematologica 2019 (in press)

56a – Infections in the Neutropenic Cancer Patient and Hematopoietic Stem Cell Recipients

Speaker: Kieren Marr, MD

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

Venetoclax

- Inhibits anti-apoptotic BCL2 – family proteins (AML, lymphoid malignancies)
- Sometimes given with hypomethylating agents for AML (ex. azacytidine)
  - Severe, prolonged neutropenia – bacterial, fungal infections
  - Drug interactions may limit use of azole prophylaxis
    - Cyp3a inhibition requires VEN dose decrease / toxicities
    - Aspergillosis increasingly recognized

Neutropenic "syndromes"

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%)

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*

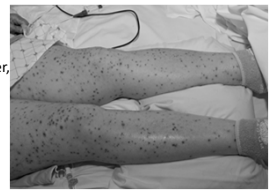
56a – Infections in the Neutropenic Cancer Patient and Hematopoietic Stem Cell Recipients

Speaker: Kieren Marr, MD

Question #2

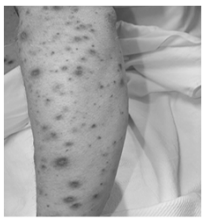
59 year old woman with AML with neutropenia for 25 days. She has been febrile for 6 days, and is receiving meropenem, vancomycin, and acyclovir. New skin lesions that are small, papular, and tender, with no central ulceration.

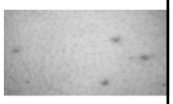
A. *Rhizopus* spp.
B. Varicella zoster virus
C. *Cryptococcus neoformans*
D. Vancomycin resistant Enterococci
E. *Candida tropicalis*

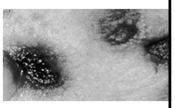


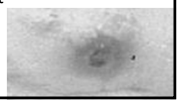
Skin Lesions

- Candidiasis
  - Small, tender papules
- Herpes
  - vesicular
- *Aspergillus*
  - ulcerative, necrotic
- Other filamentous fungi (*Fusarium, P. boydii*)
  - Multiple, erythematous, different stages
- *P. aeruginosa*
  - Ecthyma gangrenosum



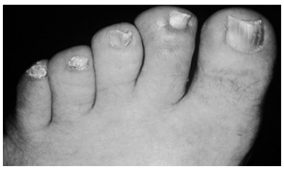






Fusarium

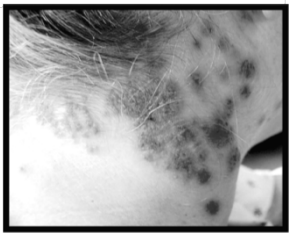
- Invasive pulmonary disease with skin lesions
- Locally invasive infections in neutropenic patients
  - Keratitis
  - Onychomycosis



Question #3

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.

Sweet's syndrome

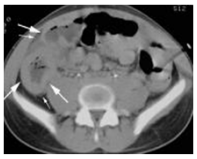
- Acute febrile neutrophilic dermatosis
- Variants: classic (idiopathic), malignancy-associated, drug induced
- Tender erythematous plaques and nodules typical; also bullous, cellulitic, necrotizing lesions
- Classic stem: neutropenia resolving with GCSF assist, fever, skin lesions, cultures - negative
- Steroids

Question #4

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*

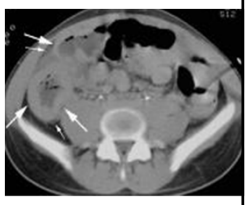


56a – Infections in the Neutropenic Cancer Patient and Hematopoietic Stem Cell Recipients

Speaker: Kieren Marr, MD

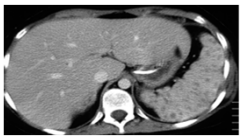
Neutropenic Enterocolitis

- 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



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

56b

Selected Syndromes in Stem Cell Transplant Recipients

Dr. Kieren Marr

56b – Selected Syndromes in Stem Cell Transplant Recipients

Speaker: Kieren Marr, MD

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

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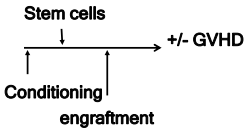
PEARLS

- **Fundamentals – risks (temporality)**
  - **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, w/in 30 days)
    - Bacterial infections
    - Fungal infections
  - Impaired cellular and humoral immunity (later, post-engraftment)
    - 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?

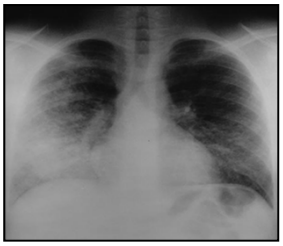
Type of BMT and timeline impacts immunity, drugs and exposures

56b – Selected Syndromes in Stem Cell Transplant Recipients

Speaker: Kieren Marr, MD

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.



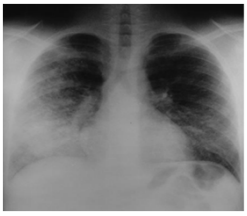
Case #1

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

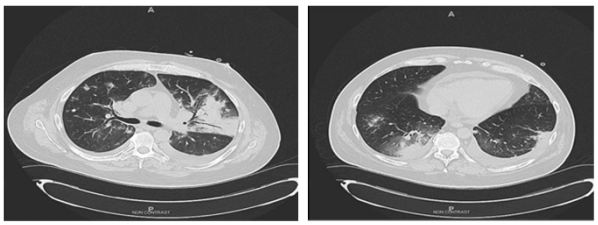
- Diffuse alveolar hemorrhage
  - Bleeding in alveolar space, heterogeneous etiology
    - Vasculitis, drug-induced injury, cancer-chemotherapy / thrombocytopenia
- Idiopathic pneumonia syndrome
  - Within 1st 120 days of HSCT, non-infectious
  - Risks: conventional ablative conditioning, acute GVHD (inflammatory pathogenesis?)

Case #2

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.)



Case # 2 (con't.)

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

56b – Selected Syndromes in Stem Cell Transplant Recipients

Speaker: Kieren Marr, MD

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

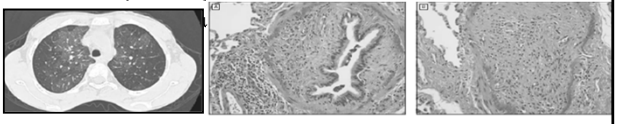
Toxoplasmosis

- 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

Ise et al, ID Week 2014
Meers 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

56b – Selected Syndromes in Stem Cell Transplant Recipients

Speaker: Kieren Marr, MD

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

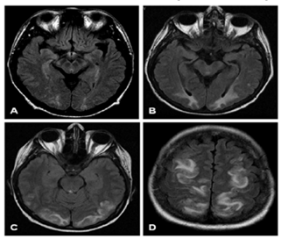
DDx of Hemorrhagic Cystitis

- 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*

Posterior reversible encephalopathy (PRES)



- Usually early after HSCT (within 1st 3 months)
- Calcineurin inhibitors: Cyclosporin*, tacrolimus
- Seizures, visual changes, MS changes

56b – Selected Syndromes in Stem Cell Transplant Recipients

Speaker: Kieren Marr, MD

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

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 (temporality)**
  - **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

57

Fungal Disease in Normal and Abnormal Hosts

Dr. John Bennett

57 – Fungal Disease in Normal and Abnormal Hosts

Speaker: John Bennett, MD

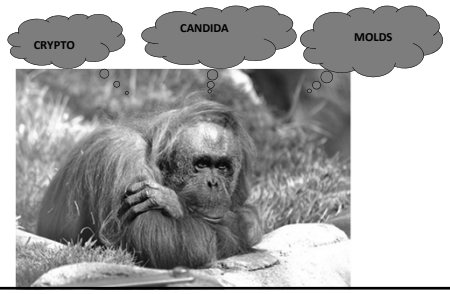
Fungal Disease in Normal and Abnormal Hosts

John E. Bennett, MD
Bethesda, Maryland

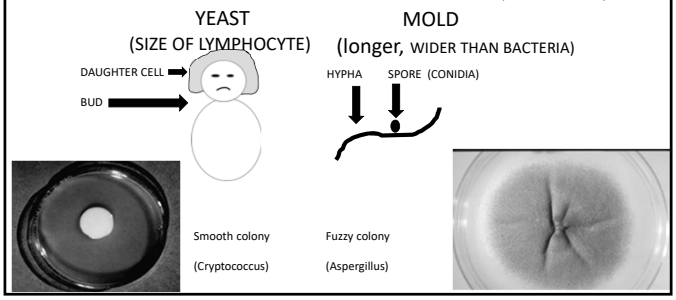
Disclosures of Financial Relationships with Relevant Commercial Interests

- **None**

There is SO much to talk about!



Start with the basics: FUNGI ARE YEASTS OR MOLDS
OR BOTH: YEAST IN THE BODY AND MOLD IN CULTURE (DIMORPHIC)

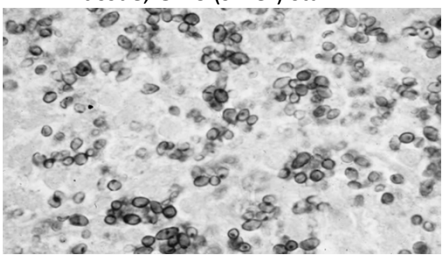


Case 1

• 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. Admission studies found her long standing anemia has worsened, with a hematocrit of 25%, platelet count 30,000, WBC 2,500 with a normal differential, alkaline phosphatase 250, ALT 120, AST 89 and creatinine 2.0 Micafungin was given for yeasts seen in peripheral blood smear that were not growing on routine culture. This infection came from:

a. Her intestinal tract
b. Human (coughing)
c. Pigeon droppings
d. Soil
e. Contaminated food

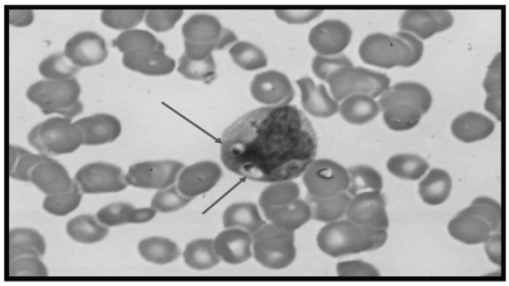
HISTOPLASMA CAPSULATUM
in tissue, GMS (silver) stain



57 – Fungal Disease in Normal and Abnormal Hosts

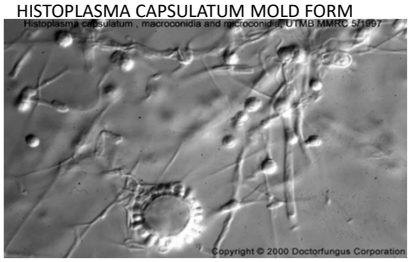
Speaker: John Bennett, MD

HISTOPLASMA CAPSULATUM YEASTS IN MONOCYTE

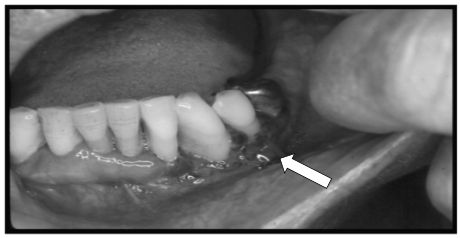


Histoplasma capsulatum growing at room temperature

- HISTOPLASMA CAPSULATUM MOLD FORM



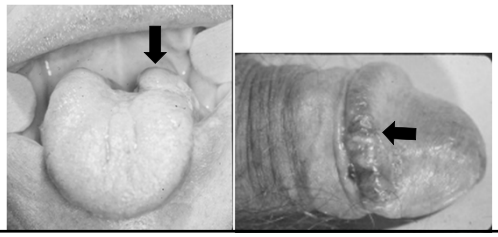
Gingival Ulcer



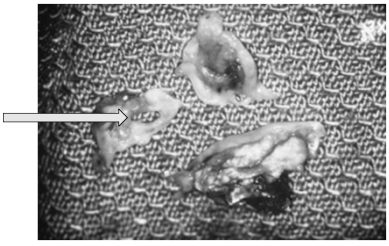
¼ CASES HAVE ORAL LESION IN DISSEMINATED HISTO

TONGUE AND PENILE LESIONS

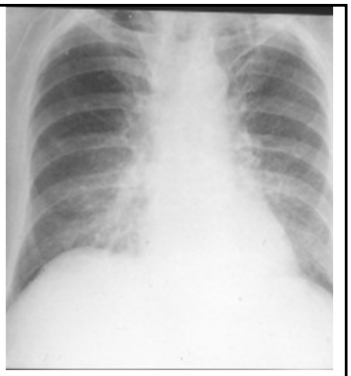
MUCOSAL LESIONS CAN RESEMBLE SQUAMOUS CARCINOMA

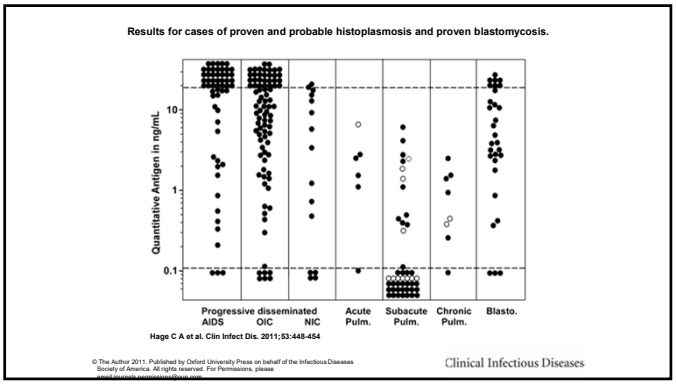


HISTOPLASMA IS A CAUSE OF "CULTURE NEGATIVE" ENDOCARDITIS (PERFORATED AORTIC VALVE)



MILIARY LUNG LESION IN DISSSEMINATED HISTOPLASMOSIS (LOOKS LIKE PCP ON IMAGING)





REVIEW:

DISSEMINATED HISTOPLASMOSIS

- TNF ALFA INHIBITORS, AIDS, CORTICOSTEROIDS, IMMUNOSUPPRESSION
- NEUTROPENIA DOESN'T PREDISPOSE

SOURCE: INHALATION OF ORGANIC SOIL ENRICHED WITH BIRD DROPPINGS

CLINICAL FEATURES: ONSET USUALLY INDOLENT

- PANCYTOPENIA, ORAL LESIONS , MILIARY LUNG LESIONS, ADDISON'S,
- BLOOD CULTURE-NEGATIVE ENDOCARDITIS

DIAGNOSIS

- YEAST IN BLOOD SMEAR OR BIOPSY. GROWS AS MOLD. (DIMORPHIC)
- ROUTINE CULTURES NEGATIVE. FUNGAL CULTURES OFTEN NEGATIVE.
- URINE OR SERUM ANTIGEN BEST (CROSS REACTS WITH BLASTOMYCOSIS)

TREATMENT:

- AMPHOTERICIN FOLLOWED BY ITRACONAZOLE
- FATAL IF UNTREATED

Case 2

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.

Case 2

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

Cryptococcosis

- Encapsulated yeast inhaled from sources in nature. C. neoformans, worldwide, pigeon droppings., C. gattii: S. California, Vancouver Island, overseas , certain trees
- C. neoformans: corticosteroids, AIDS, normal. C. gattii more often normal patient. Similar diseases.
- Symptoms: indolent onset. Usually present in CNS as headache, altered mentation
- Diagnosis: antigen in serum, CSF. Yeasts on biopsy or smear. Fungal culture good.
- Rx: ampho +/- flucytosine then fluconazole. Maintenance in HIV
- 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
- Pregnancy: use ampho until delivery (5FC is category C, azoles all teratogenic)

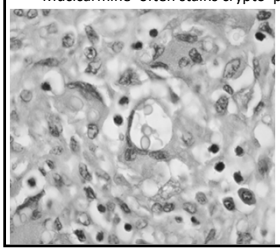
Cryptococcosis and IRIS

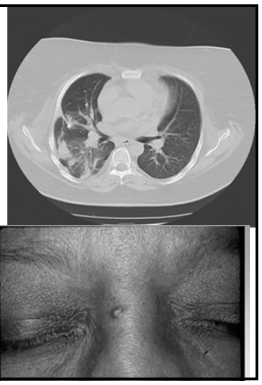
- Weeks or months after ARV and antifungal Rx for meningitis:
- Fever, headache, high opening pressure, seizures, cranial nerve palsies, new MRI lesions
- Key: all cultures negative.
- Dry cough, substernal pain
- Swollen nodes in mediastinum, hilum
- Rx: NSAIDS or prednisone

Cryptococcal lung lesions usually asymptomatic

Skin lesions can resemble molluscum contagiosum

Mucicarmine often stains crypto pink.





