GW | Office of Continuing Education in the Health Professions

29th Annual

COMPREHENSIVE REVIEW *for* INFECTIOUS DISEASE BOARD PREPARATION

VOLUME 1

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www.IDBoardReview.com

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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.

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 2024**."
4. 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.

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 - 75 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, 2024** in order **for the MOC points to count toward any MOC requirements that are due by the end of 2024.**

CEHP will continue to submit participant completion data for the course until **August 20, 2025**. **No ABIM MOC credit will be awarded for this activity after August 20, 2025**.

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 Pre- and 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>
</table>

ONLINE MATERIALS

Credit

The George Washington University School of Medicine and Health Sciences designates this enduring material for a maximum of 75 *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 75 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 75 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, 2024** in order **for the MOC points to count toward any MOC requirements that are due by the end of 2024.**

CEHP will continue to submit participant completion data for the course until **August 21, 2025. No ABIM MOC credit will be awarded for this activity after August 21, 2025**.

OVERVIEW OF ONLINE MATERIALS AND INSTRUCTIONS FOR CLAIMING CREDIT AND MOC

Online-Only Lectures	**CME Hours: 9**	**MOC Points: 9**
• These lectures feature topics that were not covered in the live course.		
Board Prep Questions	**CME Hours: 56**	**MOC Points: 56**
• There are four (4) sets of 100 board prep questions. • There is one (1) set of 100 photo opportunity questions. • There is one (1) set of 30 questions on HIV. • 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: 10**	**MOC Points: 10**
• There are eight (7) 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 info@idboardreview.com 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

Instructions for accessing the Online Materials

- Please login to your account at https://cme.smhs.gwu.edu with your username and password (created when you originally registered for the course)

- Course Page: https://cme.smhs.gwu.edu/idbr24/homepage

Important Links

Please note that you must be logged in to access.

- **Main Course Link**:
  https://cme.smhs.gwu.edu/idbr24/homepage

- **To Edit Your User Profile:**
  https://cme.smhs.gwu.edu/user/login?destination=my/edit/profile

- **To View/Download Your CME Certificate After Completing the Course**:
  https://cme.smhs.gwu.edu/user/login?destination=my/activities

- **To Access Your Receipt of Payment:**
  Click on link to "Already Registered?"
  https://cvent.me/2ka4L0

FACULTY LISTING

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

FACULTY DISCLOSURES AND RESOLUTIONS

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

FACULTY (SPEAKERS)

- David Aronoff, MD
- Taison Bell, MD
- Karen C. Bloch, MD, MPH, FIDSA, FACP
- Shireesha Dhanireddy, MD
- Susan Dorman, MD
- Rajesh Gandhi, MD
- Khalil G. Ghanem, MD
- David Gilbert, MD
- Roy M. Gulick, MD, MPH
- Steven M. Holland, MD
- Frank Maldarelli, MD
- Edward Mitre, MD
- Sandra Nelson, MD
- James Platts-Mills, MD
- Stacey R. Rose, MD, FACP
- Michael Saag, MD
- Pranita Tamma, MD
- Allan R. Tunkel, MD, PhD

PLANNERS

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

Both planners also resolved financial disclosures

STAFF

- Kelly Byrne
- Lisa Krueger
- Naomi Loughlin
- Dorothy Martinez

The following faculty members (speakers) disclosed commercial relationships:

FACULTY MEMBER (Speaker)	FINANCIAL DISCLOSURE(S)
Paul G. Auwaerter, MD	• Consulting: Gilead, Shionogi • Ownership Interest: Johnson & Johnson • Research: Pfizer
Barbara D. Alexander, MD, MHS	• Consulting: Scynexis, GSK, Astellas, Merck, HealthTrackRx, Basilea • Research Grant (Institution): Karius • Clinical Trials (Site PI/Study PI): Scynexis, F2G • Royalties (Chapter Author): UpToDate
Helen Boucher, MD	• Editor: ID Clinics of North America, Antimicrobial Agents and Chemotherapy, Sanford Guide
Henry F. Chambers, MD	• Equity: Moderna, Merck • Data Monitoring Committee: Merck
Michael Klompas, MD	• Grant Funding: Centers for Disease Control and Prevention, Agency for Healthcare Research and Quality, Massachusetts Department of Public Health • Royalties: UpToDate
Camille Kotton, MD	• Consulting: Evrys, Kamada Biotest, Merck, QIAGEN, Shire/Takeda • Adjudication Committee: Roche Diagnostics, ResTORBio, Evrys • Data Monitoring Committee: Merck • Research Funding: Kamada Biotest, QIAGEN, Roche Diagnostics • Speaker: Merck
Robin Patel, MD	• Grants: MicuRx Pharmaceuticals, BioFire • Consultant: PhAST, Day Zero Diagnostics, Abbott Laboratories, Sysmex, DEEPULL DIAGNOSTICS, S.L., Netflix, Oxford Nanopore Technologies, HealthTrackRx, CARB-X • Patent: Bordetella pertussis/parapertussis PCR issued; Device/method for sonication with royalties paid by Samsung to Mayo Clinic; Anti-biofilm substance issued • Honoraria: Up-to-Date

Andrew T. Pavia, MD	• Commercial Interests: Antimicrobial Therapy Inc, WebMD, Sanofi
David L. Thomas, MD, MPH	• Data and Safety Monitoring Board: Merck • Advisory Board: Merck, Excision Bio
Barbara W. Trautner, MD	• Research Funding: Genentech and Peptilogics, STRIVE (Shionogi arm) • Ownership interest: Abbott Laboratories, Bristol-Myers Squibb, Abbvie, Pfizer (past) • Past Advisory Board: Phiogen
Richard J. Whitley, MD	• Steering Committee: NIAID Covid-19 Recovery Study, NIAID Recover VITAL Study • Past Chairperson: NIAID Covid-19 Vaccine DSMB, Merck Letermovir DMC and GSK IDMC (Zoster) • Scientific Advisory Board: Treovir, LLC, Altesa Biosciences • Member of the Board of Directors: Evrys Bio, Virios Therapeutics
Kevin L. Winthrop, MD	• Research: Insmed • Consulting: Insmed, Spero, Paratek, AN2

Agenda Day 1: Saturday, August 17, 2024

#	Start		End	Presentation	Faculty
AM Moderators: Henry Masur and John Bennett, MD					
1	8:00 AM EDT	-	8:30 AM EDT	Introduction	John Bennett, MD and Henry Masur, MD
QP1	**8:30 AM**	**-**	**9:00 AM**	**Daily Question Preview: Day 1**	**Henry Masur, MD**
2	9:00 AM	-	10:00 AM	Core Concepts: Microbiology: What You Need to Know for the Exam	Robin Patel, MD
AM Moderator: Andrew Pavia, MD					
FC1	**10:00 AM**	**-**	**10:15 AM**	**Faculty Q&A**	**Drs. Pavia (Moderator), Bennett, and Patel**
3	10:15 AM	-	11:15 AM	Clinical Immunology and Host Defense	Steve Holland, MD
4	11:15 AM	-	12:00 PM	Core Concepts: Antifungal Drugs	Barbara Alexander, MD
	12:00 PM	-	12:30 PM	Lunch Break	
BR1	**12:30 PM**	**-**	**1:15 PM**	**Board Review Day 1**	**Drs. Pavia (Moderator), Alexander, Aronoff, Patel, and Thomas**
PM Moderator: Robin Patel, MD					
5	1:15 PM	-	1:45 PM	Core Concepts: Antiviral Drugs	Andrew Pavia, MD
FC2	**1:45 PM**	**-**	**2:00 PM**	**Faculty Q&A**	**Drs. Patel (Moderator), Alexander, Aronoff, and Pavia**
6	2:00 PM	-	3:00 PM	Respiratory Viral Infections Including Influenza, Immunocompetent, and Immunocompromised Patients	Andrew Pavia, MD
7	3:00 PM	-	3:30 PM	Nocardia, Actinomycosis, Rhodococcus, and Melioidosis	David Aronoff, MD
8	3:30 PM	-	4:15 PM	Acute Hepatitis	David Thomas, MD
9	4:15 PM	-	5:00 PM	Zoonoses	David Aronoff, MD
10	5:00 PM	-	5:45 PM	Chronic Hepatitis	David Thomas, MD
11	5:45 PM	-	6:30 PM	Helicobacter and Clostridium Difficile	David Aronoff, MD
FC3	**6:30 PM**	**-**	**6:45 PM**	**End of the Day Faculty Q&A**	**Drs. Alexander, Aronoff, Pavia, and Thomas**

Agenda Day 2: Sunday, August 18, 2024

#	Start		End	Presentation	Faculty
AM Moderator: Henry Masur, MD					
QP2	**8:00 AM EDT**	**-**	**8:30 AM EDT**	**Daily Question Preview Day 2**	**Henry Masur, MD**
12	8:30 AM	-	8:45 AM	How to Prepare for the Certification and Recertification, Including the LKA	Helen Boucher, MD
13	8:45 AM	-	9:45 AM	Core Concepts: Antibacterial Drugs I Gram Negative Organisms	Pranita Tamma, MD
14	9:45 AM	-	10:45 AM	Core Concepts: Antibacterial Drugs II Gram Positive Organisms	Helen Boucher MD
FC4	**10:45 AM**	**-**	**11:00 AM**	**Faculty Q&A**	**Drs. Bennett (Moderator), Boucher, Tamma**
15	11:00 AM	-	11:45 AM	CMV, EBV, HHV6 and HHV8 in Immunocompetent and Immunocompromised Patients	Camille Kotton, MD
	11:45 AM	-	12:15 PM	Lunch Break	
BR2	**12:15 PM**	**-**	**1:00 PM**	**Board Review Day 2**	**Drs. Alexander (Moderator), Boucher, Kotton, Platts-Mills, Saullo, Tamma, Trautner, and Whitley**
PM Moderator: Barbara Alexander, MD					
16	1:00 PM	-	2:00 PM	Infections in the Neutropenic Cancer Patient and Hematopoietic Stem Cell Recipients	Jennifer Saullo, MD
17	2:00 PM	-	3:00 PM	Infections in Solid Organ Transplantation	Barbara Alexander, MD
FC5	**3:00 PM**	**-**	**3:15 PM**	**Faculty Q&A**	**Drs. Alexander (Moderator) Kotton, and Saullo**
18	3:15 PM	-	3:45 PM	GI Infections Part 1	James Platts-Mills, MD
19	3:45 PM	-	4:30 PM	Skin and Soft Tissue Infections	Helen Boucher, MD
20	4:30 PM	-	5:00 PM	GI Infections Part 2	James Platts-Mills, MD
21	5:00 PM	-	5:45 PM	Infections of Upper and Lower Urinary Tract Infections	Barbara Trautner, MD
22	5:45 PM	-	6:15 PM	HSV and VZV in Immuno-competent and Immunocompromised Hosts	Richard Whitley, MD
FC6	**6:15 PM**	**-**	**6:30 PM**	**End of the Day Faculty Q&A**	**Drs. Alexander (Moderator), Boucher, Platts-Mills, Trautner, and Whitley**

Agenda Day 3: Monday, August 19, 2024

#	Start		End	Presentation	Faculty
AM Moderator: Paul Auwaerter, MD					
QP3	**8:00 AM EDT**	**-**	**8:30 AM EDT**	**Daily Question Preview Day 3**	**Paul Auwaerter, MD**
23	8:30 AM	-	9:00 AM	Sexually Transmitted Infections: Genital Ulcers Diseases (GUD)	Khalil Ghanem, MD
24	9:00 AM	-	9:45 AM	Fungal Diseases in Normal and Abnormal Hosts	John Bennett, MD
FC7	**9:45 AM**	**-**	**10:00 AM**	**Faculty Q&A**	**Drs. Auwaerter (Moderator), Bennett, and Ghanem**
25	10:00 AM	-	11:00 AM	Sexually Transmitted Infections: Other Diseases and Syndromes	Khalil Ghanem, MD
26	11:00 AM	-	11:45 AM	Nontuberculous Mycobacteria in Normal and Abnormal Hosts	Kevin Winthrop, MD
	11:45 AM	-	12:15 PM	Lunch Break	
BR3	**12:15 PM**	**-**	**1:00 PM**	**Board Review Day 3**	**Drs. Auwaerter (Moderator), Bell, Bennett, Dhanireddy, Dorman, Ghanem, Klompas, and Winthrop**
PM Moderator: Paul Auwaerter MD					
27	1:00 PM	-	1:45 PM	Ticks, Mites, Lice, and the Diseases They Transmit	Paul Auwaerter, MD
28	1:45 PM	-	2:30 PM	Immunizations: Domestic, Travel, and Occupational	Shireesha Dhanireddy, MD
29	2:30 PM	-	3:15 PM	Tuberculosis in Immunocompetent and Immunosuppressed Hosts	Susan Dorman, MD
FC8	**3:15 PM**	**-**	**3:30 PM**	**Faculty Q&A**	**Drs. Auwaerter (Moderator), Dhanireddy, and Dorman**
30	3:30 PM	-	4:00 PM	Lyme Disease	Paul Auwaerter, MD
31	4:00 PM	-	5:00 PM	Hospital Epidemiology	Michael Klompas, MD
32	5:00 PM	-	5:45 PM	Syndromes in the ICU that ID Physicians Should Know	Taison Bell, MD
33	5:45 PM	-	6:15 PM	Pneumonia	Paul Auwaerter, MD
FC9	**6:15 PM**	**-**	**6:30 PM**	**End of the Day Faculty Q&A**	**Drs. Auwaerter, Bell, and Klompas**

Agenda Day 4: Tuesday, August 20, 2024

AM Moderator: Roy Gulick, MD					
#	Start		End	Presentation	Faculty
QP4	8:00 AM EDT	-	8:30 AM EDT	Daily Question Preview Day 4	Roy Gulick, MD
34	8:30 AM	-	9:15 AM	Clinical Manifestations of Human Retroviral Diseases and Slow Viruses	Frank Maldarelli, MD
35	9:15 AM	-	10:00 AM	HIV-Associated Opportunistic Infections I	Henry Masur, MD
36	10:00 AM	-	10:15 AM	HIV Diagnosis	Frank Maldarelli, MD
FC10	10:15 AM	-	10:30 AM	Faculty Q&A	Drs. Gulick (Moderator), Maldarelli, and Masur
37	10:30 AM	-	11:15 AM	Antiretroviral Therapy	Roy Gulick, MD
38	11:15 AM	-	11:30 AM	HIV Drug Resistance	Michael Saag, MD
39	11:30 AM	-	12:15 PM	Antiretroviral Therapy for Special Populations	Roy Gulick, MD
	12:15 PM	-	12:45 PM	Lunch Break	
BR4	12:45 PM	-	1:30 PM	Board Review Day 4	Drs. Gulick (Moderator), Bloch, Gandhi, Maldarelli, Masur, Saag, and Tunkel
PM Moderator: Roy Gulick, MD					
40	1:30 PM	-	1:45 PM	Pharyngitis Syndromes Including Group A Strep Pharyngitis	Karen Bloch, MD
41	1:45 PM	-	2:30 PM	HIV-Associated Opportunistic Infections II	Rajesh Gandhi, MD
42	2:30 PM	-	3:15 PM	Syndromes Masquerading as Infections	Karen Bloch, MD
FC11	3:15 PM	-	3:30 PM	Faculty Q&A	Drs. Gulick (Moderator), Bloch, and Gandhi
43	3:30 PM	-	4:15 PM	Non-AIDS-Defining Complications of HIV/AIDS	Mike Saag, MD
44	4:15 PM	-	5:00 PM	Encephalitis including West Nile and Rabies	Allan Tunkel, MD
45	5:00 PM	-	5:45 PM	Photo Opportunity I: Photos and Questions to Test Your Board Preparation	Rajesh Gandhi, MD
46	5:45 PM	-	6:10 PM	What Could Be on the Exam About COVID	Roy Gulick, MD
FC12	6:10 PM	-	6:25 PM	End of the Day Faculty Q&A	Drs. Gandhi, Gulick, Saag, and Tunkel

Agenda Day 5: Wednesday, August 21, 2024

AM Moderator: John Bennett, MD					
#	**Start**		**End**	**Presentation**	**Faculty**
47	8:00 AM EDT	-	9:00 AM EDT	Endocarditis of Native and Prosthetic Devices, and Infections of Pacers and Ventricular Assist Devices	Henry Chambers, MD
48	9:00 AM	-	9:45 AM	Photo Opportunities II You Should Know for Exam	John Bennett, MD
FC13	**9:45 AM**	**-**	**10:00 AM**	**Faculty Q&A**	**Drs. Bennett (Moderator) and Chambers**
49	10:00 AM	-	10:45 AM	Staphylococcus aureus	Henry Chambers, MD
50	10:45 AM	-	11:30 AM	Bone and Joint Infections	Sandra Nelson, MD
	11:30 AM	-	11:45 AM	Lunch Break	
PM Moderator: Henry Masur, MD					
BR5	**11:45 AM**	**-**	**12:30 PM**	**Board Review Day 5**	**Drs. Masur (Moderator), Bennett, Chambers, Mitre, Nelson, and Rose**
51	12:30 PM	-	1:30 PM	Lots of Protozoa	Edward Mitre, MD
FC14	**1:30 PM**	**-**	**1:45 PM**	**Faculty Q&A**	**Drs. Masur (Moderator), Mitre, Nelson, and Rose**
52	1:45 PM	-	2:15 PM	Worms That Could Be on The Exam	Edward Mitre, MD
53	2:15 PM	-	2:30 PM	Penicillin Allergies	Sandra Nelson, MD
54	2:30 PM	-	3:15 PM	Kitchen Sink: Syndromes Not Covered Elsewhere	Stacey Rose, MD

Online Materials

Online Only Lectures

#	Duration	Title	Faculty
OL – 1	40 Mins	Bootcamp: HIV	Roy Gulick, MD
OL – 2	50 Mins	Bootcamp: Transplant	Camille Kotton, MD
OL – 3	45 Mins	Brain Abscess, Cavernous Sinus Thrombosis, and Subdural and Epidural Empyema	Allan Tunkel, MD
OL – 4	40 Mins	Viral and Bacterial Meningitis	Allan Tunkel, MD
OL – 5	33 Mins	Other Antibacterial Drugs (Macrolides, TMP, SMX, etc)	Pranita Tamma, MD
OL – 6	45 Mins	HIV-Associated Opportunistic Infections III	Rajesh Gandhi, MD
OL – 7	45 Mins	Even More Worms	Edward Mitre, MD
OL – 8	25 Mins	Statistics	Khalil Ghanem, MD
OL – 9	45 min	Epididymitis, Orchitis, and Prostatitis	Barbara Trautner, MD

Primers and Study Guides

#	Title	Faculty
P – 1	Microbiology Primer	Robin Patel, MD
P – 2	Antibacterial Resistance Primer	Robin Patel, MD
P – 3	Antifungal Resistance Primer	Barbara Alexander, MD John Bennett, MD
P – 4	Antiviral Resistance Primer	Richard Whitley, MD Andrew Pavia, MD
P – 5	HIV Drug Resistance Primer	Roy Gulick, MD
P – 6	Rickettsia Primer	Paul Auwaerter, MD John Bennett, MD
P – 7	Differential Diagnosis of Diseases presenting as Skin Nodules, Ulcers, or Ulceronodular Skin Lesion	David Gilbert, MD

Board Review Question Sets

Title	# Questions
Question Set A	100
Question Set B	100
Question Set C	100
Question Set D	100
Question Set E: Short HIV Therapy Questions You Should Know For An Exam	30
Photo Opportunities	100

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Agenda Day 1: Saturday, August 17, 2024

#	Start		End	Presentation	Faculty
AM Moderators: Henry Masur and John Bennett, MD					
1	8:00 AM EDT	-	8:30 AM EDT	Introduction	John Bennett, MD and Henry Masur, MD
QP1	**8:30 AM**	**-**	**9:00 AM**	**Daily Question Preview: Day 1**	**Henry Masur, MD**
2	9:00 AM	-	10:00 AM	Core Concepts: Microbiology: What You Need to Know for the Exam	Robin Patel, MD
AM Moderator: Andrew Pavia, MD					
FC1	**10:00 AM**	**-**	**10:15 AM**	**Faculty Q&A**	**Drs. Pavia (Moderator), Bennett, and Patel**
3	10:15 AM	-	11:15 AM	Clinical Immunology and Host Defense	Steve Holland, MD
4	11:15 AM	-	12:00 PM	Core Concepts: Antifungal Drugs	Barbara Alexander, MD
	12:00 PM	-	12:30 PM	Lunch Break	
BR1	**12:30 PM**	**-**	**1:15 PM**	**Board Review Day 1**	**Drs. Pavia (Moderator), Alexander, Aronoff, Patel, and Thomas**
PM Moderator: Robin Patel, MD					
5	1:15 PM	-	1:45 PM	Core Concepts: Antiviral Drugs	Andrew Pavia, MD
FC2	**1:45 PM**	**-**	**2:00 PM**	**Faculty Q&A**	**Drs. Patel (Moderator), Alexander, Aronoff, and Pavia**
6	2:00 PM	-	3:00 PM	Respiratory Viral Infections Including Influenza, Immunocompetent, and Immunocompromised Patients	Andrew Pavia, MD
7	3:00 PM	-	3:30 PM	Nocardia, Actinomycosis, Rhodococcus, and Melioidosis	David Aronoff, MD
8	3:30 PM	-	4:15 PM	Acute Hepatitis	David Thomas, MD
9	4:15 PM	-	5:00 PM	Zoonoses	David Aronoff, MD
10	5:00 PM	-	5:45 PM	Chronic Hepatitis	David Thomas, MD
11	5:45 PM	-	6:30 PM	Helicobacter and Clostridium Difficile	David Aronoff, MD
FC3	**6:30 PM**	**-**	**6:45 PM**	**End of the Day Faculty Q&A**	**Drs. Alexander, Aronoff, Pavia, and Thomas**

Agenda Day 2: Sunday, August 18, 2024

#	Start		End	Presentation	Faculty
AM Moderator: Henry Masur, MD					
QP2	**8:00 AM EDT**	**-**	**8:30 AM EDT**	**Daily Question Preview Day 2**	**Henry Masur, MD**
12	8:30 AM	-	8:45 AM	How to Prepare for the Certification and Recertification, Including the LKA	Helen Boucher, MD
13	8:45 AM	-	9:45 AM	Core Concepts: Antibacterial Drugs I Gram Negative Organisms	Pranita Tamma, MD
14	9:45 AM	-	10:45 AM	Core Concepts: Antibacterial Drugs II Gram Positive Organisms	Helen Boucher MD
FC4	**10:45 AM**	**-**	**11:00 AM**	**Faculty Q&A**	**Drs. Bennett (Moderator), Boucher, Tamma**
15	11:00 AM	-	11:45 AM	CMV, EBV, HHV6 and HHV8 in Immunocompetent and Immunocompromised Patients	Camille Kotton, MD
	11:45 AM	-	12:15 PM	Lunch Break	
BR2	**12:15 PM**	**-**	**1:00 PM**	**Board Review Day 2**	**Drs. Alexander (Moderator), Boucher, Kotton, Platts-Mills, Saullo, Tamma, Trautner, and Whitley**
PM Moderator: Barbara Alexander, MD					
16	1:00 PM	-	2:00 PM	Infections in the Neutropenic Cancer Patient and Hematopoietic Stem Cell Recipients	Jennifer Saullo, MD
17	2:00 PM	-	3:00 PM	Infections in Solid Organ Transplantation	Barbara Alexander, MD
FC5	**3:00 PM**	**-**	**3:15 PM**	**Faculty Q&A**	**Drs. Alexander (Moderator) Kotton, and Saullo**
18	3:15 PM	-	3:45 PM	GI Infections Part 1	James Platts-Mills, MD
19	3:45 PM	-	4:30 PM	Skin and Soft Tissue Infections	Helen Boucher, MD
20	4:30 PM	-	5:00 PM	GI Infections Part 2	James Platts-Mills, MD
21	5:00 PM	-	5:45 PM	Infections of Upper and Lower Urinary Tract Infections	Barbara Trautner, MD
22	5:45 PM	-	6:15 PM	HSV and VZV in Immuno-competent and Immunocompromised Hosts	Richard Whitley, MD
FC6	**6:15 PM**	**-**	**6:30 PM**	**End of the Day Faculty Q&A**	**Drs. Alexander (Moderator), Boucher, Platts-Mills, Trautner, and Whitley**

01

Introduction

Drs. Bennett and Masur

01 – Introduction

Speaker: John Bennett, MD and Henry Masur, MD

Introduction

Henry Masur, MD
Jack Bennett, MD

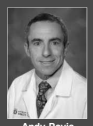
8/1/2024

IDBR Directors and Co-Directors


John Bennett


Henry Masur


Richard Whitley
University of Alabama


Andy Pavia
University of Utah


Barbara Alexander
Duke


Trip Gulick
Weill Cornell


Paul Auwaerter
Johns Hopkins


Robin Patel
Mayo


David Gilbert
University of Oregon

Recent New Faculty


Pranita Tamma
Johns Hopkins


James Platts- Mills
University of Virginia


Jennifer Saullo
Duke University

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 LKA
- **ABIM Rules**
  - We abide by confidentiality rules of ABIM
  - We will NOT tell you what has been on past exams…even if we know!!!

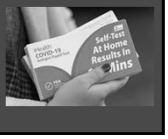
IDBR Program Resources Available Until 12/25

- **Live/Virtual course for 5 days**
  - Live board review questions
  - Rationales and daily scores published online by pin # at end of each day
- **Online board review type questions**
  - 430 Online questions with rationales plus 100 Photo Opportunities
- **Online Primers (7)**
  - Clinical Microbiology, Microbial Resistance, Rickettsia, and more
- **Online recordings of Live 2024 lectures (posted ASAP- within a few days to 2 wks after course)**
  - Also available as MP3 audio file
- **Online-only lectures (9)**
  - Talks we wished we had time for during these 5 virtual days
  - Equally important as live lectures

Covid Precautions

Still An Issue in 2024?