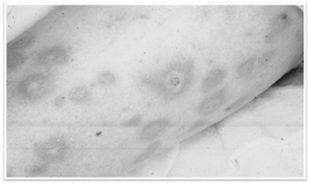
Cryptococcosis review

- Serum antigen good screen in susceptible hosts but can miss early case. LP needed if serum antigen positive. Brain MRI insensitive. CSF antigen sensitive, specific
- Relieve high intracranial pressure to prevent blindness, death
- Start with ampho with fluconazole later. Start with fluconazole if lung only and otherwise healthy
- Wait to start ARV to delay possible IRIS

Case 3

Case 3

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.

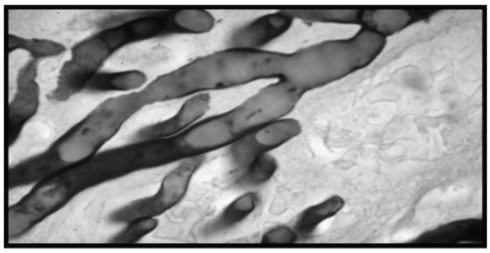


Case 3

The most likely fungus is which of the following:

A. Scedosporium apiospermum (Pseudallescheria boydii)
B. Lomentospora (Scedosporium) prolificans
C. Apophysomyces elegans
D. Fusarium multiforme
E. Alternaria alternata

Fusarium hyphae. GMS stain



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?

Case 4

- 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, Arizona 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, Routine blood chemistries normal. CSF : Glucose 55, Protein 58, WBC 330 (20% eos). Negative cryptococcal antigen on CSF, serum Lyme serology and serum RPR. MRI with contrast normal. Worsens during 2 wks of ceftriaxone. CSF cultures for bacteria, fungi, tbc neg to date.

CASE 5

The most helpful diagnostic test would be:

A. CSF cytology
B. Stool O&P
C. Dietary history
D. Fungal serology
E. Leptospirosis serology

Coccidioidomycosis=Valley Fever

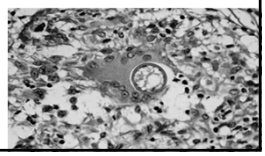
- Two species, one disease:
  - C. immitis and C. posadasii. Both serious lab hazards Southwest USA. Washington state
- Acute pneumonia 2 wks after inhalation: arthralgias or erythema nodosum may accompany. Resolves.
- Residual nodule or thin walled cavity may persist
- Dissemination: African americans, HIV, SOT, TNF inhibitors
- Bone, skin, chronic meningitis
- Rx: fluconazole. Nonmeningeal: itraconazole

COCCIDIOIDOMYCOSIS DIAGNOSIS

SEROLOGY
CSF CF serology useful. Serum CF >16 suggests dissemination, falls with Rx
Serum IgG by EIA converts to positive late, stays positive .
Serum antigen may be useful?

CULTURE
Routine cultures negative, fungal cultures positive. Lab hazard

BIOPSY
Distinctive non-budding spherules



Coccidioidomycosis review

Southwest USA, Washington state

Acute pneumonia 2 weeks after desert dust exposure

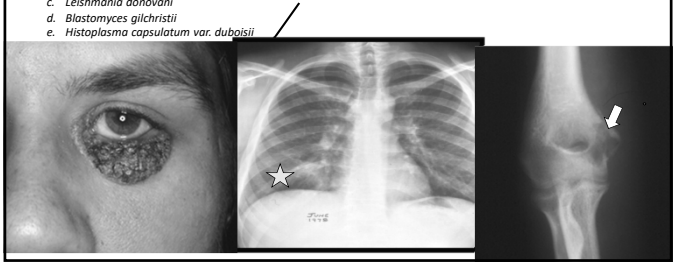
Eosinophilia in blood, CSF (low grade)

Dissemination in AA, SOT, HIV

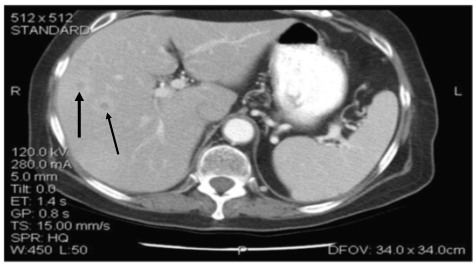
CF antibody in CSF, serum

Ampho, itra, fluconazole

CASE 5
A previously healthy 22 yr old Wisconsin man presented with a face lesion, elbow swelling and pain, had asymptomatic lung lesion on chest xray and lytic lesion on condyle of his humerus.
This is most likely which of the following:
a. Candida auris
b. Trichosporon cutaneum
c. Leishmania donovani
d. Blastomyces gilchristii
e. Histoplasma capsulatum var. duboisii



Case 6: What are these lesions in a febrile, recently neutropenic patient?



CASE 6

Which is the most likely

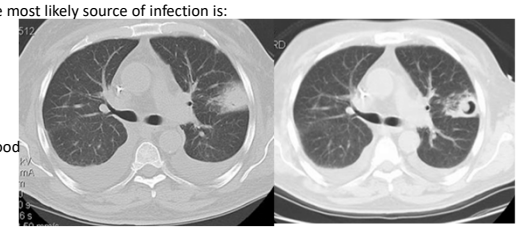
A. Babesia microti
B. Candida tropicalis
C. Fusarium oxysporum
D. Aspergillus flavus
E. Streptococcus anginosus

Candidiasis: other key points

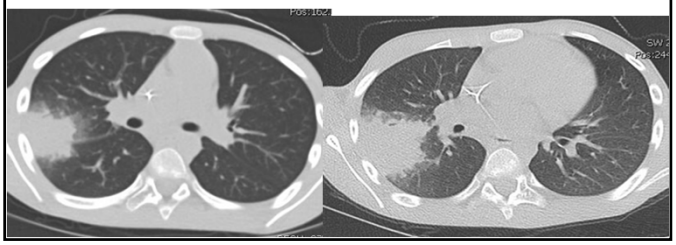
- Fundoscopy for retinal lesions in candidemia patients.
  - Intravitreal Rx may be needed
- Remove intravenous catheter with candidemia
- Candida auris hospital outbreaks
- Fluconazole resistance in C. auris, C. krusei, C. glabrata

Case 7
32 yr old male with allogeneic hematopoietic stem cell transplant recipient for AML, developed graft versus host disease , given high dose prednisone, discharged and re-admitted for fever not responding to antibacterial antibiotics. These two chest CT 's, were taken at admission and a week later while he was responding to voriconazole. The most likely source of infection is:

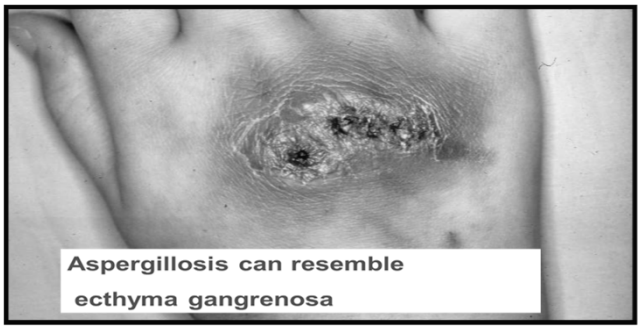
a. Dirt from his garden
b. His oral flora
c. Contaminated food
d. Intravenous catheter



Two CT's showing transient worsening of CT despite clinical improvement . Note halo sign.



ASPERGILLUS HYPHAE IN AN ARTERIOLE



Aspergillus Pneumonia (REVIEW)

Sudden onset of a dense, well circumscribed lesion in a neutropenic patient should suggest a mould pneumonia, most commonly aspergillosis but mucormycosis gives same CT findings: halo sign early, crescent sign later

Septated hyphae invade blood vessels, infarct tissue.

Galactomannan useful in CSF, BAL, blood

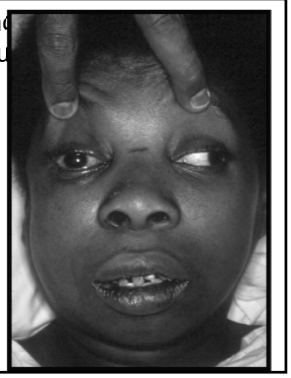
- False positives
- False negatives with azole prophylaxis

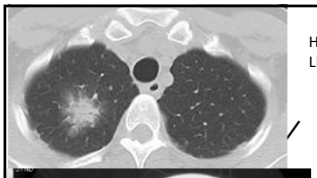
Rx. voriconazole, isavuconazole, ampho B

Mucormycosis mimics caverno following sinu

CASE 8
25 YR OLD FEMALE ADMITTED WITH DIABETIC KETOACIDOSIS AND BLINDNESS IN HER RIGHT EYE. ON EXAM THE RIGHT EYE WAS FIXED IN POSITION AND PROPTOTIC. CT SHOWED DENSE MASS IN ADJACENT ETHMOID SINUS WITH EXTENSION INTO THE ORBIT. SURGICAL EXPLORATION OF THE SINUS SHOWED BROAD, ASEPTATE HYPHAE. THE FUNGUS WAS LIKELY:

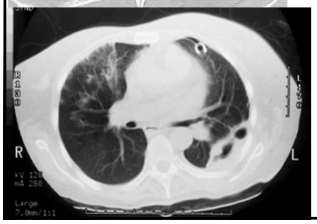
A. RHIZOPUS
B. FUSARIUM
C. ASPERGILLUS
D. SCEDOSPORIUM
E. CANDIDA





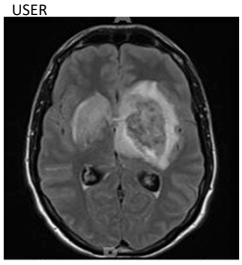
HALO SIGN IN A LEUKEMIC

MUCORMYCOSIS

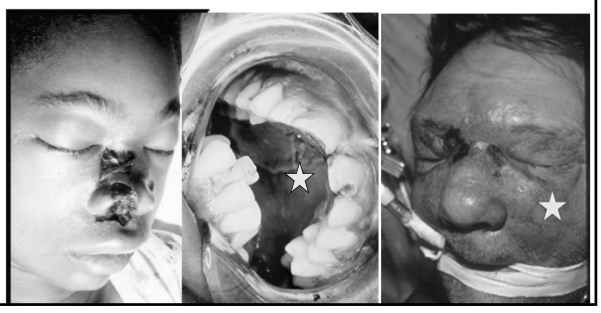


CAVITY AFTER PMN RETURN

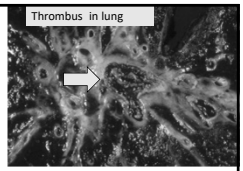
BRAIN ABSCESS IN A HEROIN USER

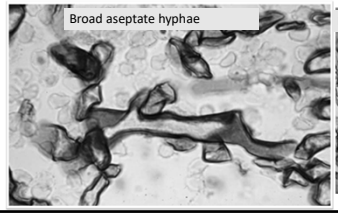


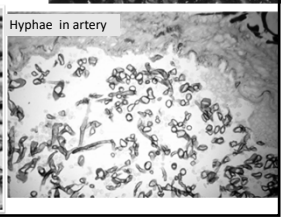
MUCORMYCOSIS
LOCAL EXTENSION FROM PARANASAL SINUS



Mucormycosis: Vascular invasion







MUCORMYCOSIS REVIEW

- Infection acquired by inhaling spores into lung or paranasal sinus
- Rhizopus, Rhizomucor, Mucor, Cunninghamella, Apophysomyces, Saksenaea
- Broad, flexible nonseptate hyphae, right angle branching
- Poorly controlled diabetes melitus, Prolonged neutropenia, corticosteroids
- Massive soft tissue trauma. IV drug abuse
- Hyphae invade blood vessels, causes infarction and necrosis. May form cavity if PMN's return.
- Negative beta d glucan, negative galactomannan
- Rx. Ampho B. Posaconazole f/u. Isavuconazole. Surgical debridement
  Control diabetes

MYCOSES WORTH MENTIONING

- SCEDOSPORIUM APIOSPERMUM: IMMUNOSUPPRESSED HOST CLINIALLY RESEMBLING ASPERGILLOSIS . BRAIN ABSCESS AFTER NEAR DROWNING IN POLLUTED WATER. AMPHOTERICIN B RESISTANT
- TRICHOSPORONOSIS: LIKE CANDIDIASIS BUT ECHINOCANDIN RESISTANT
- PARACOCCIDIOIDOMYCOSIS: RURAL CENTRAL AND SOUTH AMERICA. MAY APPEARS DECADES AFTER LEAVING ENDEMIC AREA.
- TALAROMYCOSIS (FORMERLY PENICILLIUM MARNEFFEI). SOUTHEAST ASIA, AIDS, DISSEMINATED INFECTION WITH SKIN LESIONS. YEAST IN BIOPSY, MOLD IN CULTURE.

58

Infections in Solid Organ Transplant Recipients

Dr. Barbara Alexander

58 – Infections in Solid Organ Transplant Recipients

Speaker: Barbara Alexander, MD

Infections in Solid Organ Transplant Recipients

Barbara D. Alexander, MD, MHS
Director, Transplant Infectious Diseases Service
Head, Clinical Mycology Laboratory
Director, Medical Microbiology & Transplant
Infectious Diseases Fellowship Programs
Professor of Medicine and Pathology, Duke University

Disclosures of Financial Relationships with Relevant Commercial Interests

- **Consultant: Scynexis, Astellas**
- **Research Grant to My Institution: Leadiant**
- **Clinical Trials (Site PI/Study PI): Astellas, Cidara, Scynexis, Shire, F2G**
- **Royalties (Chapter Author): UpToDate**

Infections in Solid Organ Transplant (SOT) Recipients

- SOT is a life-saving intervention
  - 857,960 SOTs performed in U.S. since 1988
  - 39,036 SOTs performed in 2020
- 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 July 13, 2021

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 PRES

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

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**
  - **Naegleria**
- **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**

FREQUENCY, TYPE & INFECTION SOURCE IN THE 1ST POST TRANSPLANT YEAR

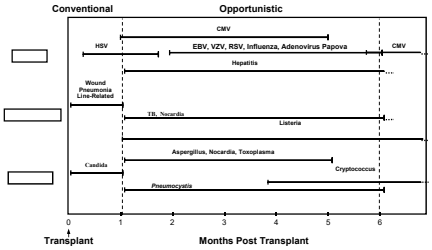
Transplant Type	Infection Episodes per Patient	Bacteremia	CMV Disease * (%)	Fungal Infections (%)	Most Common Source
Lung Heart-Lung	3.19	8-25	39	8.6	Lung
Liver	1.86	10-23	29	4.7	Abdomen & Biliary tract
Heart	1.36	8-11	25	3.4	Lung
Kidney	0.98	5-10	8	1.3	Urinary tract

*CMV, Cytomegalovirus; 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.

CLASSIC TIMING OF INFECTIONS FOLLOWING SOLID ORGAN TRANSPLANTATION

Timing altered by:
- Enhanced immunosuppression
- Prophylaxis regimen
- Unique exposures



"EARLY" BACTERIAL INFECTIONS FOLLOWING SOT

Type & site of early bacterial infection varies based on organ transplanted, surgical approach/technique & transplant center

- Risk of peritoneal soilage/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)

"LATE" BACTERIAL INFECTIONS FOLLOWING SOT

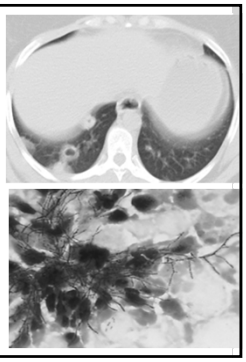
80% OF LATE BACTERIAL INFECTIONS ARE COMMUNITY ACQUIRED

- *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

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



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
PROPHYLACTIC APPROACHES

UNIVERSAL

All SOT recipients receive therapy during highest risk periods

- Expensive
- May induce resistance
- Some pts exposed unnecessarily

PREEMPTIVE

Treatment based on asymptomatic viral replication in blood

- Optimal viral threshold for initiating therapy not well defined
- Requires serial monitoring with detection assay

NOTE: Letermovir not studied or approved for use in SOT population, only HSCT

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

- Typically occurs 1-3 months post-transplant
  - Or after prophylaxis is stopped ("late onset")
- 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
GANCICLOVIR RESISTANCE

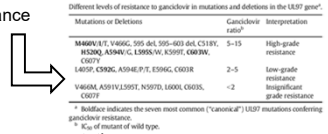
- **Suspect resistance if prolonged (> 6 weeks) ganciclovir exposure AND:**
  - No reduction in viral load after 14 days of treatment
  - No clinical improvement after 14 days of treatment
- **Management of suspected ganciclovir resistance:**
  - Reduce immunosuppression
  - Switch to foscarnet (± CMV 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
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[a].