- **Optional Self Administered Covid tests on day 0 and day 3**
  - Available at registration desk, as are masks
  - Report any positive tests to registration desk
  - If positive, registrant (or faculty) can watch from hotel room virtually
- **Distancing—this room is set up to spread out**
- **Eating and drinking allowed in conference room**

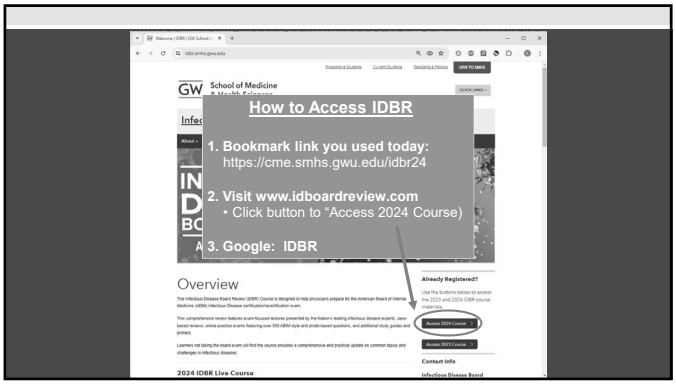


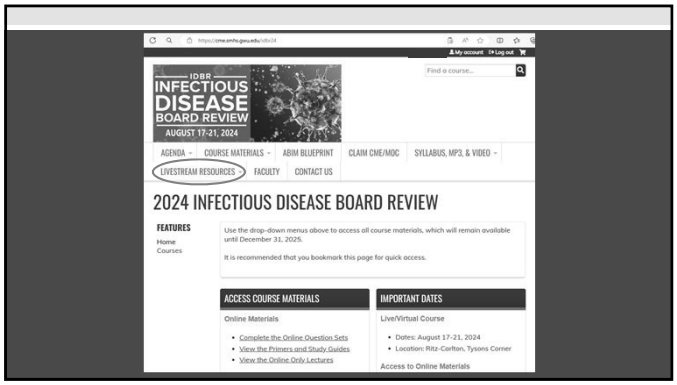
01 – Introduction

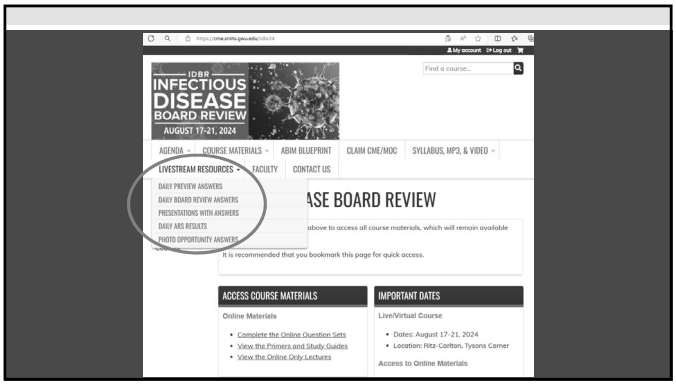
Speaker: John Bennett, MD and Henry Masur, MD

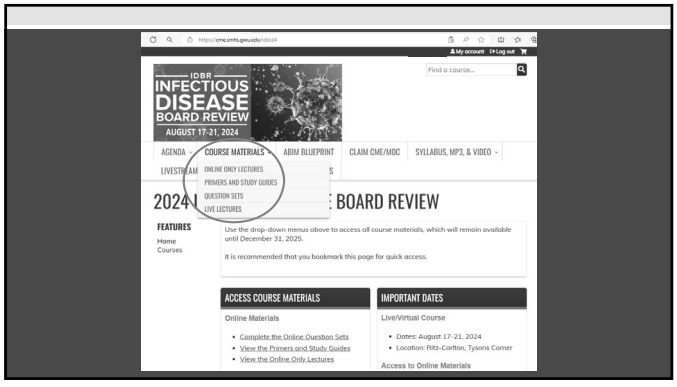
How to Interact with Faculty

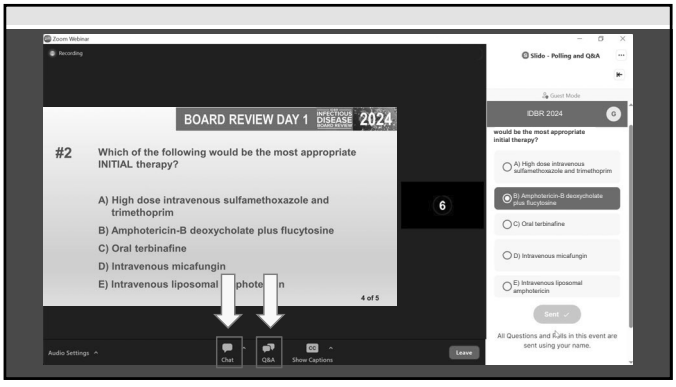
- **Virtual audience is *permanently muted***
  - For questions, use Q & A function
  - To interact with your colleagues, use Chat Box
- **In-person audience can go to microphone to ask questions**
  - Can also use Q & A function







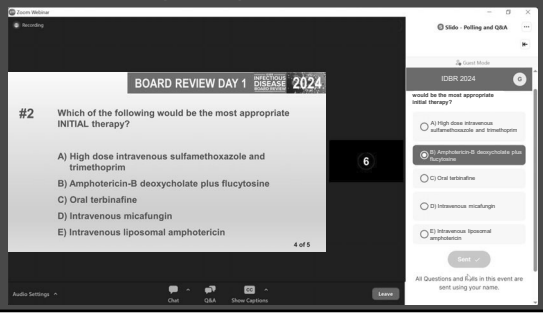




01 – Introduction

Speaker: John Bennett, MD and Henry Masur, MD

Slido Polling Integrated in Zoom Webinar



Look Up Results Each Day by SLIDO Log In

- **Log into Slido with the participant ID number assigned to you**
  - ID number emailed to you on 8/16
  - In-person participants can also find this ID number on the back of your ID badge
- **Use this ID number to log in every day**

IDBR APP

- **Download the IDBR App from Apple store or Google Play store**
  - Download Eventscribe
  - Search for course by entering "**2024IDBR**"
  - Log in with the email and password that was emailed to you
  - Problems: email info@idboardreview.com or call (301) 818-6754
- **You can use this app during the course, or until 12/2025, on your cell phone or tablet to look at the syllabus**

Problems Accessing The Course

- **Help Resources**
  - Telephone help line: **(301) 818-6754**
  - Email help hotline: info@idboardreview.com
  - Come to registration desk

CME and MOC
Total Possible: 118 CME and 118 MOC

- **CME**
  - **You must fill out lecture evaluations (via IDBR website)**
  - **You must request CME (via IDBR website)**
  - **You must complete the pre-test and post-test**
  - Total possible hours - 118
    - Lectures - 43
    - Enduring Material - 75 (Question Sets; Primers and Study Guides; Online Only Lectures)
- **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 (11/15 correct)
    - (three tries of same test permitted with rationales available after each try)

Which Will You Be?

01 – Introduction

Speaker: John Bennett, MD and Henry Masur, MD

How to Get the Most Out of 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
  - Reviewing the Preview Questions before the session will improve your experience
- **Use the Audience Response System (ARS)/Slido to Answer Questions**
  - To stay awake, be engaged, and be competitive!
  - Answer the questions and see how you compare to your peers

Behind Scenes Staff

Kelly Byrne
Management Director

Dorothy Martinez
Live Course Manager

Naomi Loughlin
Program Coordinator

Lisa Krueger
Editor

Mark LaBue
AV Director

Mike D'Anthony
Recording

Keith Hinze
Recording

Advice from Jack Bennett MD

Let's Test the ARS (Audience Response System) / SLIDO

Why are you taking this course?

1) **Initial ABIM ID Certification**
2) **Recertification**
3) **Preparing for Longitudinal Knowledge Assessment Modules**
4) **Update in ID--- unrelated to ABIM Board Certification Exam**

Question 2

Where do you work?

1) **East, United States**
2) **Midwest, United States**
3) **South, United States**
4) **West, United States**
5) **Canada**
6) **Europe**
7) **Asia**
8) **Other**

Question 3

Which parts of IDBR online materials have you looked at prior to the course?

1) **Question sets only**
2) **Primers only**
3) **Online-only lectures**
4) **Several of the above**
5) **None of the above**

Question 4

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*

Let's Begin!

The End

QP1

Daily Question Preview 1

Drs. Masur and Bennett (Moderators)

QP1 – Question Preview: Day 1

Moderator: Henry Masur, MD

Daily Question Preview: Day 1

Moderator: Henry Masur, MD

7/1/2024

PREVIEW QUESTION 2024

1.1 **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***

1 of 2

PREVIEW QUESTION 2024

1.2 **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 Klebsiella pneumoniae and *bla*$_{KPC}$.

1 of 3

PREVIEW QUESTION 2024

1.2 **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

2 of 3

PREVIEW QUESTION 2024

1.3 **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) Candida parapsilosis

B) Cryptococcus gattii

C) Candida auris

D) Candida krusei

E) Candida glabrata

1 of 2

PREVIEW QUESTION 2024

1.4 **A 37 yo 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.**

Which of the following would be most appropriate?

A) Voriconazole

B) Anidulafungin

C) Fluconazole

D) Liposomal amphotericin B

E) Itraconazole

1 of 2

QP1 – Question Preview: Day 1

Moderator: Henry Masur, MD

PREVIEW QUESTION INFECTIOUS DISEASE BOARD REVIEW 2024

1.5 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 T39, P 150, RR 24-30, BP 120/50. She has crackles throughout both bases and a gallop. Influenza PCR positive

WBC =9000/mm^3 (60% polys, 30% bands)

Creatinine 1.9

BNP and troponin markedly elevated

CXR shows diffuse bilateral infiltrates and cardiomegaly

Requires V-A ECMO

1 of 3

PREVIEW QUESTION INFECTIOUS DISEASE BOARD REVIEW 2024

1.5 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

2 of 3

PREVIEW QUESTION INFECTIOUS DISEASE BOARD REVIEW 2024

1.6 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.

1 of 3

PREVIEW QUESTION INFECTIOUS DISEASE BOARD REVIEW 2024

1.6 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

2 of 3

PREVIEW QUESTION INFECTIOUS DISEASE BOARD REVIEW 2024

1.7 54 year old man with 4 weeks of cough, low grade fevers, & left-sided chest pain.

Received a liver transplant 11 months ago, complicated by rejection, requiring high dose steroids 4 months ago.

He receives TMP/SMX three times a week.

On exam, he is stable, chronically-ill appearing, febrile (101.1°F), has clear lungs and benign abdomen.

1 of 5

PREVIEW QUESTION INFECTIOUS DISEASE BOARD REVIEW 2024

1.7 Labs reveal a normal white blood cell count, slight anemia, & normal creatinine.

Chest radiograph reveals hazy opacity in left lower lung zone.

Chest CT reveals nodular air-space consolidation in the left lower lobe with central cavitation (image).

Gram strain of bronchoalveolar lavage fluid reveals beaded gram positive filamentous organisms (image).

2 of 5

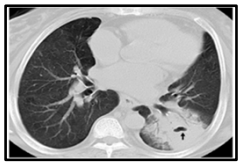
QP1 – Question Preview: Day 1

Moderator: Henry Masur, MD

PREVIEW QUESTION

1.7

Chest CT



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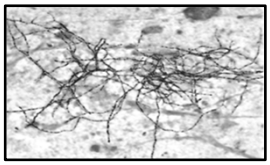


CT Image from J. Bargehr, *et al. Clinical Radiology*, 2013-05-01, Volume 68, Issue 5, Pages e266-e271.
Gram stain image from Murray, *et al.* Medical Microbiology, 7E. 2013 Saunders, Elsevier.

3 of 5

PREVIEW QUESTION

1.7 **What is the most likely cause of this patient's pneumonia?**

A) ***Cryptococcus neoformans***

B) ***Histoplasma capsulatum***

C) ***Actinomyces israellii***

D) ***Nocardia farcinica***

E) ***Aspergillus fumigatus***

4 of 5

PREVIEW QUESTION

1.8 **A 62 yr old sheep rancher from Northern Australia referred hospitalized for refractory pneumonia that failed to respond completely to multiple, prolonged courses of antibiotics over 3 months, leaving him with continued low-grade fever, productive cough & asthenia.**

Gram negative rods noted in moderate abundance on sputum Gram stain & in sputum culture. Identification by automated system failed & isolate sent to referral lab.

1 of 3

PREVIEW QUESTION

1.8 **Which of the following would have been a likely source of this infection?**

A) Hospital nebulizer while hospitalized in Australia (nosocomial superinfection)

B) Water or soil from his ranch

C) Coughing worker on his ranch

D) Sick sheep on his ranch

2 of 3

PREVIEW QUESTION

1.9 **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.

1 of 4

PREVIEW QUESTION

1.9 **Exam: T37^{o}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.

2 of 4

PREVIEW QUESTION

1.9 **Most likely dx:**

A) ***Bartonella henselae***
B) ***Treponema pallidum***
C) ***Haemophilus ducreyi***
D) ***Francisella tularensis***
E) ***Klebsiella (Calymmatobacterium) granulomatis***

3 of 4

PREVIEW QUESTION

1.10 **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.

1 of 3

PREVIEW QUESTION

1.10 **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

2 of 3

PREVIEW QUESTION

1.11 **42 year old homeless male approaches a group of ID fellows attending ID Week in San Diego.**

One fellow noticed jaundice and suggested he seek medical testing.

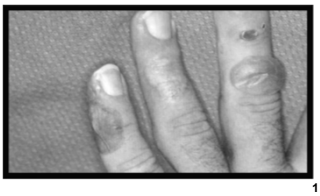
With what diagnosis was the fellow most concerned?

A) HAV
B) HBV
C) Delta
D) HCV
E) HEV

1 of 2

PREVIEW QUESTION

1.12 **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.**



1 of 3

PREVIEW QUESTION

1.12 **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

2 of 3

QP1 – Question Preview: Day 1

Moderator: Henry Masur, MD

PREVIEW QUESTION

1.13 **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.