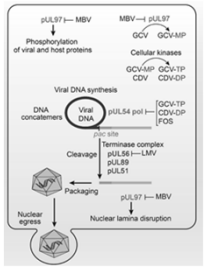
Mutations or Deletions	Ganciclovir ratio[b]	Interpretation
M460V/I/T, V466G, 595 del, 595–603 del, C518Y, **H520Q, A594V/G, L595S/W, K599T, C603W,** C607Y	5–15	High-grade resistance
L405P, **C592G**, A594E/P/T, E596G, C603R	2–5	Low-grade resistance
V466M, A591V,L595T, N597D, L600I, C603S, C607F	<2	Insignificant grade resistance

* Boldface indicates the seven most common ("canonical") UL97 mutations conferring ganciclovir resistance.
[b] K_m 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 et al Transplantation Reviews 2016.

CMV DISEASE AFTER SOT
ANTIVIRAL RESISTANCE (…ON THE HORIZON, NOT ON THE BOARDS)



Letermovir (LMV)
- Inhibits CMV terminase complex: interferes with viral genome cleavage/packaging
- Activity against strains with UL97 & UL54 mutations
  - Only a few case reports of use for GCV resistant infections some which resulted in LMV resistant dz→ ⚠
- But low resistance barrier (mutations in UL56 or less commonly UL89 or UL51)
- No activity against other herpes viruses→ ⚠

Maribavir (MBV)
- Interferes with viral nuclear egress by inhibiting UL97 kinase
- UL97 kinase activates ganciclovir (GCV), thus MBV inhibits GCV activity
  - MBV & GCV should not be used together→ ⚠
- MBV is active against many GCV resistant strains
  - Phase 3 clinical trial of GCV resistant dz just finished enrolling!

Piret J, Boivin G. Antiviral Research 2019;163:91-105.

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.

QUESTION #1

The most appropriate treatment for this condition is:

A. Cidofovir
B. Ganciclovir
C. Acyclovir
D. Cyclophosphamide
E. Rituximab

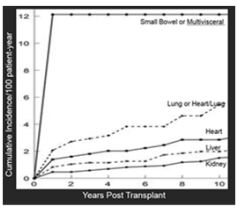
EPSTEIN BARR VIRUS POST TRANSPLANT LYMPHOPROLIFERATIVE DISORDER (PTLD)

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

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.

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

CASE 2

- 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.

QUESTION #2

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

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

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

BK VIRUS NEPHROPATHY *TREATMENT*

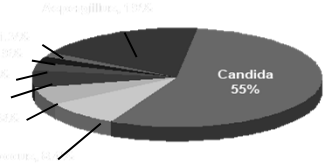
- Reduce immunosuppression
- Case series with variable success using:
  - Low-dose cidofovir
  - Leflunomide
- New drugs & randomized controlled trials needed
- Preemptive monitoring key to prevention

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.

58 – 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.

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

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

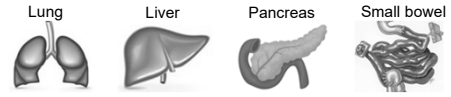
Liver
- Re-transplantation
- Pre-tx fulminant hepatic or renal failure
- Heavy *Candida* colonization peri-tx
- Large volume intra-operative transfusions
- Bleeding complications requiring re-operation
- Choledochojejunostomy

CANDIDA

Lung
- Vulnerable anastomotic site
- Continuous environmental exposure
- *Aspergillus* colonization of airways
- CMV pneumonitis
- Acute rejection
- Obliterative bronchiolitis

ASPERGILLUS

ANTIFUNGAL PROPHYLAXIS FOR SOLID ORGAN TRANSPLANT RECIPIENTS



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.

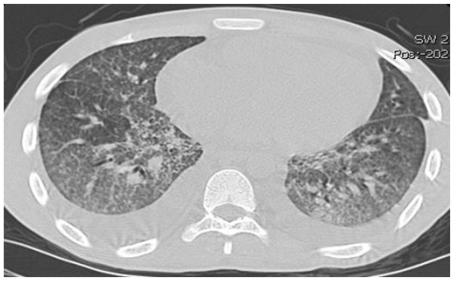
TUBERCULOSIS

- 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

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.

CHEST CT



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.

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

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
- Presents with myocarditis, pneumonitis, & meningitis
- DIAGNOSIS:
  - PCR
  - Giemsa smear of BAL
  - Brain aspirate for tachyzoites
  - Immunoperoxidase stain of endocardial biopsy or other tissue
- TREATMENT: sulfadiazine-pyrimethamine-leucovorin

CASE 4

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 #4

This presentation is most consistent with:

A. CMV encephalitis

B. HHV6 encephalitis

C. VZV encephalitis

D. Rabies encephalitis

E. Cryptococcal meningitis

58 – 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.

"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. 2006;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.

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, possible bat bites, new pet hamsters, tap water nasal irrigations, recent travel to an endemic region)

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

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:

(Delay 3–6 months to maximize response)

- Pneumococcal
- Tetanus-diphtheria toxoid
- Inactivated Influenza

Live vaccines are NOT recommended after SOT including:

- Measles Mumps Rubella
- Varicella
- Inhaled influenza
- Oral polio
- Yellow fever
- BCG
- Small pox
- Salmonella typhi (oral)

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**

KEY DRUG TOXICITIES / SYNDROMES

- Calcineurin inhibitors and TTP and PRESS (RPLS)
- 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.

OTHER PEARLS FOR BOARDS…

If you're thinking PCP but its not → think TOXO

Patient presenting atypically during first month post transplant → think donor transmitted infection
- Rabies, WNV, Coccidioides, Chagas, LCMV (look for epidemiologic clues in stem)

Remember drug interactions and syndromes
- TTP and PRESS (RPLS) induced by calcineurin inhibitors
- Sirolimus-induced pneumonitis

Remember *Strongyloides* hyperinfection syndrome

TB- Don't miss a case!

BK, CMV and EBV/PTLD – know how to diagnose and manage

Thank You!

59

Pneumonia: Some Cases that Could Be on the Exam

Dr. Paul G. Auwaerter

59 – Pneumonia: Some Cases that Could be on the Exam

Speaker: Paul Auwaerter, MD

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

Disclosures of Financial Relationships with Relevant Commercial Interests

- Consultant: Pfizer, EMD Serono
- Ownership Interest: Johnson & Johnson

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

Case 1

- 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

Question 1

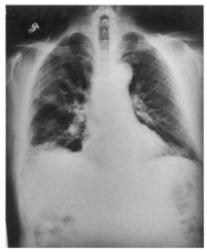
Which antibiotic will lead to the most rapid improvement?

A. Ceftriaxone

B. Gentamicin

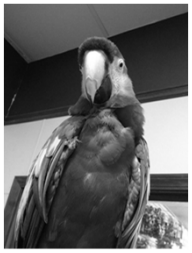
C. Doxycycline

D. Trimethoprim/sulfamethoxazole



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



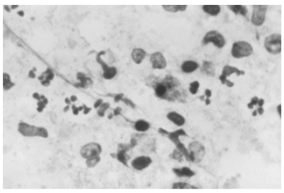
Hogerwerf L et al, Epidemiol Infect. 2017;145(15):3096

59 – 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

Chlamydia psittaci

- Range of illness:
  - Mild, bronchitic to severe/ARDS
  - Clue: temperature/pulse dissociation
    - Also seen with Salmonella typhi, C burnetii, Chlamydia, Dengue
- 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 Micrbiol Infect Dis 2018;90(3):167-170
Hogerwerf L et al, Epidemiol Infect 2017;145(15):3096-3105

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

Case 2

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 saat 90% on 6L O_2
No lymphadenopathy, no JVD
Lungs: poor air movement, basilar crackles bilaterally
Cor: no murmur
Ext: no edema

9.5
6.0 — 300K 54%^{N}, 12%^{L}, 24%^{E}

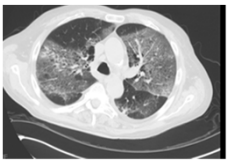
ESR 150 mm/hr NI LFTs
CRP 15 mg/dL (0.0-0.5)

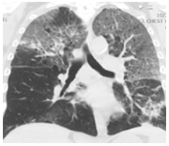
Question 2

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.





Acute eosinophilic PNA due to daptomycin [FDA black box warning]

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

59 – 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

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
AXR: no ileus

Intubation → ICU, respiratory sample:
Heavy PMNs, no organisms on Gram stain

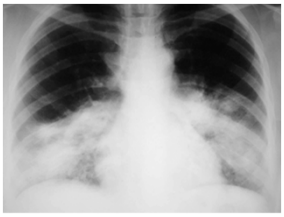
Therapy:
Vancomycin and piperacillin/tazobactam x 3 d

No improvement, febrile, respiratory culture negative
ID consultation called

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

Legionella pneumonia

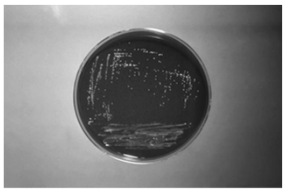
- Risks factors (and who to test)
  - Travel beyond home (e.g., hotel, hospital) last two weeks
    - May cause HAP
  - Severe pneumonia/ICU
  - Proximity to known outbreaks
  - Age > 50 yrs
  - Smoking
  - Comorbidities: diabetes, liver/renal dz, COPD, immunosuppressed
- Acquisition:
  - Aerosolization
  - Drinking water (aspiration)

1976 Bellvue Stratford Hotel, Philadelphia

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)

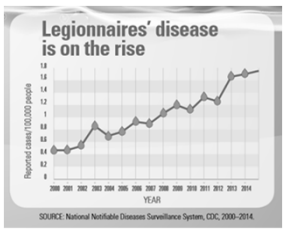
Legionella culture



Culture media: BCYE agar
Small, pearly white colonies

Outbreaks: Known and Unknown Sources

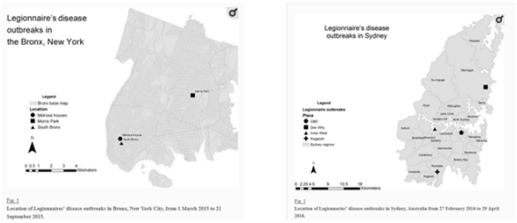
- 5,000 cases/year U.S.
  - 20 Outbreaks
- 4X > cases since 2000
- 90% of CDC investigations caused by insufficient water system management
- WHERE?
  - Hotels
  - Long-term Care Facilities
  - Hospitals



59 – 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

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	95-99	99	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, https://www.cdc.gov/legionella/clinicians/diagnostic-testing.html (accessed 6/23/21)
Avni, J Clin Micro. 2016;54(2):401–11; Muldyermans, Eur J Clin Microbiol Infect Dis 2019

	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 %

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

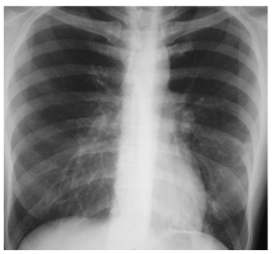
PE: Appears ill, BP 98/70, P 100
T 38.5ºC
No lymphadenopathy
Bronchial breath sounds lower fields, occasional wheezing
No murmur
No hepatosplenomegaly, abdominal tenderness
No rash

Studies

WBC 18,000
63N, 13L, 24E

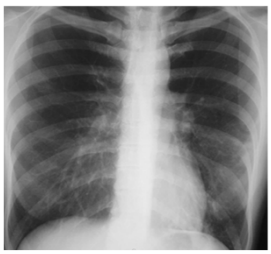
CXR: mild bilateral patchy infiltrates

Blood smear: no parasites



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



59 – 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

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

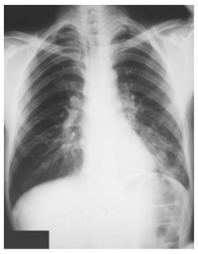
Uppal, Antimicrob Resist Infect Control 2016;5:55; Higashi, Intern Med 2018;57(2):253-258

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)

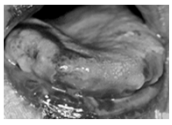
Case 5:

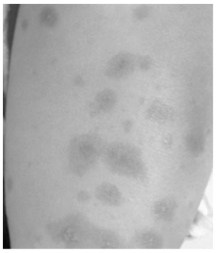
- 18F c/o fever, dry hacking cough, malaise x 3d
- Allergy: erythromycin (N/V)
- Appears well, T38ºC, RR 16, P 80, BP 110/70
  - Oropharynx: normal
  - TMs: normal
  - Chest: some crackles left lower lobe



Case 5

- Azithromycin prescribed
- Next day, full body rash and mucosal lesions develop





Case 5

What is the most likely etiology?

A. Mycoplasma pneumoniae
B. Enterovirus D68
C. Measles
D. Lyme disease
E. Drug reaction (azithromycin)

59 – 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

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

Respiratory Molecular Targets, a current FDA-approved example

Viral Targets		
Adenovirus	Coronavirus HKU1	Coronavirus NL63
Coronavirus 229E	Coronavirus OC43	Human Metapneumovirus
Human Rhinovirus/Enterovirus	Influenza A	Influenza A/H1
Influenza A/H3	Influenza A/H1-2009	Influenza B
Parainfluenza Virus 1	Parainfluenza Virus 2	Parainfluenza Virus 3
Parainfluenza Virus 4	Respiratory Syncytial Virus	
Bacterial Targets		
Bordetella pertussis		
Chlamydophila pneumoniae		
Mycoplasma pneumoniae		

Film Array
Multiplex, 20 pathogens
Results in 1 hr

Viruses and some bacteria
- Sensitivity: 87, 98-100%
- Specificity: 89, 99-100%

Leons, Front Microbiol. 2016; 7: 448

Case 6

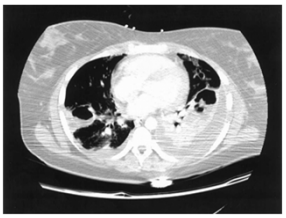
31F fever, cough, myalgia, headache, dyspnea over 1 week ago
- No help w/ azithromycin x 3d
- 18 mos daughter, recent bronchitis

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

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 (+)

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

59 – Pneumonia: Some Cases that Could be on the Exam

Speaker: Paul Auwaerter, MD

Era of molecular diagnostics

- Increasing recognition of co-pathogens
  - Multiple viruses
  - Virus + bacteria
- Still need to consider pathogens not in multiplex panels
- Mixed infections:
  - Johansson CID 2010; 50:202
    - Pathogens detected: 67%
    - Mixed: 12%
  - Jain NEJM 2015;373:415
    - Pathogens detected: 38%
    - Mixed: 3%
- Positive values from asymptomatic controls
  - Especially viral
  - Prolonged shedding (especially immunocompromised)

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Board Review Session 5

Drs. Auwaerter (Moderator), Alexander, Bennett, Marr, and Mitre

60 – Board Review Day 5

Speaker: Drs. Auwaerter (Moderator), Alexander, Bennett, Marr, and Mitre

Board Review: Day 5

Moderator: Dr. Auwaerter
Faculty: Drs. Alexander, Bennett, Marr, and Mitre

#61 **In late August, a 19-year-old male hailing from northern Minnesota was transported to his local emergency department for two days of headache and a generalized seizure.**

He had been working as a landscaper before starting college a few days ago in September. His health has been excellent, though he vaped and used marijuana.

At presentation, he had a temperature of 38.1˚C and was slightly groggy but had no focal neurological deficits or meningismus. No rash was present.

#61 **A head CT without contrast was unremarkable.**

A lumbar puncture yielded clear fluid, CSF findings: protein 56 mg/dL (normal 14-45 mg/dL), glucose 66 mg/dL (50-80 mg/dL), RBC 4 (0-5), WBC 188 with 12% lymphocytes and 88% PMNs.