1 of 3

PREVIEW QUESTION

1.13 **What do you recommend?**

A) Hold rituximab

B) Hold prednisone

C) Entecavir 0.5 mg

D) HCV PCR

2 of 3

PREVIEW QUESTION

1.14 **A 25-year-old 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

1 of 2

PREVIEW QUESTION

1.15 **67 year old woman develops diarrhea while hospitalized for community acquired pneumonia.**

She is afebrile, WBC count is 12,000/ml, 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.

1 of 3

PREVIEW QUESTION

1.15 **Which of the following therapies is recommended?**

A) Metronidazole 500 mg po TID x 10 days

B) Vancomycin 500 mg PO qid x 10 days

C) Fidaxomicin 200 mg PO BID x 10 days

D) Bezlotoxumab + vancomycin x 10 days

E) Fidaxomicin 200 mg PO BID + metronidazole 500 mg PO TID x 10 days

2 of 3

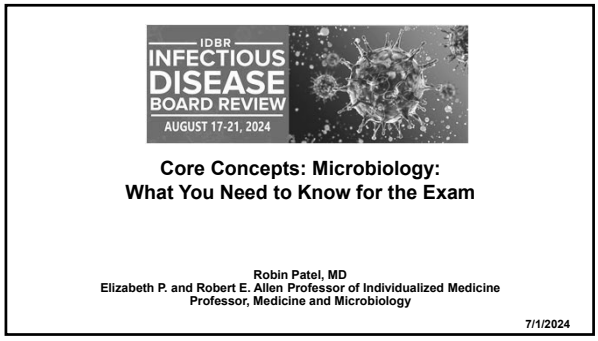
02

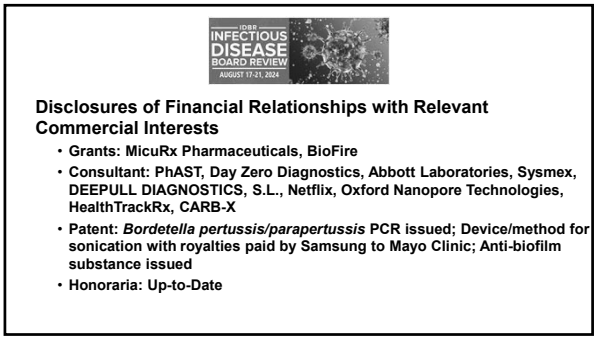
Core Concepts - Microbiology: What You Need to Know for The Exam

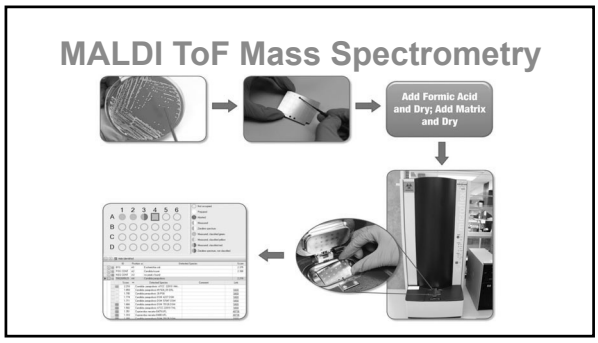
Dr. Robin Patel

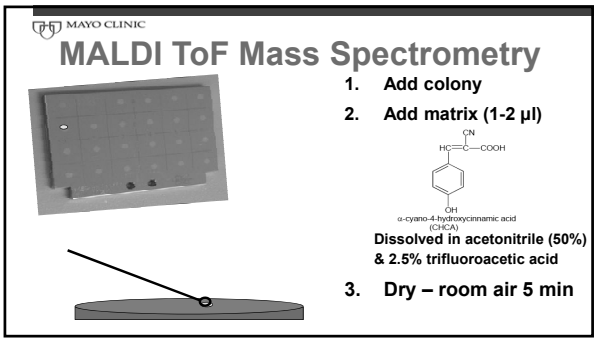
02 – Core Concepts: Microbiology: What You Need to Know for the Exam

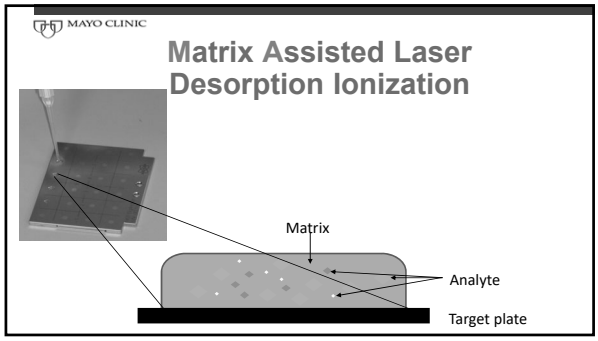
Speaker: Robin Patel, MD

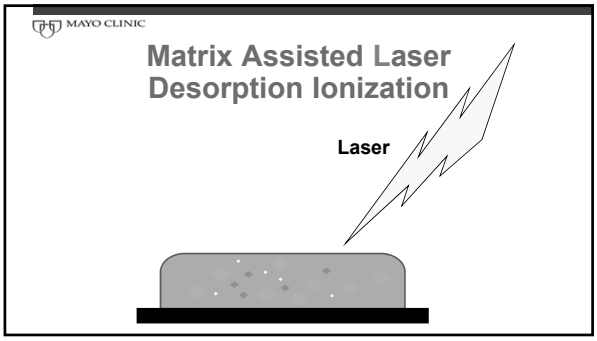












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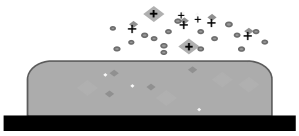
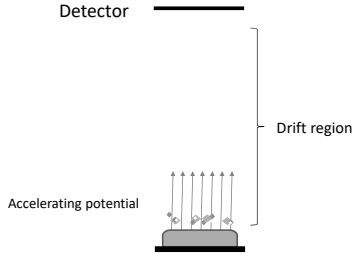
MAYO CLINIC

Matrix Assisted Laser Desorption Ionization



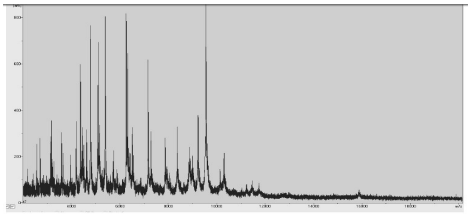
MAYO CLINIC

Time of Flight



MAYO CLINIC

Mass Spectrum Generated Compared with Library (Database)



QUESTION #1

PREVIEW QUESTION

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 (+/-)**
- ***Burkholderia 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
- *Legionella micdadei* and some *Corynebacterium* species
  - [But not *Cutibacterium* 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

- Postexposure antimicrobial prophylaxis
  - Trimethoprim-sulfamethoxazole
  - Doxycycline
  - Amoxicillin–clavulanic acid

Peacock SJ et al. Emerg Infect Dis. 2008 Jul http://wwwnc.cdc.gov/eid/article/14/7/07-1501

QUESTION #4

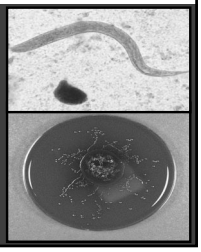
Which of the following, if present in a clinical specimen, poses a hazard for laboratory personnel?

A. *Entamoeba histolytica*
B. *Trichuris trichiura*
C. *Enterobius vermicularis*
D. *Strongyloides stercoralis*
E. *Babesia microti*

Strongyloides stercoralis

- Larvae - two forms
  1. Rhabditiform (in stool)
  2. Filariform

  Infectious stage that develops in soil and occasionally in patient (leads to autoinfection and is hazardous to laboratory personnel)
- Larvae detected
  - Microscopically (top) or
  - By placing feces on plate and detecting migrating larvae where they leave a trail of bacterial colonies (bottom)



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

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LABORATORY- ACQUIRED BACTERIAL, FUNGAL AND PARASITIC INFECTIONS (SELECTED)

- *Bacillus anthracis*
- *Brucella* species
- *Burkholderia pseudomallei*
  - (*Burkholderia mallei*)
- *Coxiella burnetii*
- *Coccidioides immitis/posadasii* (*Blastomyces dermatitidis*, *Histoplasma capsulatum*)
- Dermatophytes
- Enteric pathogens
- *Francisella tularensis*
- *Mycobacterium tuberculosis*
- *Neisseria meningitidis*
- *Salmonella enterica* subsp. *enterica* serovar Typhi
- *Staphylococcus aureus*
- *Strongyloides stercoralis*
- *Yersinia pestis*

ORGANISMS ABOUT WHICH THE LABORATORY SHOULD BE NOTIFIED IF SUSPECTED

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

	Verigene EP	xTAG® GPP	BioFire GIP	BioCode®	Claster DX
Campylobacter species	✓	✓	✓	✓	✓
Salmonella species	✓	✓	✓	✓	✓
Shigella species/Enteroinvasive *E. coli*	✓	✓	✓	✓	✓
Vibrio species	✓		✓	✓	
Vibrio vulnificus					✓
Vibrio parahemolyticus				✓	✓
Vibrio cholerae		✓	✓		✓
Yersinia enterocolitica	✓	✓	✓	✓	✓
Escherichia coli 0157		✓	✓	✓	✓
Enterotoxigenic *E. coli*		✓	✓	✓	✓
Enteropathogenic *E. coli*			✓		✓
Enteroaggregative *E. coli*			✓	✓	✓
Plesiomonas shigelloides			✓		✓
Shiga toxin-producing *E. coli*	✓	✓	✓	✓	✓
Clostridioides difficile		✓	✓	✓	✓
Norovirus	✓	✓	✓	✓	✓
Rotavirus A	✓	✓	✓	✓	✓
Astrovirus			✓		✓
Adenovirus 40/41		✓	✓	✓	✓
Sapovirus			✓		✓
Cryptosporidium species		✓	✓	✓	✓
Entamoeba histolytica		✓	✓	✓	✓
Giardia lamblia		✓	✓	✓	✓
Cyclospora cayetanensis			✓		✓

*

GASTROENTERITIS PANEL TESTING KEY POINTS

- If available, culture independent methods of diagnosis recommended
- Indications: Dysentery, moderate-to-severe disease, and symptoms lasting >7 days (define etiology, inform potential treatment)
- Not recommended for chronic diarrhea
- If *C. difficile* main consideration, test for *C. difficile* alone
- *Aerococcus* species not included

Riddle et al. Am J Gastroenterol 2016;111:602–622

BIOFIRE FILMARRAY MENINGITIS/ENCEPHALITIS PANEL (for reference)

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		

MENINGITIS/ENCEPHALITIS PANEL KEY POINTS

- Doesn't nullify need for cell count, differential, protein, glucose, Gram stain, culture
- Cryptococcal antigen more sensitive than PCR
- *Streptococcus pneumoniae* antigen plus HSV, enterovirus and possibly VZV PCR an alternative
- May be helpful with current/recent antibiotic treatment
- HHV-6 & CMV may not be clinically significant

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MAYO CLINIC

Lower Respiratory Tract Panels (for reference)

	Curetis Unyvero	BioFire
Bacteria		
Acinetobacter spp.	✓	
Acinetobacter calcoaceticus-baumannii complex		✓
Chlamydia pneumoniae		✓
Citrobacter freundii	✓	
Klebsiella aerogenes		✓
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)		✓
Fungi		
Pneumocystis jirovecii	✓	
Resistance genes		
bla_{KPC}	✓	✓
bla_{NDM}	✓	✓
bla_{IMP}		✓
bla_{OXA-23}	✓	
bla_{OXA-24}	✓	
bla_{OXA-48}	✓	
$bla_{OXA-58-like}$		✓
bla_{VIM}	✓	✓
bla_{CTX-M}	✓	✓
bla_{PDM}	✓	
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***

MAYO CLINIC

FDA-Approved Multiplex Panels for Detection of Gram-Positive Bacteria in Positive Blood Cultures (for reference)

	FilmArray MDx-Chex BCID2	VERIGENE® Gram-Positive Blood Culture Test	cobas® eplex BCID-GP Panel	cobas® eplex BCID-GN Panel
Staphylococcus species	✓	✓	✓	
Staphylococcus aureus	✓	✓	✓	
Staphylococcus epidermidis	✓	✓	✓	
Staphylococcus lugdunensis	✓	✓	✓	
Streptococcus species	✓	✓	✓	
Streptococcus agalactiae	✓	✓	✓	
Streptococcus pyogenes	✓	✓	✓	
Streptococcus pneumoniae	✓	✓	✓	
Streptococcus anginosus group		✓	✓	
Enterococcus species			✓	
Enterococcus faecalis	✓		✓	
Enterococcus faecium	✓	✓	✓	
Listeria species		✓	✓	
Listeria monocytogenes	✓		✓	
Bacillus cereus group			✓	
Bacillus subtilis group			✓	
Corynebacterium species			✓	
Cutibacterium acnes			✓	
Lactobacillus species			✓	
Micrococcus species		✓	✓	
Pan Gram-Positive				✓

*

MAYO CLINIC

FDA-Approved Multiplex Panels for Detection of Gram-Negative Bacteria in Positive Blood Cultures (for reference), continued