A CSF Gram stain was negative.

Fevers persisted, and mental status declined over the next three days while on vancomycin, ceftriaxone, and acyclovir.

CSF cultures are negative, as was a CSF HSV PCR.

#61 **Which of the following would be the most likely?**

A) Powassan virus

B) West Nile virus

C) Rickettsia rickettsii

D) Listeria monocytogenes

E) Naegleria fowleri

#62 **A 2-year-old child is admitted to a pediatric hospital with pertussis.**

#62 **What preventive therapy should be given to the mother?**

A) Treat only if the mother becomes symptomatic

B) Culture the oropharynx and treat only if positive

C) Administer pertussis immune globulin only

D) Administer Tdap only if the mother was never immunized

E) Treat with a 5-day course of azithromycin

60 – Board Review Day 5

Speaker: Drs. Auwaerter (Moderator), Alexander, Bennett, Marr, and Mitre

BOARD REVIEW DAY 5

#63 A CMV seronegative renal transplant recipient received his allograft from a CMV seropositive donor.

BOARD REVIEW DAY 5

#63 The recommended post-transplant antiviral prophylaxis is:

A) No prophylaxis unless a CMV PCR test on blood returns positive

B) Acyclovir intravenously during the transplant hospitalization, then step down to valacyclovir for 6 months

C) Ganciclovir until tolerating orals then stepdown to valganciclovir for 6 months

D) Ganciclovir until tolerating orals then stepdown to valganciclovir for life

BOARD REVIEW DAY 5

#64 A lung transplant recipient developed fatigue, fevers, and diarrhea seven months post-transplant.

She had been receiving valganciclovir prophylaxis since transplant based on her high CMV serologic risk status (donor seropositive, recipient seronegative), but in the context of improving renal function without adjustments in her valganciclovir dosing.

At the time of presentation with fever and fatigue, her CMV viral load on blood was positive at 135,000 IU/ml and her WBC, hemoglobin, platelets, and creatinine clearance were within normal limits.

BOARD REVIEW DAY 5

#64 You recommend:

A) Hold on treatment pending a colonoscopy with colon biopsy to document invasive CMV colitis

B) Increase valganciclovir to prophylactic dosing appropriate for current renal function and recheck CMV viral load in one week

C) Send blood for CMV resistance genotyping and start ganciclovir treatment, double dose

D) Start letermovir

BOARD REVIEW DAY 5

#65 A 23-year-old college student is seen for intermittent fevers, headaches and arthralgias.

He came to the US from the Central African Republic (central Africa) two months ago to attend college.

He says his symptoms have been present for at least the last four months, and it is hard for him to concentrate on his studies.

On exam his temperature is 100.6F; he has a soft, moveable posterior cervical node 3cm by 3cm; and his liver and spleen are palpable.

BOARD REVIEW DAY 5

#65 Which one of the following is the most likely diagnosis?

A) Malaria

B) Rift Valley Fever

C) Rickettsia africae infection

D) Typhoid Fever

E) African trypanosomiasis

60 – Board Review Day 5

Speaker: Drs. Auwaerter (Moderator), Alexander, Bennett, Marr, and Mitre

BOARD REVIEW DAY 5

#66 A 24 y/o male has acute pre-B cell lymphoblastic leukemia that has been refractory to multiple courses of conventional therapy.

After an unsuccessful allogeneic stem cell transplant from his brother, his bone marrow biopsy is packed with blasts and peripheral smear show relapsed pre-B cell leukemia.

He is referred for CD19 CAR T cell therapy (Chimeric antigen receptor T cells), which he received following a preparative regimen consisting of fludarabine plus cyclophosphamide.

BOARD REVIEW DAY 5

#66 On day 10 following CAR T cell infusion, the patient developed fever to 39C on several serial measurements, and capillary leak syndrome with hypoxia and diffuse pulmonary infiltrates on chest xray.

He has been receiving prophylaxis with acyclovir 800 mg po twice daily and micafungin 100 mg IV once daily.

He is transferred to the ICU where his is administered 2 liters of saline, given low dose norepinephrine to bring his mean blood pressure to >60mm/Hg, and placed on supplemental oxygen because his O2 saturation on room air was 90%.

BOARD REVIEW DAY 5

#66 Labs reveal that he is profoundly neutropenic (Absolute neutrophil count < 100), with serum creatinine rising from 1.3mg/dl to 2.4mg/dl, and transaminases rising from 1.5 x normal to 3x normal.

Blood cultures are drawn and piperacillin-tazobactam begun.

BOARD REVIEW DAY 5

#66 What is the most likely cause of his abrupt deterioration?

A) Bacterial sepsis

B) Pneumocystis pneumonia

C) Cytokine release syndrome

D) GI bleed

E) Cardiogenic shock

BOARD REVIEW DAY 5

#67 A 28-year-old woman who is 9 days post receipt of allogeneic HSCT for acute myeloid leukemia presents with 2 days of altered mental status.

Last night, her nurse witnessed what may have been a self-limited focal seizure.

MRI with FLAIR imaging is shown below.

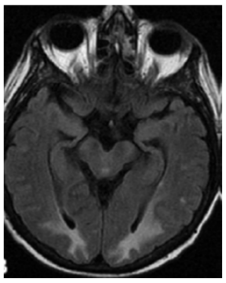
She is lethargic and confused but complains of headache.

She is still severely neutropenic.

BOARD REVIEW DAY 5

#67 She is from Haiti and has a history of latent TB, which was treated for 9 months prior to transplant with INH.

Post-transplant, she is not yet engrafted, and her current serum creatinine is 3.2.



60 – Board Review Day 5

Speaker: Drs. Auwaerter (Moderator), Alexander, Bennett, Marr, and Mitre

BOARD REVIEW DAY 5

#67 Her blood pressures have been increasingly high, now ranging from 140–170 systolic.

Her current medications include tacrolimus (her last level was within the therapeutic range), and prednisone at 10 mg.

She is receiving fluconazole and valacyclovir prophylaxis.

BOARD REVIEW DAY 5

#67 Which of the following is the best explanation of her current process?

A) Tuberculosis

B) HHV-6

C) Cryptococcosis

D) Tacrolimus toxicity

E) Polyoma virus

BOARD REVIEW DAY 5

#68 A 20-year-old patient from Jamaica with aplastic anemia received a cord blood transplant 5 months ago in Bethesda.

He pretransplant serology was CMV IgG positive, toxo IgG positive and HSV positive.

He has had excellent engraftment, and is maintained on tacrolimus plus prophylactic antimicrobials.

BOARD REVIEW DAY 5

#68 Two weeks before admission (4 months post-transplant) he developed progressive fever, shortness of breath, and a slight cough. He has bilateral crackles on lung exam but no wheezes.

There is significant hypoxemia (pO2=90mmHg on room air) but no skin rash or diarrhea.

BOARD REVIEW DAY 5

#68 He has not taken his trimethoprim-sulfamethoxazole, fluconazole, or acyclovir because he thinks they made him nauseated, but he did take his tacrolimus.

- His chest CT scan showed diffuse, bilateral ground glass infiltrates.
- WBC=5000 cells/uL (90% polys)
- Bronchoalveolar lavage: Direct stains negative for pneumocystis by DFA, bacteria by Gram stain, fungi by calcofluor, and AFB by auramine-rhodamine. Lavage fluid was negative on respiratory film array for RSV, coronavirus, influenza and human metapneumovirus.
- BAL PCR was positive for CMV, but blood CMV PCR negative
- BAL PCR was positive for Toxoplasma

BOARD REVIEW DAY 5

#68 What is the most likely cause of his pulmonary process?

A) Cytomegalovirus

B) Engraftment Syndrome

C) Bronchiolitis obliterans

D) Toxoplasmosis

E) Candidiasis

60 – Board Review Day 5

Speaker: Drs. Auwaerter (Moderator), Alexander, Bennett, Marr, and Mitre

BOARD REVIEW DAY 5

#69 A 47-year-old male from Maryland with myelodysplastic syndrome and prolonged neutropenia underwent an allogeneic bone marrow transplant after myeloablative chemotherapy.

Post bone marrow transplant he was placed on prophylactic acyclovir and fluconazole.

Two years ago, he spent 3 months on an island off the coast of Venezuela.

BOARD REVIEW DAY 5

#69 On day 5 following transplant, with an absolute neutrophil count of zero, he became febrile to 40˚C with hypotension. Piperacillin-tazobactam and vancomycin were begun.

The next day, new necrotic skin lesions were noted. The lesions were 2 to 3 cm in diameter and deep in the subcutaneous tissue and reddish purple in color.

Chest CT showed a small peripheral consolidation in right lower lobe. Voriconazole was added.

On day 6 the laboratory reported two routine blood cultures positive for septated hyphae.

BOARD REVIEW DAY 5

#69 The most likely diagnosis is:

A) Disseminated aspergillosis

B) Disseminated mucormycosis

C) Disseminated paracoccidioidomycosis

D) Disseminated Talaromyces marneffei

E) Disseminated fusariosis

BOARD REVIEW DAY 5

#70 A 34-year-old woman in Columbus, Ohio was admitted to the hospital because of high fever, prostration, and extreme malaise of increasing severity over the past week.

Her past history was notable for Crohn's disease being treated with adalimumab (Humira) for the past two months. Prior prednisone therapy had been discontinued.

She was born in Nicaragua but had lived in the United States with her husband and children for the past five years, working in a daycare center.

BOARD REVIEW DAY 5

#70 On examination, she was flushed and dyspneic, with pulse oximetry at 92% saturation.

Chest x-ray showed a faint diffuse infiltrate.

Admission studies found her long standing anemia has worsened, with a hematocrit of 25%, platelet count 30,000, WBC 2,500 with a normal differential, alkaline phosphatase 250, ALT 120, AST 89 and creatinine 2.0.

BOARD REVIEW DAY 5

#70 She was transferred to intensive care and given intravenous cefepime and levofloxacin plus oral doxycycline.

Admission and subsequent daily blood cultures remained negative.

At the end of the first week, micafungin was begun because yeast cells were seen in her peripheral blood smear.

60 – Board Review Day 5

Speaker: Drs. Auwaerter (Moderator), Alexander, Bennett, Marr, and Mitre

BOARD REVIEW DAY 5

#70 The most likely source of her infection was which of the following:

A) A human in Nicaragua

B) A human in her day care center

C) Her intestinal tract

D) Pigeon droppings

E) Soil

BOARD REVIEW DAY 5

#71 A 62-year-old with end stage renal disease and on hemodialysis is under consideration for kidney transplantation.

He immigrated to the U.S. from South Africa 40 years prior.

He notes that his mother died with tuberculosis when he was 12 years old and that he and his father cared for her in their two-room home during her illness.

He has never been treated for tuberculosis. He currently denies cough, weight loss and night sweats. A chest radiograph is clear.

BOARD REVIEW DAY 5

#71 You recommend:

A) Treatment for latent tuberculosis

B) Treatment for latent tuberculosis only if a Tuberculin Skin Test (TST) reactivity is ≥ 10 mm

C) Treatment for latent tuberculosis only if an interferon-gamma release assay (IGRA) for tuberculosis is positive

D) No treatment since his exposure was more than 25 years ago

BOARD REVIEW DAY 5

#72 A 30-year-old HIV-infected man who has sex with men (CD4 count 780 cells/mm^3 with an undetectable HIV RNA) with no significant past medical history complains of pain and decreased vision in his right eye.

He was well until three days prior to presentation when he developed discomfort in his eye and blurry vision.

He denied any history of trauma.

He had just returned from a 10-day trip to North Africa and Western Europe one week prior to the onset of symptoms.

BOARD REVIEW DAY 5

#72 On examination, he has a maculopapular rash on his trunk and diffuse lymphadenopathy. He is referred to an ophthalmologist and is diagnosed with panuveitis.

A CBC, complete metabolic panel, RPR, and chest radiograph are unremarkable.

He had a negative ppd three months earlier.

BOARD REVIEW DAY 5

#72 Which of the following tests is most likely to be abnormal?

A) Toxoplasma serum IgG

B) Cerebrospinal fluid JC virus PCR

C) Cerebrospinal fluid TB PCR

D) Serum treponemal EIA

E) Serum Quantiferon

60 – Board Review Day 5

Speaker: Drs. Auwaerter (Moderator), Alexander, Bennett, Marr, and Mitre

BOARD REVIEW DAY 5

#73 **A 58 y/o man developed a decline in mental status and "sepsis-like picture" 16 days following bilateral lung transplantation.**

He had never travelled outside of the US and worked in an office as an accountant.

Blood cultures were negative and his only remarkable laboratory finding was an elevated ammonia level (490 µmol/L).

BOARD REVIEW DAY 5

#73 **Which of the following would be the most likely cause of this "sepsis like picture" occurring in this setting?**

A) *Mycoplasma genitalium*

B) *Ureaplasma parvum*

C) *Streptobacillus moniliformis*

D) *Brucella melitensis*

E) *Bacteroides thetaiotaomicron*

BOARD REVIEW DAY 5

#74 **A 27 yr old African-American female was hospitalized with severe malaria after returning to the U.S. from a trip in Ghana. She had a peak parasitemia of 7% and exhibited rapid improvement after initiation of artesunate. Nine days after discharge she presents to the Emergency Department with shortness of breath. Oxygenation on room air is 95%, BP 101/55, pulse 92. Hemoglobin is 4.1 gm/dl, compared to her discharge value of 8.3 mg/dl. Serum lactate dehydrogenase level is elevated and haptoglobin is below the level of detection. Chest x-ray is normal.**

BOARD REVIEW DAY 5

#74 **The most likely cause of this deterioration is which of the following:**

A. Glucose-6 phosphate dehydrogenase deficiency (G6PD)

B. Methemoglobinemia

C. Pulmonary embolism

D. Delayed post-artesunate hemolysis

E. Drug resistant malaria

BOARD REVIEW DAY 5

#75 **A 23-year-old, previously healthy man was seen in an emergency room in Kentucky in August for a severe headache that had been present for one day.**

He eats homemade cheese made from raw cow's milk. Two days before he became ill, he had a Jet Ski accident on a man-made lake, ingested a fair amount of lake water, and sustained a minor injury to his leg; there was no head trauma. He was awake, alert, and oriented but had a stiff neck.

The rest of the examination was unremarkable.

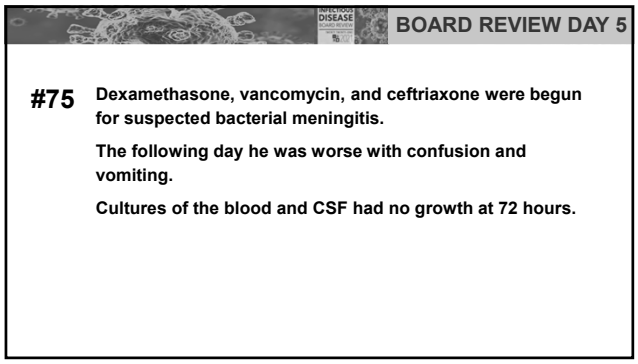
BOARD REVIEW DAY 5

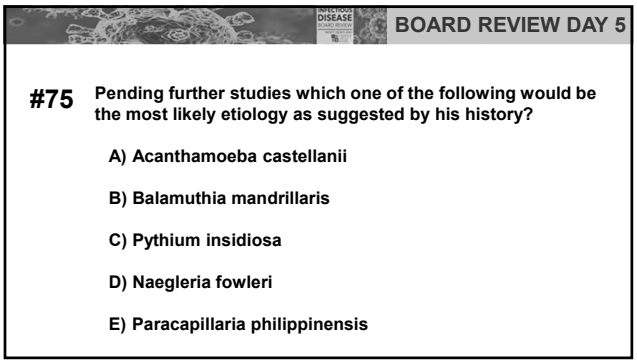
#75 **His CSF showed the following:**

- **WBC: 1740 (82% neutrophils)**
- **RBC: 30**
- **Glucose: 18**
- **Protein: 420**
- **Gram stain: negative**

60 – Board Review Day 5

Speaker: Drs. Auwaerter (Moderator), Alexander, Bennett, Marr, and Mitre





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Ticks, Mites, Lice and the Diseases They Transmit

Dr. Paul G. Auwaerter

61 – Ticks, Mites, Lice and The Diseases They Transmit

Speaker: Paul Auwaerter, MD

Ticks, Mites, Lice, and The Diseases They Transmit

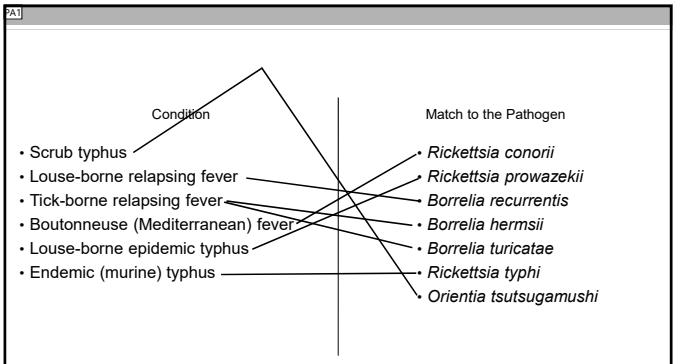
Paul G. Auwaerter, MD
Sherrilyn and Ken Fisher Professor of Medicine
Clinical Director, Division of Infectious Diseases
Johns Hopkins University School of Medicine

Disclosures of Financial Relationships with Relevant Commercial Interests

- Consultant: Pfizer, EMD Serono
- Ownership Interest: Johnson & Johnson

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 (separate talk)
- Rocky Mountain spotted fever (RMSF)
- Ehrlichioses
- Anaplasmosis
- Relapsing fever (*Borrelia* spp.)
- Babesia spp.

Other Tick-borne Diseases of North America

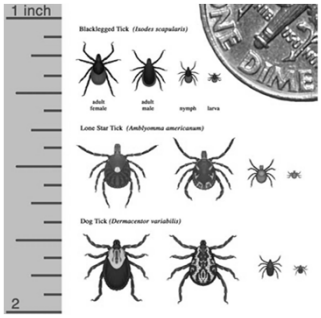
- Tick paralysis
- Southern tick associated rash illness (STARI)
- Viruses:
  - Powassan (Deer Tick Virus Lineage II, flavivirus)
  - Colorado tick fever (coltivirus)
  - Heartland virus (phlebovirus)
  - Bourbon virus (thogotovirus)
- Spotted Fever Group Rickettsia (partial)
  - R. parkeri
  - Rickettsia 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

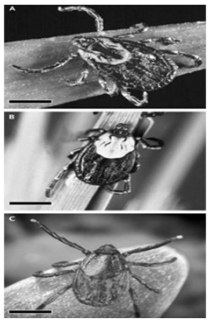


Common North American Hard Ticks (Ixodidae) 2

Amblyomma americanum (Lone star tick)

Common North American Hard Ticks (Ixodidae) 3

Dog ticks

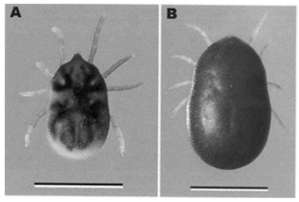


D. variabilis

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:

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)

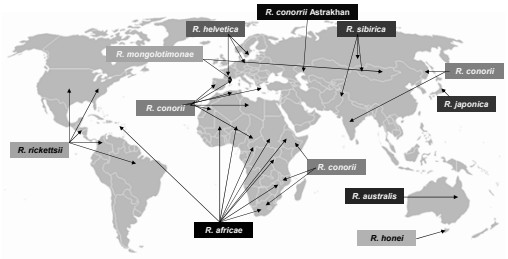
Spotted Fever Group (SFG)

- RMSF (R. rickettsii)
- R. parkeri
- Rickettsia sp. 364D
- Rickettsialpox (R. akari)
- R. conorii
- R. africae
- R. japonica
- R. australis
- …many more

Typhus Group

- 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.

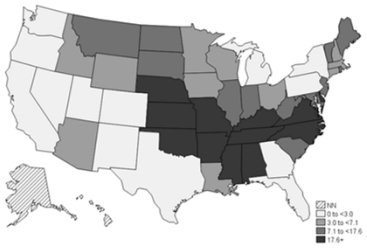
Parola, Clin Microbiol Rev 2013;26(4):657-702

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 6/22/21)
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 6/21/21)

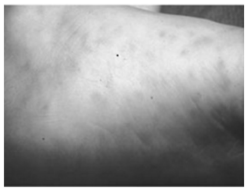
Risk Factors for Fatal RMSF ('99-'07)

- Native Americans
- Age extremes: 5-9, 70+
- Use of chloramphenicol (not doxycycline)
- Delay in diagnosis:
  - Treatment after 5 days illness
- Immunosuppression

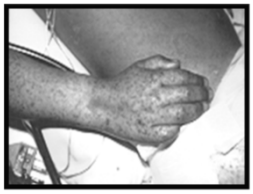
Am J Trop Med Hyg 2012;86:713-9

Rocky Mountain Spotted Fever

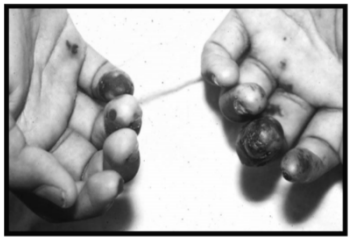
Early: rash absent or maculopapular
Starts on extremities



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, e.g., Carolinas
        - 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

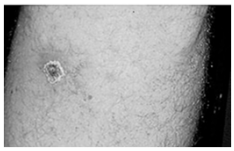
Question #2:

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

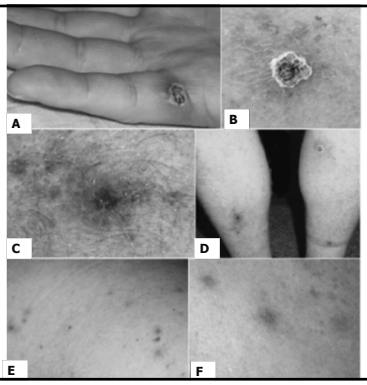


"American Boutonneuse Fever" Rickettsia parkeri

- 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
CID 2008; 47:1188-96

Darker color: Gulf Coast tick range; lighter color: Lone star tick; Red dots: R. parkeri

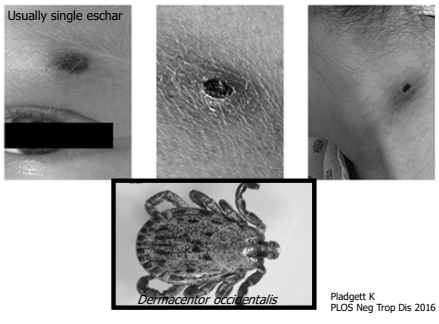
Pacific Coast Tick Fever

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



Pladgett K
PLOS Neg Trop Dis 2016

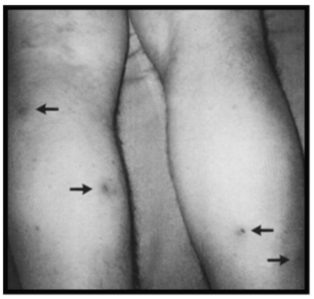
Question 3

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)



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

Figure 4

Figure 4. Distribution of the cases of Mediterranean spotted fever (MSF) in the world and incidence of the disease in countries where MSF is endemic.

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

Rickettsioses 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

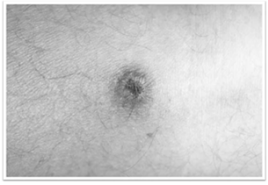
Jensenius M, CID, 2004; 39: 1493-9
Inter J Infect Dis 2004; 8: 139

Question #4:

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:

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

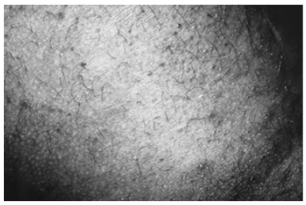
Rickettsialpox

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

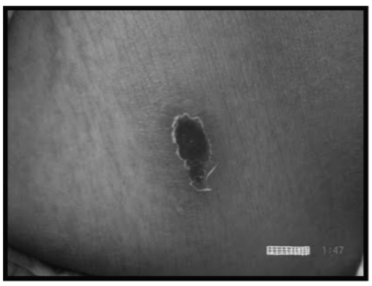
Organism
- O. tsutsugamushi (> 70 strains)

Vector
- Trombiculid mite (chiggers)

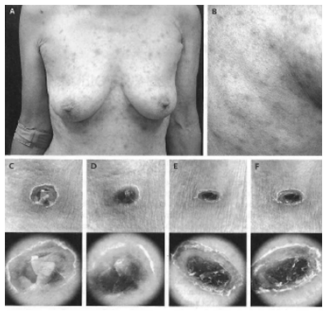
Geography
- Triangle from Japan to Eastern Australia to Southern Russia (rural)
  - Southern China an endemic focus (Yunnan province)

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.

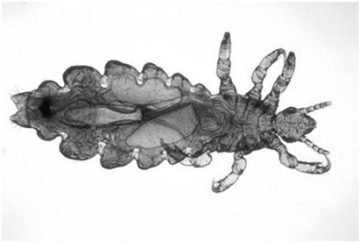
Exam is notable only for fever (39.6^0; no rash), tachycardia (P110)

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

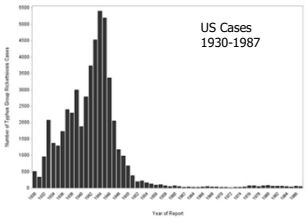
Typhus: Two Forms

	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:

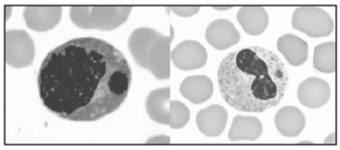
- 43F visited southern Missouri on vacation, returns 7d later with fever, headache and diffuse myalgia x 3d
- Physical examination: no findings
- Laboratory evaluation :
  - WBC: 2.1/mm³ (80% PMNs, 10% lymphocytes, 8% monocytes
  - Hemoglobin: 7.0 g/dL, hematocrit: 24%
  - Platelets: 105,000/mm³
  - 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

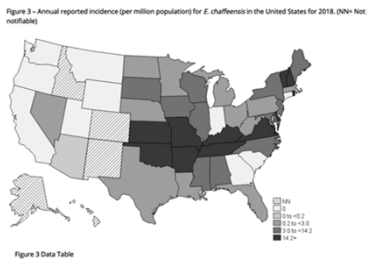
Morulae



HME HGA

Human Monocytic Ehrlichiosis (HME)

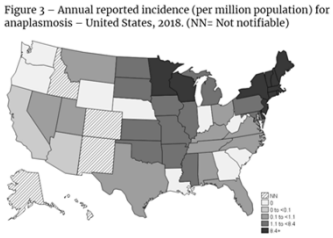
- E. chaffeensis
- Vector: Lone star tick
- Rash: ~30%
  - Maculopapular or petechial
- Labs: LFTs ↑, leukopenia, thrombocytopenia
- Mortality 2.7%
- Diagnosis
  - PCR
  - Morulae (2-38%)
  - Serology: acute/convalescent
  - Treatment: doxycycline



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:

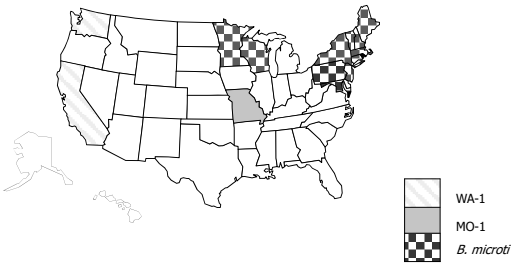
- The best recommended next step:

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

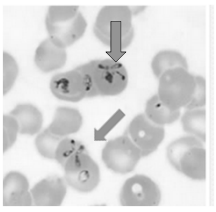
- n=34, Long Island NY
- Clinical manifestations
  - 41% Multi-organ failure
    - ARDS, DIC, CHF, ARF
  - 3 deaths
- Risk factors:
  - age >60
  - splenectomy,
  - immunosuppression (e.g., HIV, rituximab)
- Labs
  - increased LTFs,
  - thrombocytopenia
  - anemia (Hb<10),
  - parasitemia (>10%)

Mortality in immunocompromised > 20%

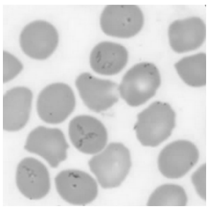
Hatcher JC, et al. Clin Infect Dis 2001; 32:1117-25

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 + clindamycin (now an alternative)
  - 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
    - Severe hemolytic anemia or multi-organ failure
- Mild-moderate severity
  - Azithromycin PO plus atovaquone PO

Krause, et al CID 2021; 72 (2) e49-65

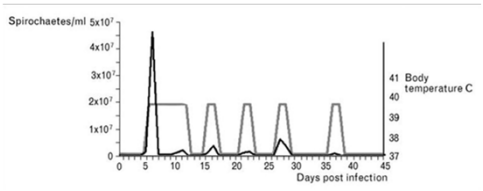
Tickborne Relapsing Fever US

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

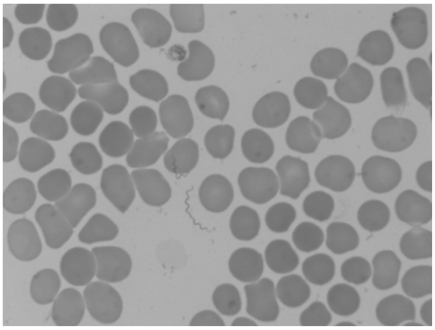
Clinical Manifestations
- Fever (relapsing), HA, myalgia, N/V
  - Can be severe : ARDS
- Laboratory
  - AKI, ↓ platelets,
- **Rx: PCN, doxycycline**
  - Jarisch Herxheimer reaction in 54%

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.



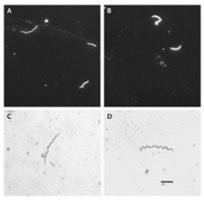
Diagnosis: observation of spirochetes in blood film, PCR

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

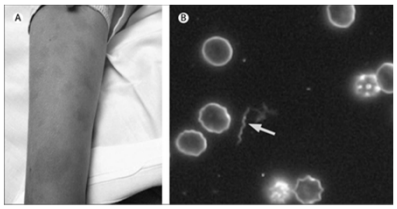


Spirochetes in CSF

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. man 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

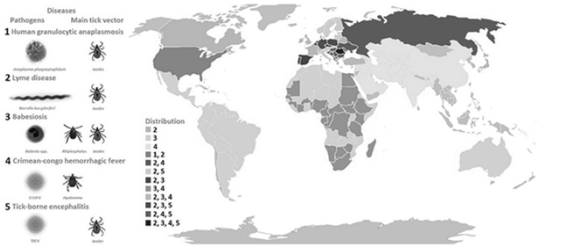
Suspect ehrlichiosis (but no morulae on blood smear)

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

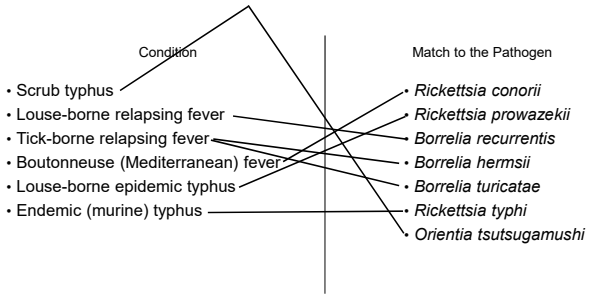
Tick-borne infections: some testable points?

- Babesia:
  - Most common cause of blood transfusion infection in US
  - Splenectomy or immunocompromise = risk severe infection risk
- 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.

62

Worms and More Worms

Dr. Edward Mitre

Worms and More Worms

Edward Mitre, MD
Bethesda, MD

Disclosures of Financial Relationships with Relevant Commercial Interests

- **None**

What are helminths?

What are helminths?