	FilmArray MDx-Chex BCID2	VERIGENE® Gram-Negative Blood Culture Test	cobas® eplex BCID-GP Panel	cobas® eplex BCID-GN Panel
Klebsiella oxytoca	✓	✓		✓
Klebsiella pneumoniae		✓		
Klebsiella pneumoniae group	✓			✓
Klebsiella aerogenes	✓	*		*
Salmonella species	✓			✓
Morganella morganii				✓
Stenotrophomonas maltophilia	✓			✓
Serratia species				✓
Serratia marcescens	✓			✓
Proteus species	✓	✓		✓
Proteus mirabilis				✓
Acinetobacter species		✓		
Acinetobacter baumannii				✓
Acinetobacter calcoaceticus-baumannii complex	✓			
Hemophilus influenzae	✓			✓
Cronobacter sakazakii				✓
Neisseria meningitidis	✓			✓
Pseudomonas aeruginosa	✓	✓		✓
Enterobacterales	✓			
Escherichia coli	✓	✓		✓
Enterobacter species		✓		✓
Enterobacter cloacae complex	✓			✓
Citrobacter species		✓		✓
Bacteroides fragilis	✓			✓
Fusobacterium necrophorum				✓
Fusobacterium nucleatum				✓
Pan Gram-Negative			✓	

†Detected as Enterobacter species

*

MAYO CLINIC

FDA-Approved Multiplex Panels for Detection of Select Resistance Genes in Positive Blood Cultures (for reference), continued

	FilmArray MDx-Chex BCID2	VERIGENE® Gram-Positive Blood Culture Test	VERIGENE® Gram-Negative Blood Culture Test	cobas® eplex BCID-GP Panel	cobas® eplex BCID-GN Panel
mecA		✓		✓	
mecC				✓	
mecA/C	✓				
mecA/C and MREJ	✓				
vanA		✓		✓	
vanB		✓		✓	
vanA/B	✓				
bla_{KPC}	✓		✓		✓
bla_{NDM}	✓		✓		✓
bla_{OXA}	✓		✓		✓
bla_{VIM}	✓		✓		✓
bla_{IMP}	✓		✓		✓
bla_{CTX-M}	✓		✓		✓
mcr-1	✓				

*

MAYO CLINIC

FDA-Approved Multiplex Panels for Detection of Fungi in Positive Blood Cultures (for reference), continued

	FilmArray MDx-Chex BCID2	cobas®		
		ePlex BCID-GP Panel	eplex BCID-FP Panel	eplex BCID-GN Panel
Candida albicans	✓		✓	
Candida auris	✓		✓	
Candida dubliniensis			✓	
Candida famata			✓	
Nakaseomyces glabrata	✓		✓	
Candida guilliermondii			✓	
Candida kefyr			✓	
Pichia kudriavzevii	✓		✓	
Candida lusitaniae			✓	
Candida parapsilosis	✓		✓	
Candida tropicalis	✓		✓	
Cryptococcus gattii			✓	
Cryptococcus neoformans			✓	
C. neoformans/gattii	✓			
Fusarium species			✓	
Rhodotorula species			✓	
* Pan *Candida*		✓		✓

STAPHYLOCOCCI
METHICILLIN RESISTANCE

- Methicillin resistance mediated by *mecA* (or rarely *mecC*) gene products
  - Penicillin binding protein (PBP) target altered (PBP2a)
    - Confers resistance to <u>all available β-lactams</u> (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*)

FDA-APPROVED RAPID PHENOTYPIC SUSCEPTIBILITY TESTS - POSITIVE BLOOD CULTURE BOTTLES

- **Accelerate Diagnostics**
  - **Gram-negative and –positive bacteria**
- **Selux Dx**
  - **Gram-negative bacteria**

MAYO CLINIC

T2Direct Diagnostics
<u>Direct</u> from Blood

- Multiplex PCR and T2 magnetic resonance, average turnaround time 4.3 hours
- T2Candida Panel
  - *Candida albicans*
  - *Candida tropicalis*
  - *Pichia kudriavzevii*
  - *Nakaseomyces glabrata*
  - *Candida parapsilosis*
- T2Bacteria Panel
  - *Enterococcus faecium*
  - *Staphylococcus aureus*
  - *Klebsiella pneumoniae*
  - *Pseudomonas aeruginosa*
  - *Escherichia coli*

MAYO CLINIC

BioFire Joint Infection Panel (Synovial Fluid)

Anaerococcus prevotii/vaginalis	*Escherichia coli*
Clostridium perfringens	*Haemophilus influenzae*
Cutibacterium avidum/granulosum	*Kingella kingae*
Enterococcus faecalis	*Klebsiella aerogenes*
Enterococcus faecium	*Klebsiella pneumoniae* group
Finegoldia magna	*Morganella morganii*
Parvimonas micra	*Neisseria gonorrhoeae*
Peptoniphilus	*Proteus* spp.
Peptostreptococcus anaerobius	*Pseudomonas aeruginosa*
Staphylococcus aureus	*Salmonella* spp.
Staphylococcus lugdunensis	*Serratia marcescens*
Streptococcus species	*Candida* spp.
Streptococcus agalactiae	*Candida albicans*
Streptococcus pneumoniae	bla_{IMP}, bla_{KPC}, bla_{NDM}, $bla_{OXA-48-like}$,
Streptococcus pyogenes	bla_{VIM}, bla_{CTX-M}
Bacteroides fragilis	*mecA/C* and MREJ
Citrobacter	*vanA/B*
Enterobacter cloacae complex	

QUESTION #6

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

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QUESTION #7 PREVIEW QUESTION

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 *Klebsiella pneumoniae* and bla_{KPC}.

QUESTION #7 PREVIEW QUESTION

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 bla_{KPC}-PRODUCER

Klebsiella pneumoniae

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

Ampicillin	>16 R	**Ampicillin/Sulbactam**	>16/8 R	**Piperacillin/Tazobactam**	S/R*
Cefazolin	>16 R	**Oral cephalosporins**	R	**Cefepime**	S/SDD/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

*Not currently recommended for infection outside of urinary tract

TYPICAL SUSCEPTIBILITY OF INDUCIBLE, CHROMOSOMALLY-ENCODED AmpC β-LACTAMASE PRODUCER

*Enterobacter cloacae**

Ampicillin	>16 R	**Ampicillin/Sulbactam**	>16/8 R	**Piperacillin/Tazobactam**	S/R*
Cefazolin	>16 R	**Oral cephalosporins**	R	**Cefepime**	S/SDD
Ceftazidime	>16 R	**Ceftriaxone**	>32 R**	**Ertapenem**	≤0.5 S
Meropenem	≤1 S	**Aztreonam**	S/R	**Ciprofloxacin**	≤1 S
Levofloxacin	≤2 S	**Amikacin**	≤8 S	**Gentamicin**	≤1 S
Tobramycin	4 S	**Tigecycline**	2 S	**TMP/SMX**	>2/38 R

Enterobacter cloacae, Klebsiella aerogenes, Citrobacter freundii
****Avoid ceftriaxone or ceftazidime even if test susceptible; cefepime an acceptable choice**
IDSA Guidance on the Treatment of Antimicrobial-Resistant Gram-Negative Infections (idsociety.org)

QUESTION #8

Which of the following susceptibility patterns would be typical for an *Escherichia coli* isolate carrying a New Delhi metallo-β-lactamase (NDM)?

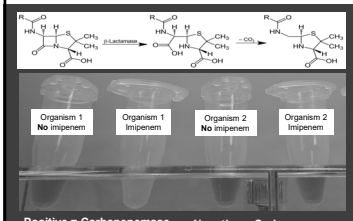
	Cefazolin	Cefotaxime	Ceftazidime	Piperacillin/ tazobactam	Imipenem	Aztreonam
A.	R	S	S	S	S	S
B.	R	R	R	S	S	R
C.	R	R	R	R	S	R
C.	R	R	R	R	R	R

QUESTION #9

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

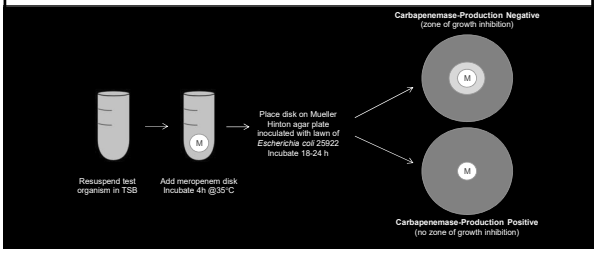


Positive = Carbapenemase Producer

Negative = Carbapenemase Non-Producer

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

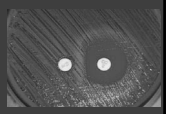
CARBAPENEMASE PRODUCTION TEST
MODIFIED CARBAPENEM INACTIVATION



QUESTION #10

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?



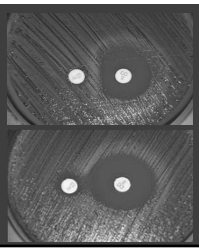
A. **Erythromycin susceptibility, inducible clindamycin resistance**
B. **Erythromycin resistance, constitutive clindamycin resistance**
C. **Erythromycin resistance, inducible clindamycin resistance**
D. **Erythromycin susceptibility, constitutive clindamycin resistance**

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)**

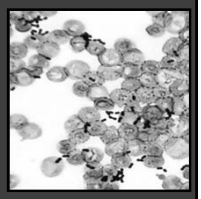
INDUCIBLE CLINDAMYCIN RESISTANCE (D-TEST)

- **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 #11

- 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 #11

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 #12

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 #12

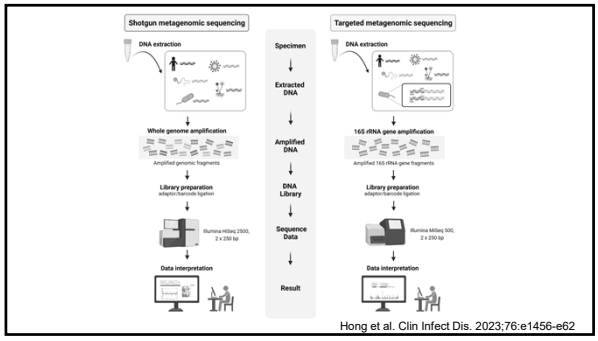
Which of the following is the most appropriate empiric antibiotic to treat this patient?

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



Hong et al. Clin Infect Dis. 2023;76:e1456-e62

2023 DUKE-INTERNATIONAL SOCIETY FOR CARDIOVASCULAR INFECTIOUS DISEASES CRITERIA FOR INFECTIVE ENDOCARDITIS (IE)

- Pathologic Criteria - Microorganisms detected (appropriate sample) - PCR, amplicon/metagenomic sequencing, *in situ* hybridization
- Blood cultures - Removed required timing (and separation) venipunctures for blood cultures
- MAJOR CRITERIA
  - Positive blood cultures - Microorganisms that commonly cause IE ≥2 blood culture sets (typical) or that occasionally or rarely cause IE ≥3 blood culture sets (nontypical)
    - Typical: *Staphylococcus aureus*; HACEK group; *Staphylococcus lugdunensis*; *Enterococcus faecalis*; all streptococcal species (except for *Streptococcus pneumoniae* and *pyogenes*), *Granulicatella* and *Abiotrophia* spp., *Gemella* spp. In setting of intracardiac prosthetic material, include these as "typical" pathogens: coagulase negative staphylococci, *Corynebacterium striatum* and *jeikeium*, *Serratia marcescens*, *Pseudomonas aeruginosa*, *Cutibacterium acnes*, nontuberculous mycobacteria (especially *M. chimaerae*), *Candida* spp.
  - Blood PCR or amplicon/metagenomic sequencing detection of *Coxiella burnetii*, *Bartonella* spp., *Tropheryma whipplei*
  - IFA ≥1:800 for IgG antibodies *Bartonella henselae* or *B. quintana*
- MINOR CRITERIA - Positive culture, PCR, or other nucleic acid-based test (amplicon/metagenomic sequencing, *in situ* hybridization) organism consistent with IE from sterile body site other than cardiac tissue, cardiac prosthesis, or arterial embolus; or single finding of skin bacterium by PCR on valve or wire without additional clinical or microbiological supporting evidence

Fowler et al. Clin Infect Dis. 2023;77:518-26.

QUESTION #13

A transplant hepatologist calls to inquire about ganciclovir resistance testing on a liver transplant patient with CMV colitis and the following CMV viral loads:

7/04/23: 26,000 IU/ml (day of diagnosis)
7/14/23: 25,000 IU/ml
7/23/23: 22,000 IU/ml
8/13/23: 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 4th and his diarrhea is unchanged.**

QUESTION #13

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 #14

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)**
- **≥2 weeks full-dose therapy before testing**

Gene	Drug(s) affected
UL97	Ganciclovir, marabavir
UL54	Ganciclovir and cidofovir (if selected for by these agents); foscarnet (if selected for by foscarnet)
UL56	Letermovir

Kotton CN et al. Transplantation 2013;96:333 and Chou S. Curr Opin Infect Dis 2015;28:293

QUESTION #15

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 #15

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 #16

A 76-year-old woman presents with three days of cough, difficulty breathing and fever. She has never received a COVID-19 vaccine and has never been diagnosed with COVID-19. Which of the following COVID-19 tests is recommended?

A. Antigen
B. Serology
C. NAAT

COVID-19 DIAGNOSTICS

- NAAT generally preferred over antigen testing
  - Symptomatic individuals suspected of having COVID-19
  - Asymptomatic individuals exposed to SARS-CoV-2 infection
  - Interpret Ct values with caution
- Healthcare provider or patient collected specimens acceptable
- Swabs from nasopharynx, anterior nares, oropharynx, or mid-turbinate regions; saliva or mouth gargle acceptable
  - Compared to nasopharyngeal swabs, anterior nares or oropharynx swabs alone yield more false-negative results than combined anterior nares/oropharynx swabs, mid-turbinate swabs, saliva, or mouth gargle
- Suspected lower respiratory infection → upper respiratory sample; if negative, lower respiratory sample

IDSA Guidelines on the Diagnosis of COVID-19

FDA-APPROVED/CLEARED MULTIPLEX PANELS FOR GASTROINTESTINAL PATHOGENS IN STOOL (for reference)

	Verigene EP	xTAG® GPP	BioFire GIP	BioCode®	Qiastat-DX
Campylobacter species	✓	✓	✓	✓	✓
Salmonella species	✓	✓	✓	✓	✓
Shigella species/Enteroinvasive *E. coli*	✓	✓	✓	✓	✓
Vibrio species	✓		✓	✓	
Vibrio vulnificus					✓
Vibrio parahemolyticus				✓	✓
Vibrio cholerae		✓	✓		✓
Yersinia enterocolitica	✓	✓	✓	✓	✓
Escherichia coli 0157		✓	✓	✓	✓
Enterotoxigenic *E. coli*		✓	✓	✓	✓
Enteropathogenic *E. coli*			✓		✓
Enteroaggregative *E. coli*			✓	✓	✓
Plesiomonas shigelloides			✓		✓
Shiga toxin-producing *E. coli*	✓	✓	✓	✓	✓
Clostridioides difficile		✓	✓	✓	✓
Norovirus	✓	✓	✓	✓	✓
Rotavirus A	✓	✓	✓	✓	✓
Astrovirus			✓		✓
Adenovirus 40/41		✓	✓	✓	✓
Sapovirus			✓		✓
Cryptosporidium species		✓	✓	✓	✓
Entamoeba histolytica		✓	✓	✓	✓
Giardia lamblia		✓	✓	✓	✓
Cyclospora cayetanensis			✓		✓

*

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Lower Respiratory Tract Panels
(for reference)

	Curetis Unyvero	BioFire
Bacteria		
Acinetobacter spp.	✓	
Acinetobacter calcoaceticus-baumannii complex		✓
Chlamydia pneumoniae	✓	✓
Citrobacter freundii	✓	
Klebsiella aerogenes		✓
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)		✓
Fungi		
Pneumocystis jirovecii	✓	
Resistance genes		
bla_{KPC}	✓	✓
bla_{NDM}	✓	✓
bla_{IMP}		✓
bla_{OXA-23}	✓	
bla_{OXA-24}	✓	
bla_{OXA-48}	✓	
bla_{OXA-58}		
$bla_{OXA-48-like}$		✓
bla_{VIM}	✓	✓
bla_{CTX-M}	✓	✓
bla_{TEM}	✓	
mecA	✓	
mecA/C and *MREJ*		✓

*

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

Speaker: Robin Patel, MD

Enlarged Slides: 28, 29

MAYO CLINIC

FDA-Approved Multiplex Panels for Detection of Gram-Positive Bacteria in Positive Blood Cultures (for reference)

	FilmArray MDx-Chex BCID2	VERIGENE®	cobas®	
		Gram-Positive Blood Culture Test	eplex BCID-GP Panel	eplex BCID-GN Panel
***Staphylococcus* species**	✓	✓	✓	
Staphylococcus aureus	✓	✓	✓	
Staphylococcus epidermidis	✓	✓	✓	
Staphylococcus lugdunensis	✓	✓	✓	
***Streptococcus* species**	✓	✓	✓	
Streptococcus agalactiae	✓	✓	✓	
Streptococcus pyogenes	✓	✓	✓	
Streptococcus pneumoniae	✓	✓	✓	
***Streptococcus anginosus* group**		✓	✓	
***Enterococcus* species**			✓	
Enterococcus faecalis	✓		✓	
Enterococcus faecium	✓	✓	✓	
***Listeria* species**		✓	✓	
Listeria monocytogenes	✓		✓	
***Bacillus cereus* group**			✓	
***Bacillus subtilis* group**			✓	
***Corynebacterium* species**			✓	
Cutibacterium acnes			✓	
***Lactobacillus* species**			✓	
***Micrococcus* species**		✓	✓	
* **Pan Gram-Positive**				✓

MAYO CLINIC

FDA-Approved Multiplex Panels for Detection of Gram-Negative Bacteria in Positive Blood Cultures (for reference), continued

	FilmArray MDx-Chex BCID2	VERIGENE®	cobas®	
		Gram-Negative Blood Culture Test	eplex BCID-GP Panel	eplex BCID-GN Panel
Klebsiella oxytoca	✓	✓		✓
Klebsiella pneumoniae		✓		
***Klebsiella pneumoniae* group**	✓			✓
Klebsiella aerogenes	✓	*		*
***Salmonella* species**	✓			✓
Morganella morganii				✓
Stenotrophomonas maltophilia	✓			✓
***Serratia* species**				✓
Serratia marcescens	✓			✓
***Proteus* species**	✓	✓		✓
Proteus mirabilis				✓
***Acinetobacter* species**		✓		
Acinetobacter baumannii				✓
***Acinetobacter calcoaceticus-baumannii* complex**	✓			
Hemophilus influenzae	✓			✓
Cronobacter sakazakii				✓
Neisseria meningitidis	✓			✓
Pseudomonas aeruginosa	✓	✓		✓
Enterobacterales	✓			
Escherichia coli	✓	✓		✓
***Enterobacter* species**		✓		✓
***Enterobacter cloacae* complex**	✓			✓
***Citrobacter* species**		✓		✓
Bacteroides fragilis	✓			✓
Fusobacterium necrophorum				✓
Fusobacterium nucleatum				✓
* **Pan Gram-Negative**			✓	

*Detected as *Enterobacter* species

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

Speaker: Robin Patel, MD

Enlarged Slides: 30, 31

MAYO CLINIC

FDA-Approved Multiplex Panels for Detection of Select Resistance Genes in Positive Blood Cultures (for reference), continued

	FilmArray MDx-Chex BCID2	VERIGENE®		cobas®	
		Gram-Positive Blood Culture Test	Gram-Negative Blood Culture Test	eplex BCID-GP Panel	eplex BCID-GN Panel
mecA		✓		✓	
mecC				✓	
mecA/C	✓				
***mecA/C* and MREJ**	✓				
vanA		✓		✓	
vanB		✓		✓	
vanA/B	✓				
bla_{KPC}	✓		✓		✓
bla_{NDM}	✓		✓		✓
bla_{OXA}	✓		✓		✓
bla_{VIM}	✓		✓		✓
bla_{IMP}	✓		✓		✓
bla_{CTX-M}	✓		✓		✓
mcr-1	✓				

*

MAYO CLINIC

FDA-Approved Multiplex Panels for Detection of Fungi in Positive Blood Cultures (for reference), continued

	FilmArray MDx-Chex BCID2	cobas®		
		ePlex BCID-GP Panel	eplex BCID-FP Panel	eplex BCID-GN Panel
Candida albicans	✓		✓	
Candida auris	✓		✓	
Candida dubliniensis			✓	
Candida famata			✓	
Nakaseomyces glabrata	✓		✓	
Candida guilliermondii			✓	
Candida kefyr			✓	
Pichia kudriavzevii	✓		✓	
Candida lusitaniae			✓	
Candida parapsilosis	✓		✓	
Candida tropicalis	✓		✓	
Cryptococcus gattii			✓	
Cryptococcus neoformans			✓	
C. neoformans/gattii	✓			
***Fusarium* species**			✓	
***Rhodotorula* species**			✓	
Pan *Candida*		✓		✓

*

03

Clinical Immunology and Host Defense

Dr. Steven Holland

03 - Clinical Immunology and Host Defense

Speaker: Steven Holland, MD

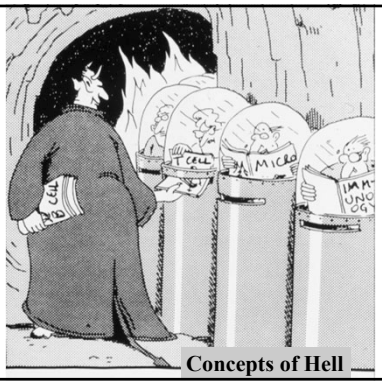
Clinical Immunology and Host Defense

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

7/1/2024

Disclosures of Financial Relationships with Relevant Commercial Interests

- **None**



Concepts of Hell

Host Immune Defense

Humoral
- Complement
- Mannose binding lectin
- Antibody

Cellular
- Neutrophils
- Monocytes
- Eosinophils
- 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

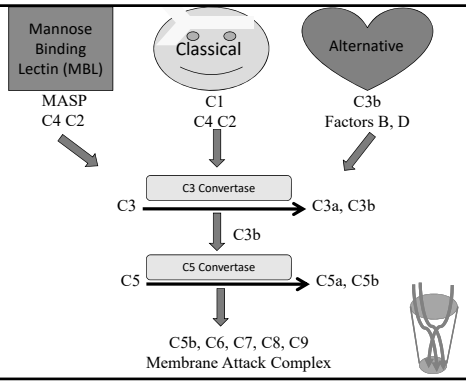
In vitro testing is tricky and variable, genetics is not

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* complex
- *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?

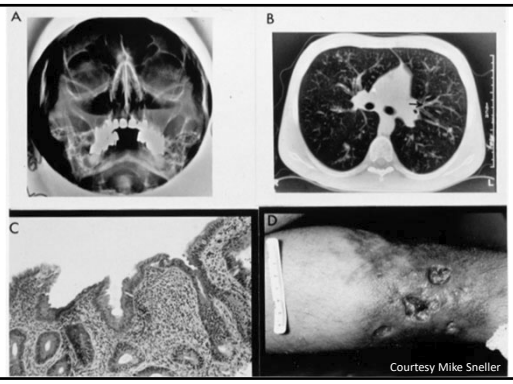
J Clin Immunol 2020 May;40(4):576-591

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, impaired response to new or recall immunization; ↑ autoimmunity and cancer

Rx- treat infections, Ig replacement

Cunningham-Rundles C. Immunol Rev. 2019 Jan;287(1):145-161.

Preview Question

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)

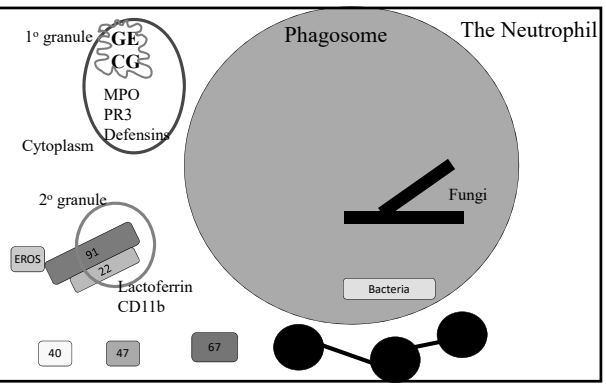
IgM 165 (normal 37-200)

Preview Question

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.

The Neutrophil



Neutrophils: They're a big deal!

Average count 5000/mcl
(5,000,000/ml)
(5,000,000,000/L)

Make around 10^{11}/day

Most are in bone marrow

Can go up 10-fold in emergency

Circulating half life 7 hours

About 50% marginated

Cyclic and Severe Chronic Neutropenias

Cyclic and SCN: *ELANE* mutations (AD)

Kostmann SCN: *HAX1* mutations (AR)

digital, oral, perineal infections, usually self-healing with recovery of counts, bacteremia uncommon

relatively low baseline PMN count with profound neutropenia, about every 3-4 weeks

Dx- molecular; periodicity, family history, genetics

Rx- G-CSF, BMT

Hematol Oncol Clin North Am. 2019;33:533-551

Other Causes of Neutropenia

X-linked	Recessive	**Drugs**
WAS	G6PC3	Splenomegaly/ sequestration
GATA1	HAX1	
TAZ	JAGN	autoimmunity
	USB1	
Dominant	CSF3R	
GFI1	VPS45	
ELA2	GSD1B	
GATA2	SBDS	
DNM2		
SRP54		
CXCR4		

52 year old man

referred from his Family Practitioner.

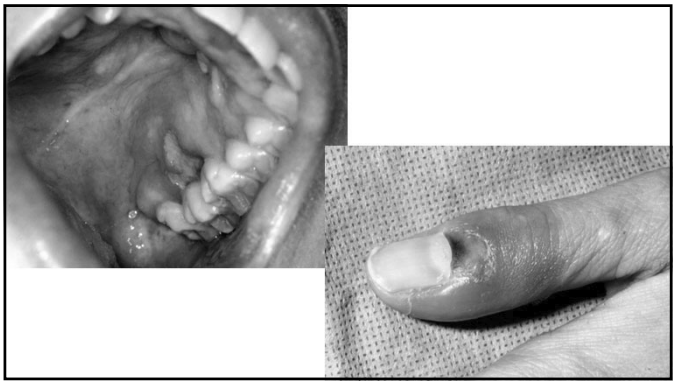
Recurrent digital and oral ulcers occurring every month or so for the last 4 months.

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".

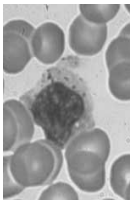
Spleen tip felt.



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.