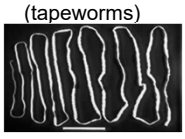
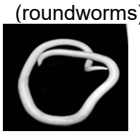
The most complex and fascinating organisms that routinely infect people

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 → typically about 5% of board exam

In addition to all helminths, includes:

- Protozoa
- Ectoparasites
- Principles of Travel Medicine

Question #1

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*
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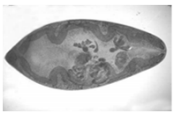
Lung flukes *Paragonimus westermani*		
Intestinal flukes *Fasciolopsis buski* *Metagonimus yokagawai*		

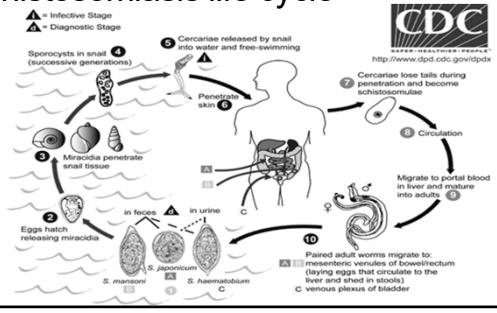
Trematodes (flukes)



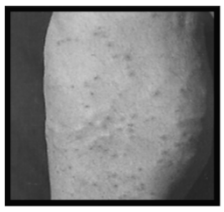
Paragonimus (CDC DpDx)

- 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*)

Schistosomiasis life cycle



Acute Schistosomiasis (Cercarial dermatitis or Swimmer's Itch)



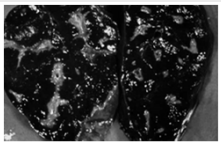
Urticarial plaques and pruritic papules upon reexposure to cercariae penetrating skin in a sensitized individual.

Can occur in response to human or avian schistosomes.

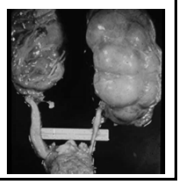
Acute Schistosomiasis: Katayama Fever

- 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*)

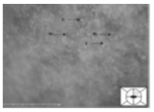


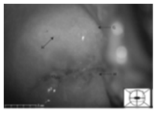
→ granulomatous cystitis *(S. haematobium)*
→ bladder fibrosis and cancer *(S. haematobium)*
→ obstructive uropathy (S. haematobium)

→ CNS disease (eggs to brain/spinal cord, esp *S. japonicum*)

Schistosomiasis

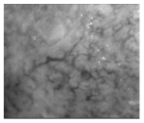
Chronic genital disease
increasingly recognized
primarily due to *S. haematobium*

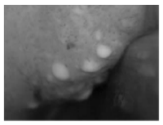

sand grains


sandy yellow patches

men
- epididymitis
- prostatitis

women (see vaginal and cervical lesions)
- pelvic pain
- dysmenorrhea
- dyspareunia
- post-coital bleeding
- endometritis/salpingitis


abnormal vessels


rubbery papules

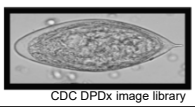
WHO Female Genital Schistosomiasis Pocket Atlas

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

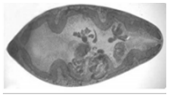
Opisthorchis viverrini

"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

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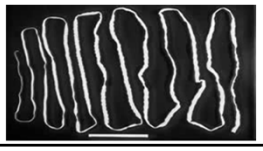
Lung flukes *Paragonimus westermani*		
Intestinal flukes *Fasciolopsis buski* *Metagonimus yokagawai*		

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

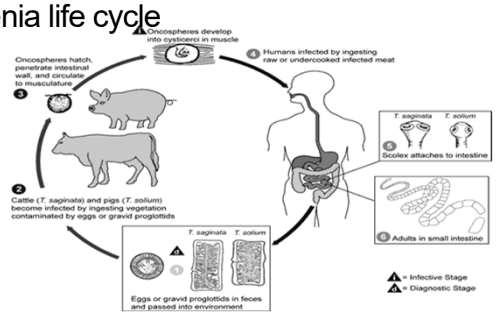
Taenia solium
tapeworm is acquired by eating larvae in pork
adult tapeworm causes few symptoms

Taenia saginatum
acquired by eating larvae in undercooked beef
causes few symptoms
can grow to 10 m

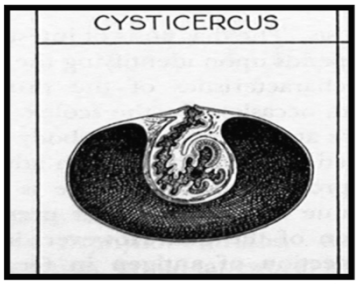
Diphyllobothrium latum *(can grow > 10 m)*
acquired by ingesting fish with larvae
***B12 deficiency in up to 40% of patients**

Dx: eggs/proglottids in stool **Rx**: praziquantel (not FDA-approved)

Taenia life cycle

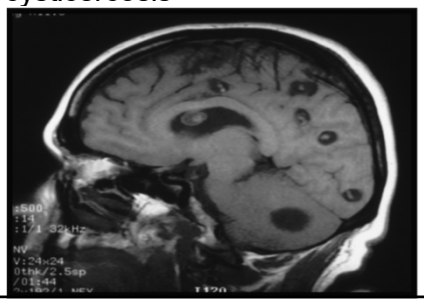


Cysticercus: a fluid filled bladder containing the invaginated head (scolex) of the larval form of a tapeworm.



Neva and Brown, Basic Clinical Parasitology 6th Edition

Neurocysticercosis



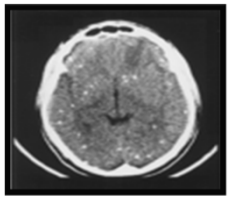
Neurocysticercosis

Can cause:

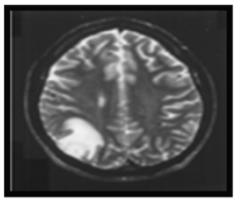
- seizures
- hydrocephalus
- headaches
- focal neurologic deficits

Neurocysticerosis

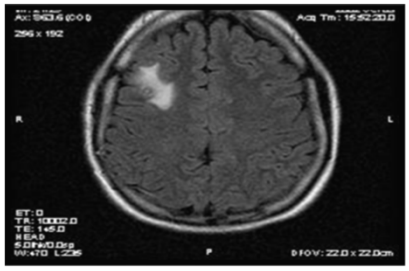
Multiple old calcifications



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

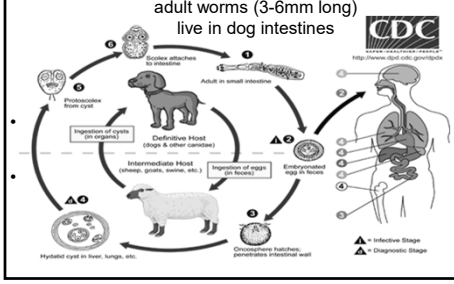
If no increased ICP: 1-2 viable cysts → albendazole for 1-2 viable cysts
> 2 viable cysts → albendazole + praziquantel

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

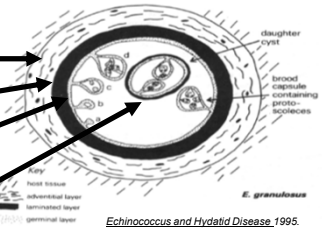
hydatic cyst = "watery vessel"

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

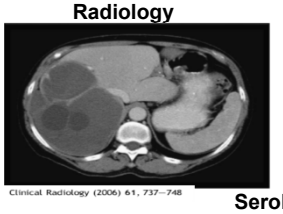
Most cysts (65%) in the liver
25% in the lung, usually in the right lower lobe
Rest occur practically everywhere else in the body

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

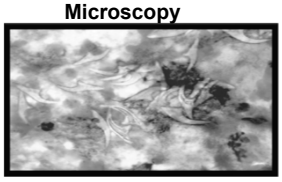
Echinococcus granulosus - diagnosis

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

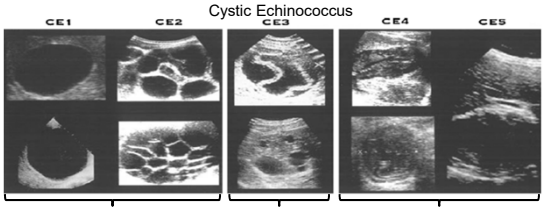
Echinococcus granulosus – treatment

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

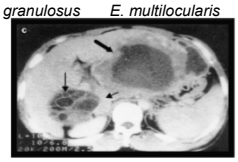
ACTIVE		TRANSITIONAL	INACTIVE
Unilocular Simply cyst Cyst wall visible	Multivesicular Multiseptated cysts	Anechoic content Detached membrane Solid matrix	Heterogenous, hypoechoic or hyperechoic No daughter cysts CE5 with thick calfied wall
---PAIR or SURGERY---	---SURGERY---	---SURGERY--- ---PAIR if 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*

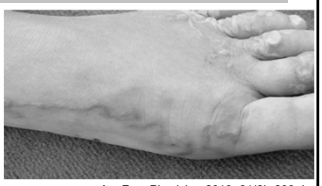


Lancet 2003; 362:1295-304

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 caninum*



Am Fam Physician 2010, 81(2): 203-4.

Major Helminth Pathogens

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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

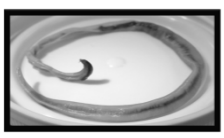
SKIN → LUNGS → GUT

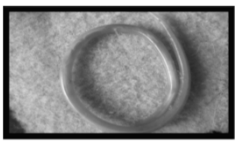
Ascaris

GUT → LIVER → LUNGS → GUT

Ascaris lumbricoides

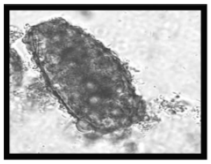
- Large numbers of worms can cause abdominal distention and pain or intestinal obstruction
- can cause "Loeffler's syndrome" - an eosinophilic pneumonitis with transient pulmonary infiltrates
- cholangitis and/or pancreatitis b/c aberrant migration

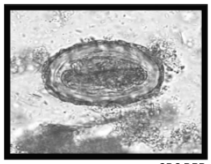




Ascaris lumbricoides - Diagnosis

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
also Ancylostoma ceylanicum (zoonotic from dogs/cats in Asia)

- 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

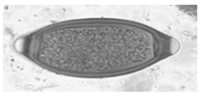
Trichuris trichiura (whipworm)

4cm long nematode

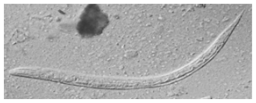
Life cycle: Fecal-oral

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 --

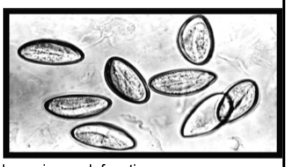
Strongyloides stercoralis

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 (rare: appendicitis)

Dx: stool o&p exams not very helpful
→ "pinworm paddle test" early am before showering or defecating
→ eggs have one flat side

Rx: pyrantel pamoate, albendazole, or mebendazole single dose
→ **treat all members of household**
→ **retreat everyone in two weeks**
→ careful trimming of fingernails, handwashing,
washing of bedclothes to rid house of eggs

Question #4

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:

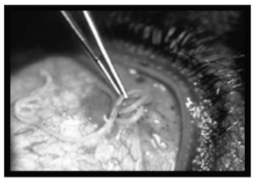
A. *Anisakis simplex*
B. *Onchocerca volvulus*
C. *Enterobius vermicularis*
D. *Toxocara canis*
E. *Anyclostoma braziliense*

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

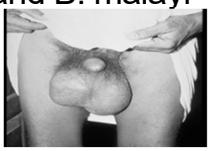
	Adults	Microfilariae
Wuchereria bancrofti *Brugia malayi* (lymphatic filariasis) --mosquitoes--	lymphatics	blood (night)
Loa loa (eyeworm) --Chrysops flies--	SQ tissues (moving)	blood (day)
Onchocerciasis (river blindness) --blackflies--	SQ tissues (nodules)	skin

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

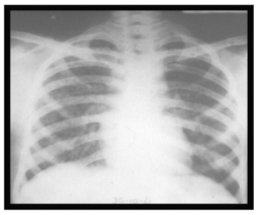


- Asymptomatic microfilaremia
- Lymphangitis
  - retrograde (filarial lymphangitis)
  - bacterial skin/soft tissue infections (dermatolymphangioadenitis)
- Lymphatic obstruction
  - Lymphedema, elephantiasis, hydrocele, chyluria

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

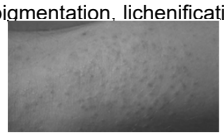


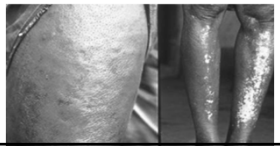
Lymphatic filariasis: diagnosis

- 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

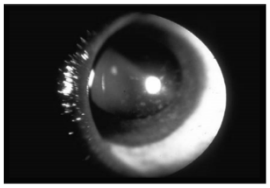
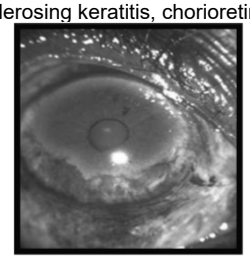
Skin: nodules, pruritus, rash, depigmentation, lichenification



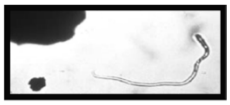
Manifestations of Onchocerciasis

- 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

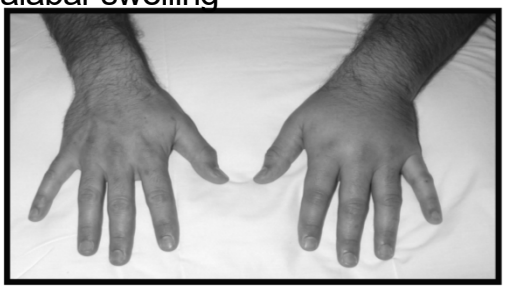
May be due to cross-reactive antibodies, triggered by Onchocerca infection, that recognize leiomodin-1 in the hippocampus

Johnson et al, Science Translational Medicine 2017 v9 issue 377

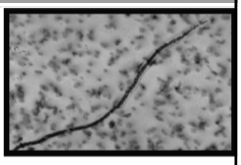
Loiasis: clinical manifestations

- 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

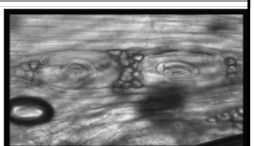


Definitive diagnosis
- Identification of adult worm in subconjunctiva
- Detection of Loa microfilaria in **noon blood**

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

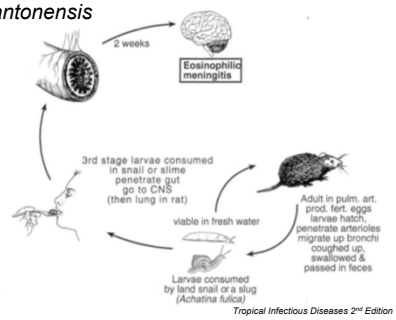
Angiostrongylus cantonensis

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_fIIK93ZIE



Tropical Infectious Diseases 2nd Edition

Angiostrongylus cantonensis

→ *Case reports in Hawaii past few 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

63

Lyme Disease

Dr. Paul G. Auwaerter

63 – Lyme Disease

Speaker: Paul Auwaerter, MD

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

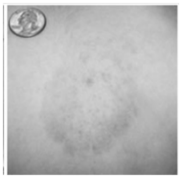
Disclosures of Financial Relationships with Relevant Commercial Interests

- Consultant: Pfizer, EMD Serono, Medical-Legal
- Ownership Interest: Johnson & Johnson

Question # 1

A 56 y.o man from southern Missouri
Onset in July:
- Myalgia and malaise
- Rash of two days duration
- Tick bite 1 week ago

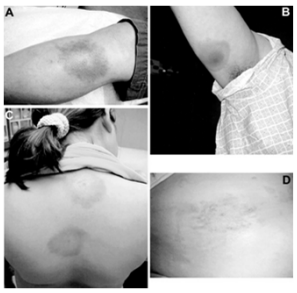
Exam: T 37.0°C
Annular "bulls-eye" ~6 cm
(same area that engorged tick was removed earlier in the week)



Question # 1

Which of the following is the most likely diagnosis?