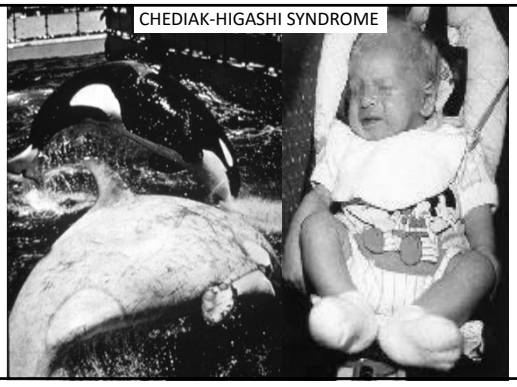
Myeloperoxidase (MPO) deficiency (AR)

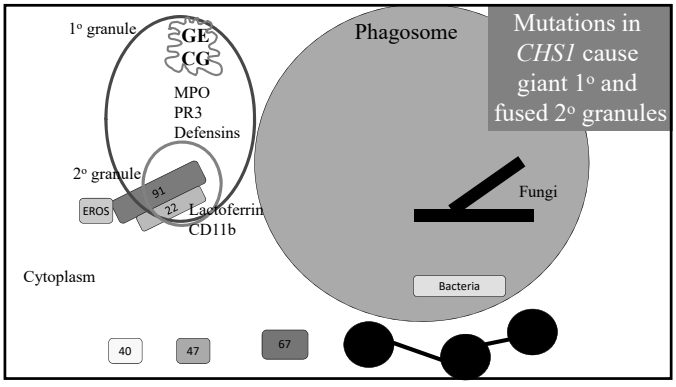
most common neutrophil disorder (1/2000)
- not a pathologic condition *per se*
- failure of H_2O_2 -----MPO-----> HOCl
- compensated by increased H_2O_2 production
- appears to need another condition to potentiate, such as diabetes mellitus

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):185-98

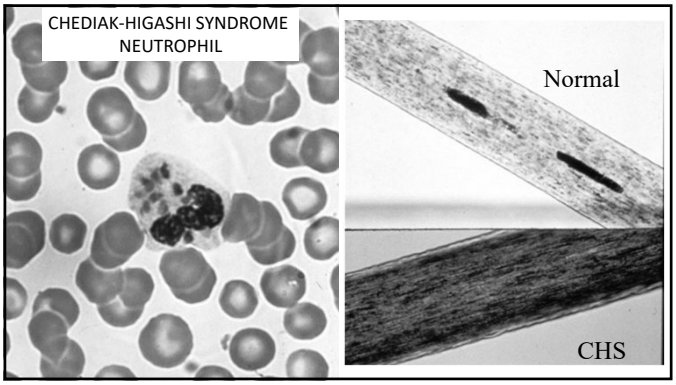




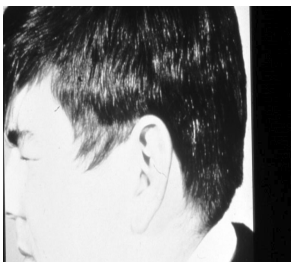
Chediak-Higashi Syndrome (AR)

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

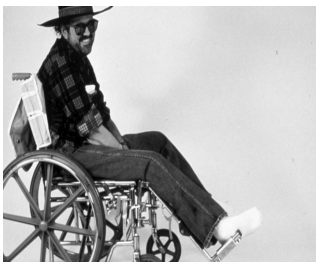
Drug Discov Today Dis Models. 2020;31:31-36



SILVERY SHEEN

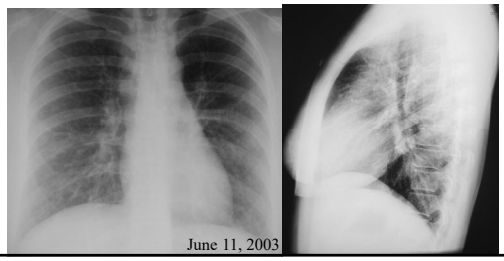


PERIPHERAL NEUROPATHY



23 yo woman; athletic coach

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



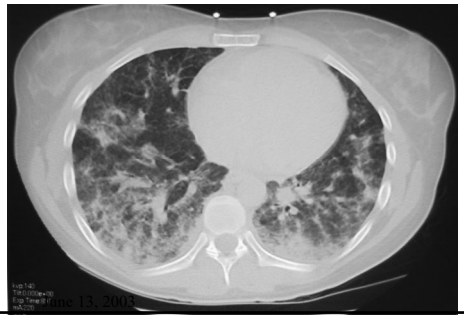
ER presentation

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

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

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

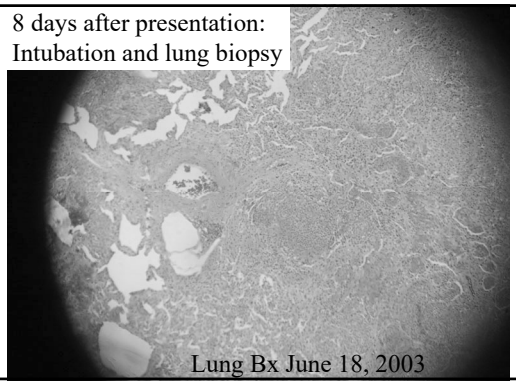
2 days later, hypoxia and fever

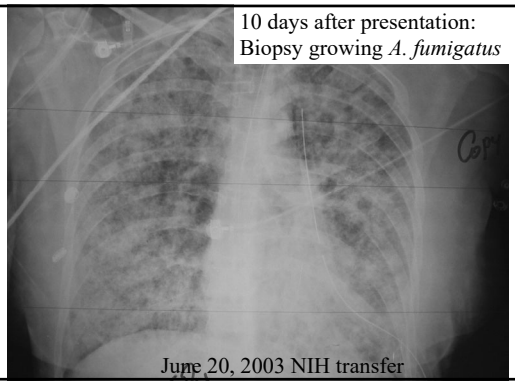


Hospital Course

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

8 days after presentation:
Intubation and lung biopsy





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

Preview Question

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

a) Allergic bronchopulmonary aspergillosis
b) Cystic fibrosis
c) Lymphocyte dysfunction (SCID)
d) Phagocyte defect
e) Acute HIV

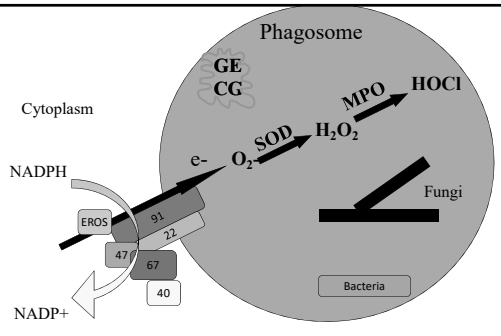
What is so special about phagocytes?

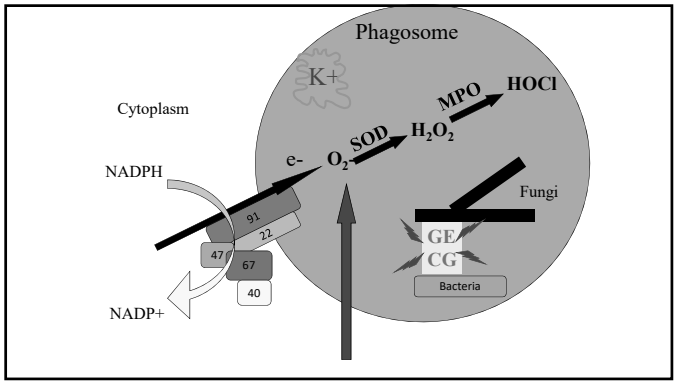
neutrophils, monocytes, macrophages, eosinophils, basophils

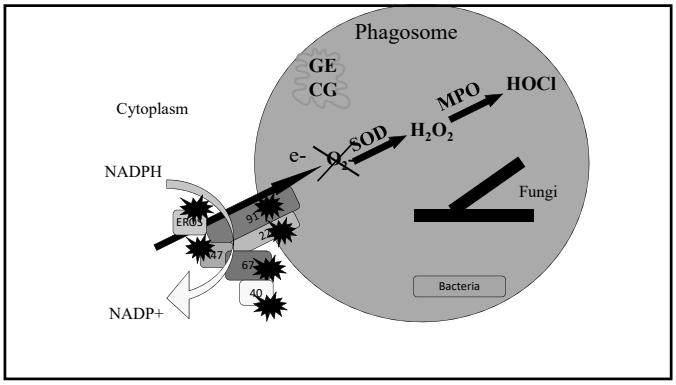
Preformed cytoplasmic granules with stored enzymes

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

Half life of neutrophils in the circulation?
7 hours







Chronic Granulomatous Disease (X, AR)

Failure to make the phagocyte respiratory burst

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 (nuanced)
- tissue granuloma formation
- **infections**: lung, liver, lymph nodes, skin, bone
- **Bacteremia:** uncommon but bad

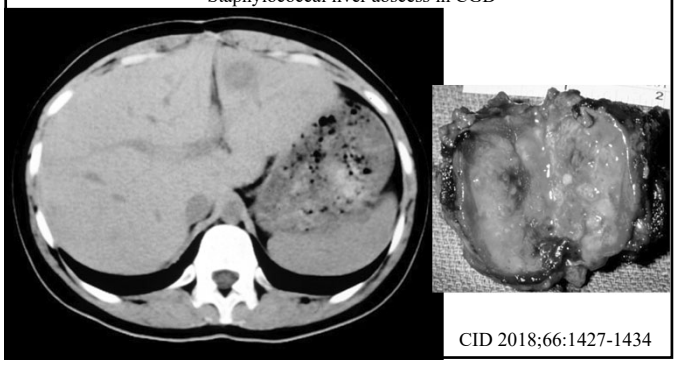
Infections in CGD

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**.**

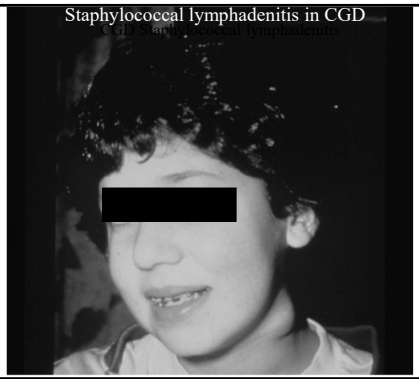
Pediatric Health Med Ther 2020 Jul 22;11:257-268

Staphylococcal liver abscess in CGD

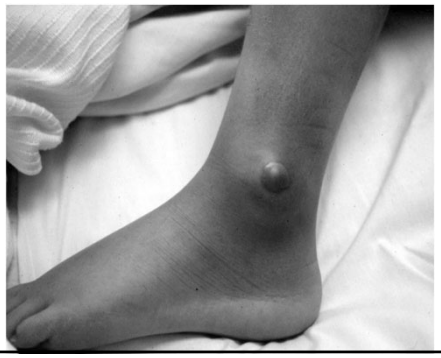


CID 2018;66:1427-1434

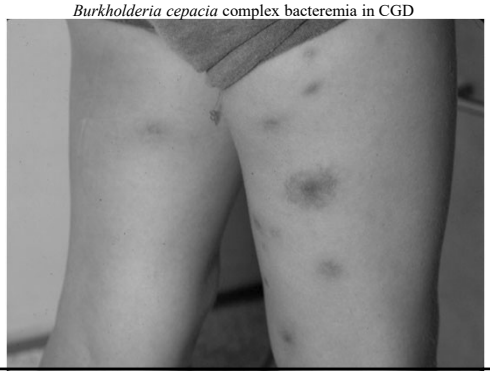
Staphylococcal lymphadenitis in CGD

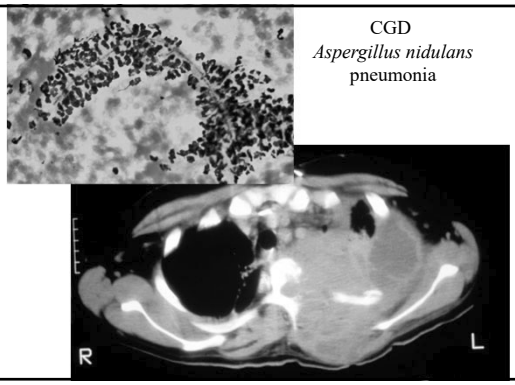


Staph aureus osteomyelitis in CGD



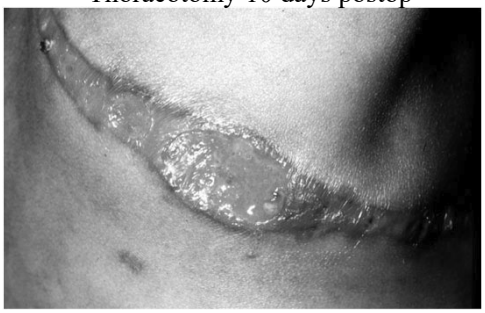
Burkholderia cepacia complex bacteremia in CGD





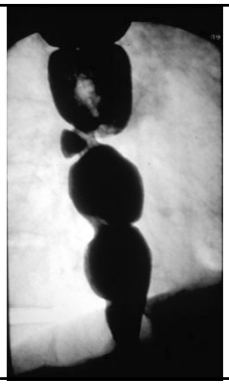
CGD
Aspergillus nidulans
pneumonia

Thoracotomy 10 days postop

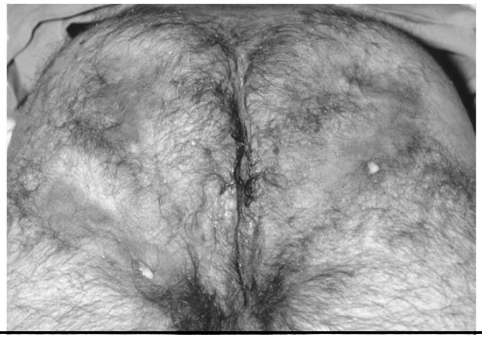


CGD granulomatous wound dehiscence

CGD
granulomatous
esophageal
obstruction



CGD Inflammatory Bowel Disease



Chronic Granulomatous Disease

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)

Dx- PMN dihydrorhodamine 123 oxidation (DHR)
[PMN nitroblue tetrazolium reduction (NBT) is the old test]
(MPO Deficiency gives a FALSE ABNORMAL DHR)

BE CAREFUL ABOUT THE LAB AND HOW YOU DISCUSS IT!