A. Lyme disease (*Borrelia burgdorferi* infection)
B. Human Monocytic Ehrlichiosis (*Ehrlichia chaffeensis)*
C. *Borrelia mayonii*
D. Southern tick-associated rash illness (STARI)
E. B. lonestarii 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, typically given

No sequelae

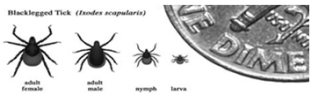
James AM, J Infect Dis 2001;183:1810

63 – Lyme Disease

Speaker: Paul 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 6/22/21

Lyme Borreliosis

USA

- *Borrelia burgdorferi*
  - Geographically localized
    - ~20-30,000 cases reported annually in US
      - Actual >10x more than reported
    - 95% cases in 14 states
    - Coastal, lake and river environs
      - New England
      - Mid-Atlantic
      - Upper Midwest

Europe

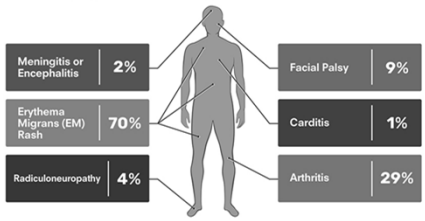
- *Borrelia afzelii & Borrelia garinii >> Borrelia burgdorferi*
- Occasionally others
- Genus name: changing to *Borreliella?*

Lyme Disease Presentations

- Early, localized
  - Rash: erythema migrans
- Early, disseminated
  - Rash: multiple erythema migrans
  - Cardiac
  - Neurologic
- Late
  - Lyme arthritis
  - Neurologic (rare)
  - Dermatologic (Europe)
- Overlapping presentations possible

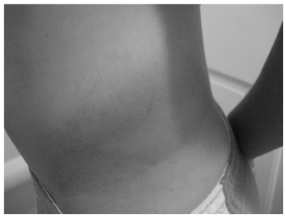
LYME DISEASE

Relative frequency of clinical features among confirmed cases – United States, 2008–2019



(based on 62% of 311,561 confirmed cases reported--probably favoring later presentations, Source CDC: accessed 6/21/21)
http://www.cdc.gov/lyme/stats/chartstables/casesbysymptom.html

Question # 2



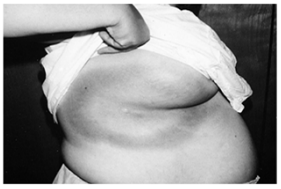
July, 18M living in suburban Maryland, with this rash growing to ~12 cm, first noted 4d, ago, asymptomatic. Landscaper, had tick bite 10d ago. PCP gave cephalexin 2d ago.

Which of the following is true

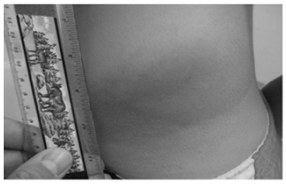
A. Lack of response to cephalexin is consistent with erythema migrans
B. Lack of systemic symptoms makes this unlikely to be Lyme disease
C. Ordering *B. burgdorferi* 2-tier serology will likely confirm Lyme disease
D. Whole blood *B. burgdorferi* PCR is superior to serology in early infection
E. Tick should be submitted for detection of *B. burgdorferi* by PCR

Early, localized LD: Erythema migrans

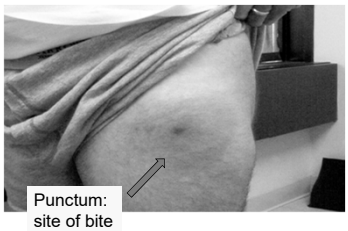
Classic: "bull's eye"
with central clearing upon expansion



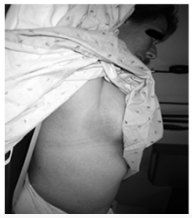
Most common: homogeneous, pink-red ovoid



Typical Erythema Migrans

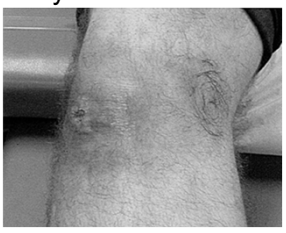


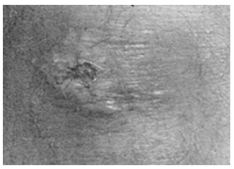
Punctum:
site of bite



Lesions: occur typically below neck and above knees & elbows

Spider bite?: differential diagnosis may also be confused with MRSA, cellulitis



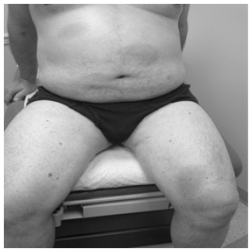


Less typical erythema migrans: skin punch biopsy *B. burgdorferi* culture positive (research labs only)

Erythema migrans

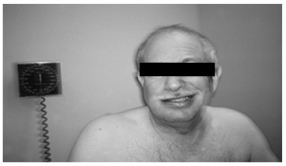
- Primary lesion: occurs 3-30d [7-14d average] @ site tick bite site
  - > 5cm = more secure diagnosis
    - Ddx: includes cellulitis, tinea, erythema marginatum, tick hypersensitivity reaction (smaller)
  - Diagnosis: characteristic rash + epidemiology
    - Serologic testing not recommended, rash sufficient
    - 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 palsies: seen less
        - e.g., III, VI, VIII
  - Radiculoneuritis
  - Mononeuritis multiplex

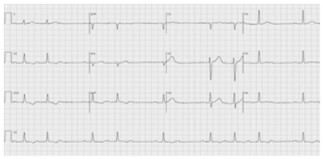
Diagnosis – Facial Palsy

- 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
  - Not required
- Most would recover without antibiotic therapy[2]
  - Main role of abx: prevent later disease manifestations

[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

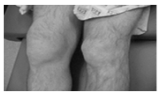
56M Long Island, NY with R knee pain and swelling x 3 weeks. Thought this was a wrenched knee from yardwork.

No fever, rash, tick bite or Lyme disease history

PMH: HTN, hyperlipidemia

PE: afebrile, mildly warm knee, moderate effusion, reduced ROM

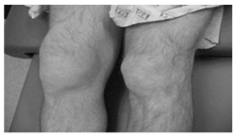
Labs: nl CBC



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 ~30% untreated patients (historically 50-60%)
- May remit, recur in different joints over period of wks to mos w/o abx Rx

Ann Int Med 1987; 107:725
Lantos, CID Nov 30, 2020

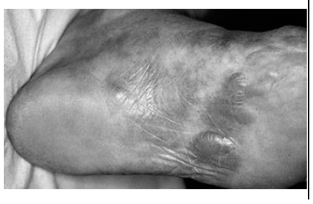
Late Lyme disease (2): Neurologic

- 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

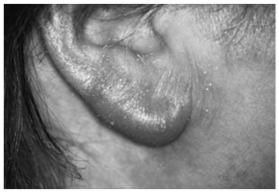
Late Lyme disease (3): Dermatologic

Europe only

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 twice daily x 14 days
B. Doxycycline 100 mg twice daily x 28 days
C. Repeat Lyme serology (two tier: EIA w/ reflex WB)
D. Lyme C6 antibody assay
E. Neither additional Lyme disease testing nor 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: Initial Regimens

Treatment Disease Manifestation	Route	Medication[a]	Duration (days)[b]
Lyme disease			
Erythema migrans	Oral	Doxycycline or Amoxicillin or Cefuroxime axetil	10 14 14
Meningitis/radiculopathy	Oral IV[c]	Doxycycline Ceftriaxone	14-21 14-21
Cranial nerve palsy	Oral	Doxycycline	14-21
Encephalomyelitis	IV[c]	Ceftriaxone	14-28
Carditis	Oral	Doxycycline or Amoxicillin or Cefuroxime axetil	14-21
	IV[c]	Ceftriaxone	14-21
Arthritis	Oral	Doxycycline or Amoxicillin or Cefuroxime axetil	28

[a]Further details regarding adult and pediatric dosing can be found in the 2021 Guideline[
[b]Ranges are given if available studies are insufficient to determine the optimal duration.
[c]Cefotaxime and penicillin G are alternative IV options.
[d]Parenteral therapy is used for hospitalized patients, who, with improvement, may transition to oral antibiotics to complete the treatment course.

Lantos et al, IDSA/AAN/ACR Lyme GL, CID 2021; 72(1)e1-e48

Treatment: Late Lyme arthritis

- Initial treatment: amoxicillin or doxycycline PO x 28d
  - If lack of response: second course orals or ceftriaxone IV x 14-28d
- ~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. Söwati, 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
ALT 80 AST 58 Tot Bili 2.4

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

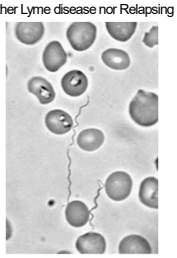
Lyme disease: co-infections

- 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 2020

B. miyamotoi--Ixodes spp. vector

Neither Lyme disease nor Relapsing Fever

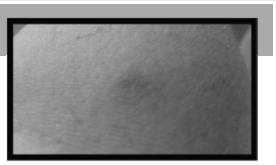


Telford, et al. Clin Lab Med 2015; 35(4):867

- 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
  - Spirochetes on fluid H&E
  - 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, a tick on his arm removed 2d earlier. Now heading out of town for a beach vacation.

Today, 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

64

Lots of Protozoa

Dr. Edward Mitre

64 – Lots of Protozoa

Speaker: Edward Mitre, MD

Lots of Protozoa

Edward Mitre, MD
Bethesda, MD

Disclosures of Financial Relationships with Relevant Commercial Interests

- **None**

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

National Institutes of Health

National Institute of Allergy and Infectious Diseases **Not Protozoa**

Kingdom Fungi: Microsporidiosis agents
Kingdom Chromista: Blastocystis

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

National Institutes of Health

National Institute of Allergy and Infectious Diseases **Not Protozoa**

Kingdom Fungi: Microsporidiosis agents
Kingdom Chromista: Blastocystis

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*.

National Institutes of Health

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**

National Institute of Allergy and Infectious Diseases

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

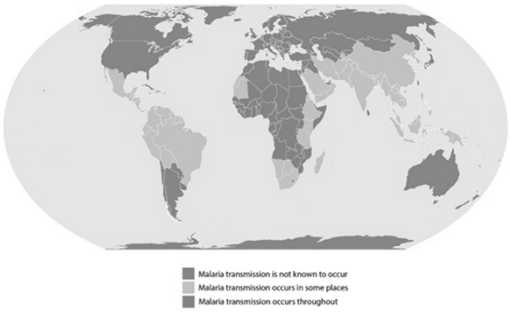
highly morbid and can be lethal

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 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**

64 – Lots of Protozoa

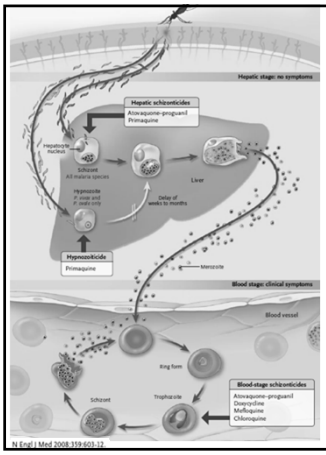
Speaker: Edward Mitre, MD

---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



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)

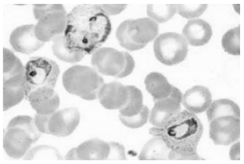
} Often seen in children of endemic countries. Adults more often get multiorgan failure.

- 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%.

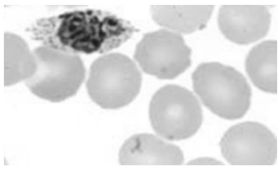
NOTE: in the absence of end organ damage, parasitemia >10% is often used as the cut-off to treat for severe malaria

P. vivax or ovale



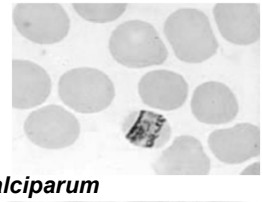
Both have
- intracellular Schüffner's dots
- enlarged infected cells

P. ovale



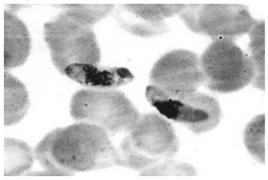
P. ovale
-elongated or oval
-6-12 merozoites (vs 12-24 for vivax)

P. malariae



-band form
(also seen in *P. knowlesi*)

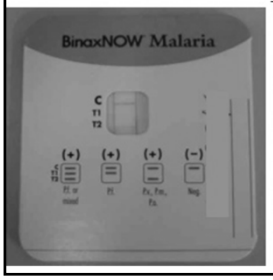
P. falciparum



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

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?

National Institutes of Health

A. Doxycycline
B. Chloroquine
C. Mefloquine
D. Atovaquone/progruanil
E. No prophylaxis

National Institute of Allergy and Infectious Diseases

Malaria Chemoprophylaxis (note: no vax for travelers)

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

** Tafenoquine can precipitate severe hemolytic anemia in individuals that are G6PD deficient*

*** FDA black box warning in 2013 that mefloquine can cause neurologic symptoms, hallucinations, and feelings of anxiety, mistrust, and depression. Can also cause QT prolongation. Thus, many U.S. practitioners now reserve mefloquine for pregnant travelers to areas with chloroquine resistance*

64 – Lots of Protozoa

Speaker: Edward Mitre, MD

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 and then…

- primaquine –weight based dosing and duration as determined by G6PD activity
  (usually 0.5 mg/kg primaquine base x 14 days if normal G6PD activity, if G6PD activity < 30% then can treat with 0.75mg/kg weekly for 8 weeks)

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

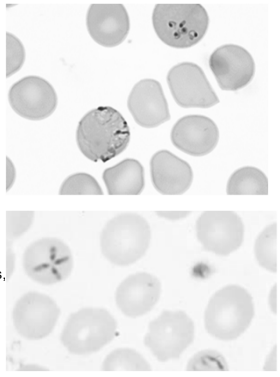
- Ixodes ticks in Northeast and upper midwest
  →co-infection with Lyme and Anaplasma
- Transfusion (approx. 1/20k in NE if un unscreened…Ab screening tests approved by FDA in 2018)

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

National Institutes of Health
National Institute of Allergy and Infectious Diseases

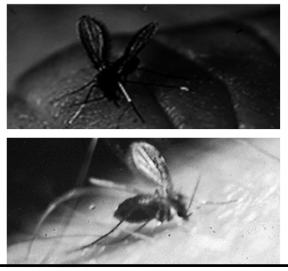
Not Protozoa
Kingdom Fungi: Microsporidiosis agents
Kingdom Chromista: Blastocystis

Leishmaniasis

→obligate intracellular protozoan infection
→transmitted by sand flies (noiseless, active in evenings)

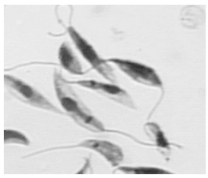
Lutzomyia
New world leishmaniasis

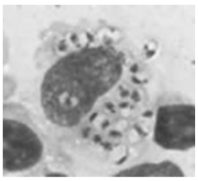
Phlebotomus
Old world leishmaniasis



Leishmania life cycle – Two stages

Promastigote	Amastigote
extracellular, in sand fly	Intracellular (macrophages)
2µm wide x 20µm long	Round or oval
+ flagella	Wright-Giemsa:
large central nucleus	dark-purple nucleus
band shaped kinetoplast	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?

National Institutes of Health

A. L. mexicana
B. L. braziliensis
C. L. peruviana
D. L. infantum chagasi
E. L. major

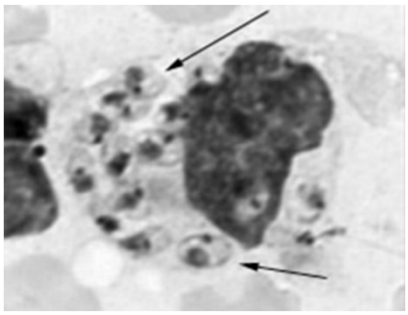
National Institute of Allergy and Infectious Diseases

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**

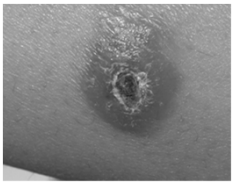
Here are some very clear amastigotes
→ intracellular organisms with nucleus and kinetoplast

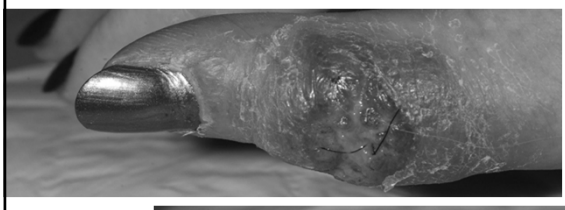


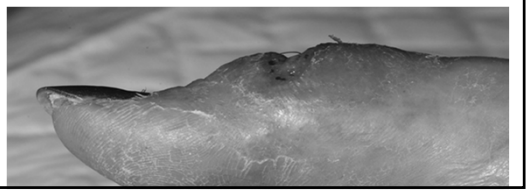
http://www.dpd.cdc.gov/dpdx/HTML/Leishmaniasis.htm

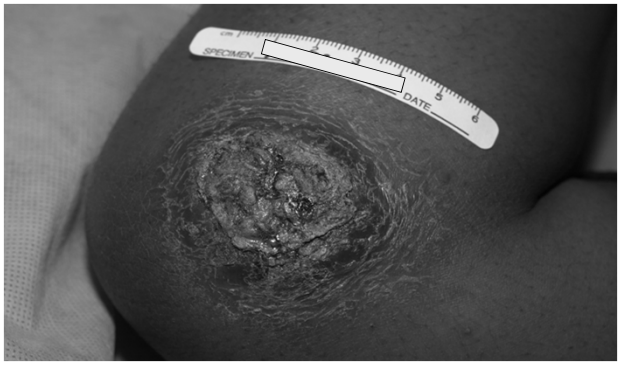
Cutaneous Leishmaniasis – Clinical Presentation

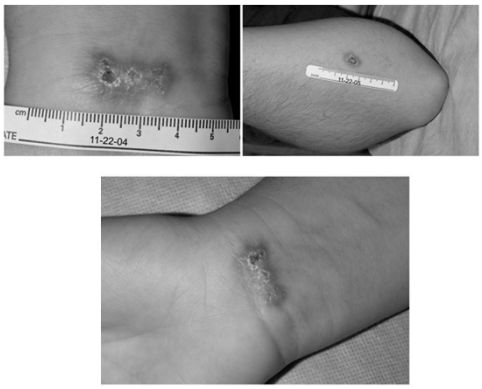
- **papule → nodule →ulcerative lesion → atrophic scar**
  - **ulcerative lesion may have:**
    - **induration,**
    - **scaliness**
    - **central depression**
    - **raised border**
- **takes weeks to months to develop**
- **usually painless, unless superinfected**
- **most lesions will eventually resolve on their own**

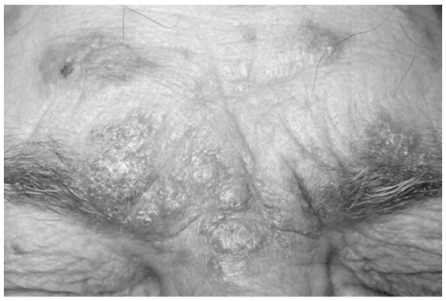












Cutaneous Leishmaniasis – Diagnosis

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

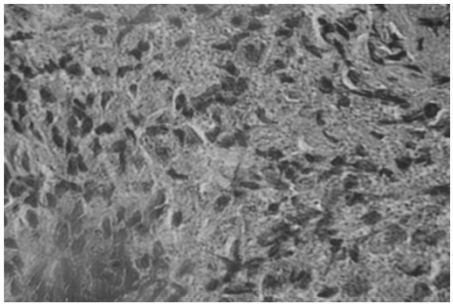
Culture on triple N media (may take weeks to grow)

(Nicolle's modification of Novy and MacNeal's medium – biphasic)

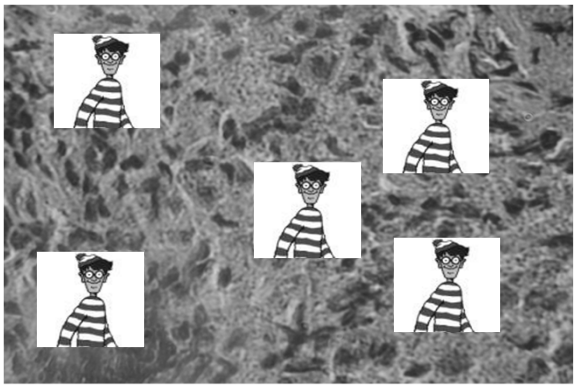
Histology

PCR

Amastigotes in tissue sample



Amastigotes in tissue sample



Cutaneous Leishmaniasis – Treatment Recommendations

→ **Treat <u>systemically</u> 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

<u>Treatment Options</u>

local: heat with radiotherapy (FDA approved), cryotherapy, intralesional therapy
systemic
oral: miltefosine for certain species (2014 FDA approved)
ketoconazole, fluconazole (off-label)
IV: liposomal amphotericin B (off-label)

(June 2021:pentavalent antimony aka stibogluconate no longer avaialable from CDC on IND)

*****2016 IDSA GUIDELINES FOR TREATMENT OF LEISHMANIA*****
http://www.idsociety.org/Guidelines/Patient_Care/IDSA_Practice_Guidelines/Infections_by_Organism/Parasites/Leishmaniasis/

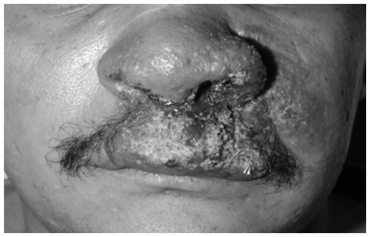
Mucosal leishmaniasis

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



<u>Treatment:</u>
IV liposomal amphotericin (off-label)
IV antimony (not available)
oral miltefosine (FDA approved for *L. braziliensis*)

Note: infection of Leishmania organisms with <u>Leishmaniavirus</u>, a double-stranded RNA virus, may be associated with increased risk of mucocutaneous disease
J Infect Dis. 2016 Jan 1;213(1):112-21

<u>Visceral Leishmaniasis</u>
L. donovani *(South Asia, East Africa)*
L. infantum chagasi *(Middle East, Central Asia, Mediterranean, Central and S. America)*

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

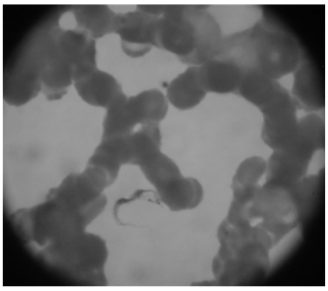
Weeks/months: fevers, chills, fatigue, hepatosplenomegaly

pancytopenia & hypergammaglobulinemia

<u>Diagnosis:</u> intracellular amastigotes in bone marrow or splenic aspirate
antibody to rK39 recombinant Ag (dipstick test)

<u>Treatment</u>: liposomal ampho B (FDA approved)
miltefosine (oral) FDA approved for *L. donovani*

<u>Question 4</u>: 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?

National Institutes of Health

A. Leishmania donovani
B. Plasmodium vivax
C. Trypanosoma brucei
D. Wuchereria bancrofti
E. Leptospira interrogans

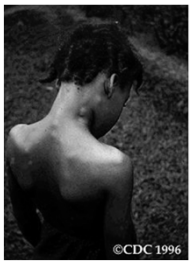
National Institute of Allergy and Infectious Diseases

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: <u>chancre</u> at Tse Tse fly bite
regional <u>lymphadenopathy</u>

for weeks: fever, hepatosplenomegaly, lymphadenopathy, faint rash, headache

late: mental status changes, <u>terminal somnolent state</u>


W.H.O.

African Trypanosomiasis – Lab findings

<u>Non-specific lab findings</u>
- anemia
- thrombocytopenia
- elevated IgM
- hypergammaglobulinemia

<u>Diagnostic lab findings</u>
- 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 <u>card agglutination test</u> 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

64 – Lots of Protozoa
Speaker: Edward Mitre, MD

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

West African (T. gambiense)

If < 6 yo or < 20 kg: lumbar puncture
- CSF < 5 WBC/ul → iv pentamidine
- CSF > 5 WBC/ul → iv eflornithine + nifurtimox

If adult: confusion, ataxia, anxiety, abnl speech, motor weakness, abnl gait?
- no suspicion of late disease → oral fexinidazole
- if suspicion of CNS disease → obtain lumbar puncture
  - CSF < 100 cells/ul (non-severe 2nd stage) → oral fexinidazole
  - CSF > 100 cells/ul → iv eflornithine+ nifurtimox

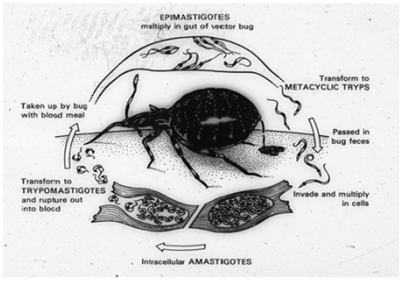
East African (T. rhodesiense): Rx always guided by lumbar puncture
- CSF < 5 WBC/ul → suramin
- CSF > 5 WBC/ul → melarsoprol

Juy 16, 2021: Oral fexinidazole FDA approved for T. gambiense

Notes: 1) Melarsoprol associated with ~5% death rate due to reactive encephalopathy.
2) This is reduced by co-administration of corticosteroids.

Chagas disease

- transmitted by *Trypanosoma cruzi* (also blood transfusion and congenitally)
- vector: reduviid (triatomine) bugs
- reservoirs: opossums, rats, armadillos, raccoons, dogs, cats

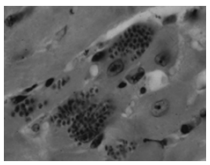


Chagas – Clinical Disease

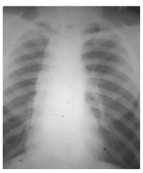
Acute (starts 1 week after infection, can persist for 8 weeks)
- fever
- local lymphadenopathy
- unilateral, painless periorbital edema

Indeterminate stage
- serology positive, no evidence of disease

Chronic



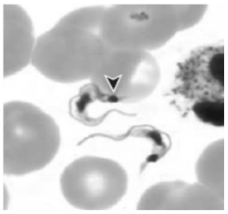
dilated cardiomyopathy, R>L (CHF, syncope, arrythmia)



megaesophagus

64 – 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 antibody tests using different antigens and different techniques recommended for dx**
(research: xenodiagnosis, hemoculture, PCR)

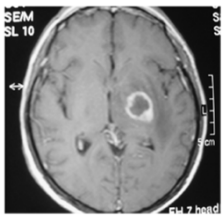
NOTE: U.S. blood supply screened for 1st time donors

Treatment

Benznidazole for 30 – 60 d, alternative: Nifurtimox (both FDA approved)
Benznidazole AEs: peripheral neuropathy, granulocytopenia, rash
Nifurtimox AEs: abdominal pain/vomiting, tremors, peripheral neuropathy

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

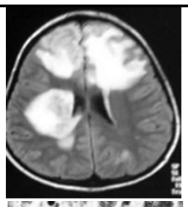
ALSO…. reactivation myocarditis occurs in ~40% of patients that receive heart transplant because of Chagas cardiomyopathy

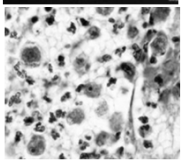
Protozoa

Protozoa - Extraintestinal	Protozoa - Intestinal
Apicomplexa Plasmodium Babesia (Toxoplasma)	**Apicomplexa** Cryptosporidium Cyclospora Cystoisospora
Flagellates Leishmania Trypanosomes (Trichomonas)	**Flagellates** Giardia Dientamoeba
National Institutes of Health **Amoebae** Naegleria Acanthamoeba Balamuthia	**Amoebae** Entamoeba
	Ciliates Balantidium

National Institute of Allergy and Infectious Diseases **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

National Institutes of Health
- 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

National Institute of Allergy and Infectious Diseases
Outcome → often fatal (amphotericin B, azoles, pentamidine, others tried)

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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.

64 – Lots of Protozoa

Speaker: Edward Mitre, MD

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

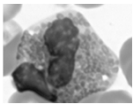
Intestinal Apicomplexa: clinical clues

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!

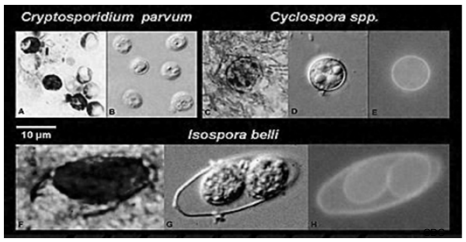
- abrupt onset with nausea, vomiting, and fever early
- anorexia, weight loss, fatigue late in course
- food associated outbreaks: raspberries, lettuce, herbs
- esp. Nepal, Peru, Guatemala

Cystoisospora 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
Cystoisospora	20 μm	m acid-fast	TMP/SMX



Molecular tests

stool multiplex PCR detects cryptosporidium AND Cyclospora but NOT Cystoisospora

stool Ag tests commercially available for cryptosporidium

Morbidity and Mortality Weekly Report

Cryptosporidiosis Outbreaks — United States, 2009–2017

MMWR / June 28, 2019 / Vol. 68 / No. 25

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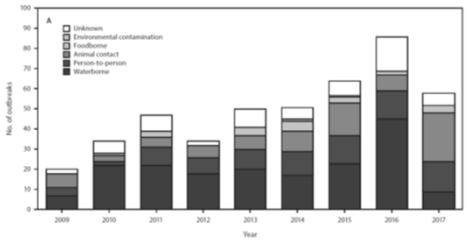


"The number of reported outbreaks has increased an average of approximately 13% per year."

64 – 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?

National Institutes of Health

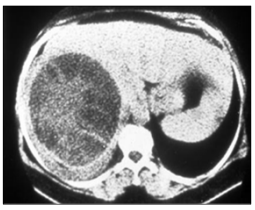
A. Balantidium coli
B. Entamoeba histolytica
C. Giardia lamblia
D. Dientamoeba fragilis
E. Endolimax nana

National Institute of Allergy and Infectious Diseases

Entamoeba histolytica

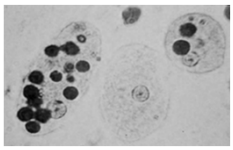
- strictly human pathogen – therefore acquired by food/water contaminated with human feces
- kill cells by small bites (trogocytosis)!!

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 PCR (multiplex or single)
- **close to 100% sensitivity and specificity**

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%)

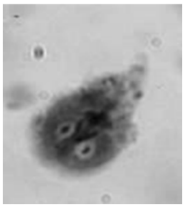
Stool antigen testing > 85% sensitive for intestinal disease

Serology
- helpful in amebic liver abscess (95% sensitive)
- can be helpful (about 85% sensitive) in intestinal amebiasis

Treatment
tinidazole or metronidazole
followed by an agent such as paromomycin to eliminate intraluminal cysts

Giardia duodenalis → *described by Antony van Leeuwenhoek in 1681!*

cool biology: *cysts and trophozoites, ventral disks, strict anaerobes, beavers are always blamed, flagella made of tubulin (not the flagellin protein bacteria use), have 150 variant-specific surface proteins and only express one at a time, TETRAPLOIDY, falling-leaf motility, have genes for meiosis but sexual reproduction not observed*



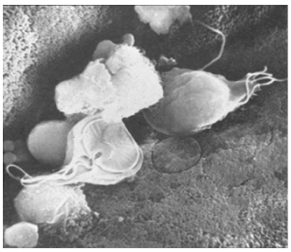
Flagellated protozoan
- fecal/oral via ingestion of cyst form in food/water
- cyst is chlorine resistant
- cysts from humans (beavers, muskrats)

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"

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
- stool multiplex PCR

Treatment
tinidazole (FDA approved)
metronidazole (off-label), nitazoxanide (FDA-approved), 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)

64 – Lots of Protozoa

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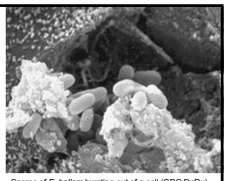
National Institutes of Health

National Institute of Allergy and Infectious Diseases **Not Protozoa**

Kingdom Fungi: Microsporidiosis agents
Kingdom Chromista: Blastocystis

Microsporidia – obligate intracellular fungi!

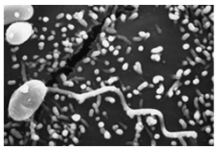
→Produce extracellular, 1-2 micron, infective spores
→Spores have a coiled organelle called a polar tubule
→After ingestion, the spore germinates and the polar tubule is used to inject sporoplasm into a host cell



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)

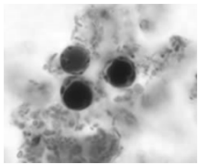
DIAGNOSIS: modified trichrome stain, Calcofluor white, IFA
TREATMENT: albendazole (not effective for *E. bieneusi*)

Blastocystis

What is it?

Nobody really knows!! Might be a protozoa.

Might also be a 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 of stool samples

Treatment?
metronidazole, tinidazole, 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

NOAA photo library

Edward Mitre, M.D.
edwardmitre@gmail.com