CGD Management and Treatment

90% overall long-term survival

follow CRP, radiographs

prophylactic antibiotics and antifungals
- TMP/SMX, itraconazole

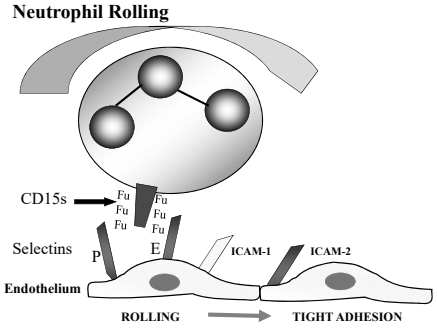
prophylactic interferon gamma
- 50 µg/m2 subcutaneously three times weekly

aggressive search for and treatment of infections

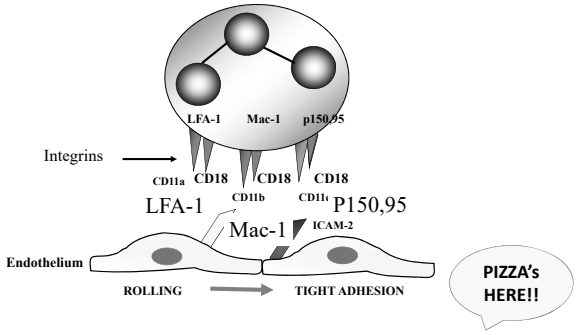
BMT (gene therapy)

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

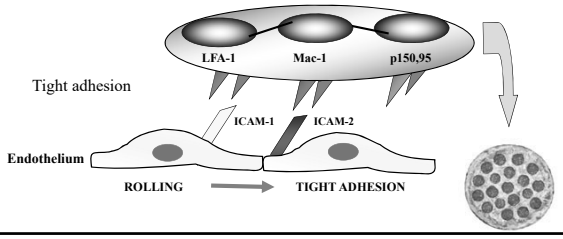
Neutrophil Rolling



Neutrophil adhesion

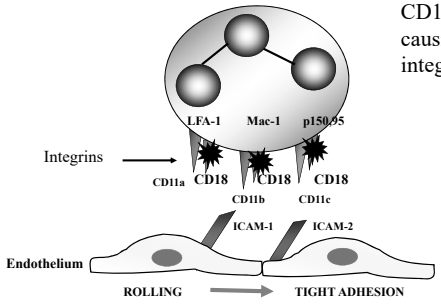


Neutrophil tissue entry (diapedesis)



Leukocyte Adhesion Deficiency type 1

LAD1 is due to CD18 deficiency, causing loss of integrins



Leukocyte Adhesion Deficiency Type 1 (AR)

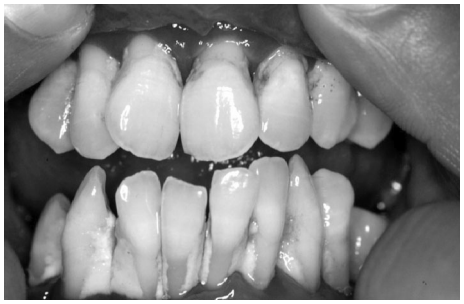
Failure to attach to the endothelium due to mutations CD18
Recurrent necrotizing infections: skin, perineum, lung, gut
Enteric GNR, GPC, NOT fungi or *Candida*
baseline leukocytosis, further WBC increase to infection
rare, consanguinity common

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

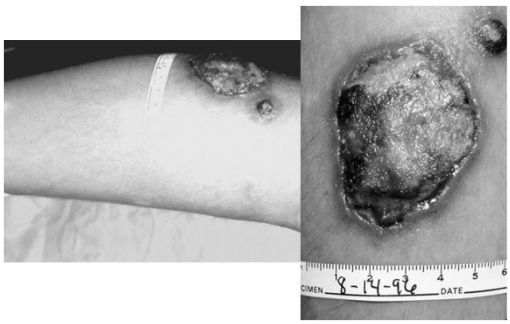
Leukocyte Adhesion Deficiency I

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

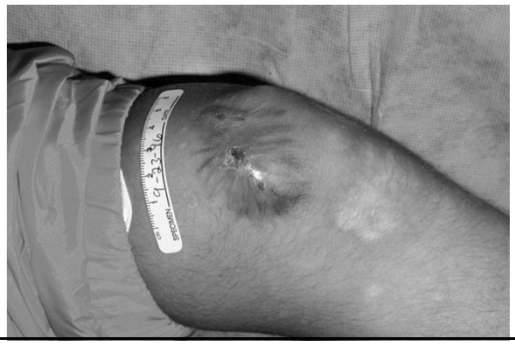
Almost universal tooth loss in LAD1 by adulthood

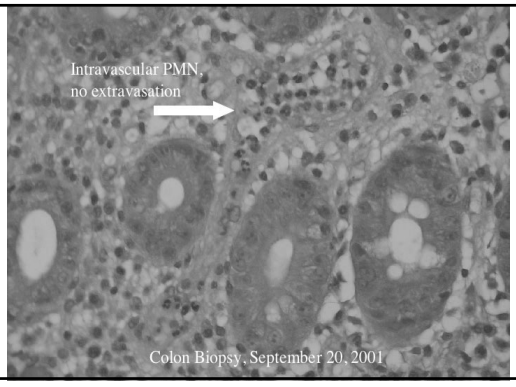


Impaired wound healing in LAD1



Cigarette paper scarring





IDBR INFECTIOUS DISEASE BOARD REVIEW COURSE Preview Question

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.

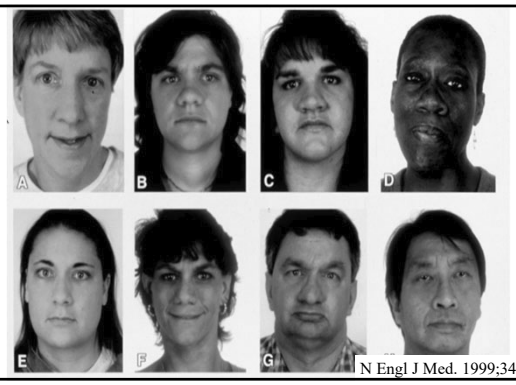
c) He is the product of a first cousin union.

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

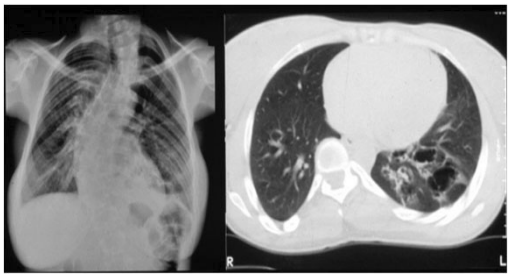
Referred from her internist for recurrent boils with *S. aureus*
IgE of 12,376 IU.
"Bronchitis and sinusitis at least once a year"
Persistent eczema requiring topical steroids.
Never hospitalized but having "more trouble" lately.



N Engl J Med. 1999;340:692-702

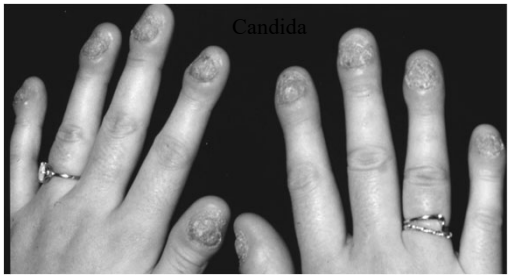
HIE (Job's) Syndrome History and Exam

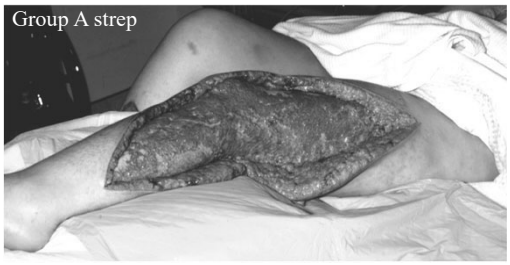
Eczema	100%
Facies	100% (≥16y)
Boils	87%
Pneumonia	87%
Mucocutaneous Candidiasis	83%
Pulmonary Cysts	77%
Scoliosis	76% (≥ 16y)
Delayed dental deciduation	72%
Coronary artery aneurysms	65%
Pathologic fractures	57%



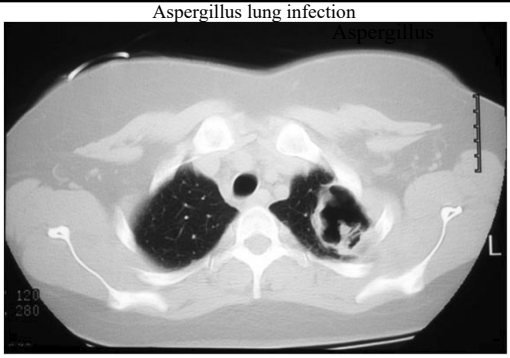
Pulmonary Pathogens in HIE

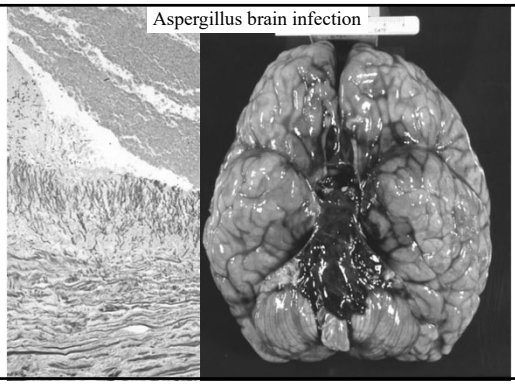
Primary pathogens:
Staphylococcus aureus
Streptococcus pneumoniae
Hemophilus influenzae
Secondary pathogens:
Pseudomonas aeruginosa
Aspergillus fumigatus
Others:
Pneumocystis jiroveci, M. avium complex



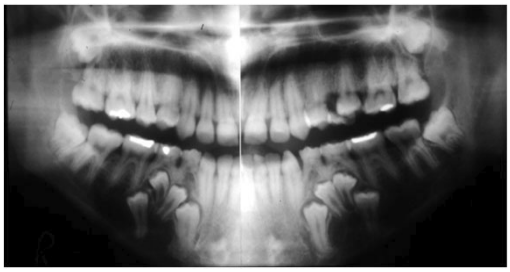


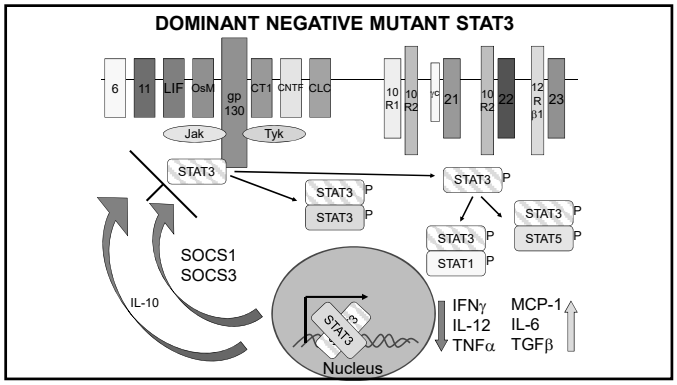
Aspergillus lung infection





Failure of primary dental deciduation





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
Job's: pneumonia, lung cysts, skeletal, mutations in *STAT3*
Rx- treatment of infections, prophylactic antibiotics, antifungals.
BMT

J Clin Immunol. 2021;41:864-880

DOCK8 Deficiency

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

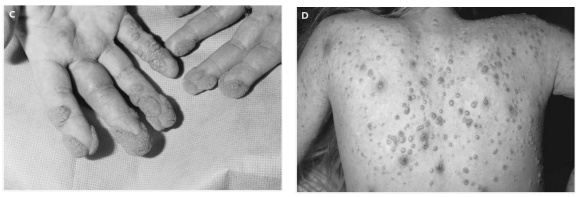
Candida, Cryptococcus, Histoplasma

HPV, HSV, molluscum

Squamous cell carcinomas, lymphoma

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

DOCK8 Deficiency

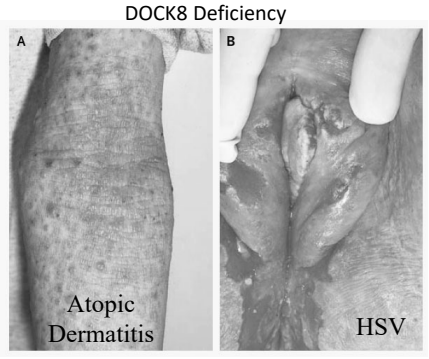


HPV

Molluscum contagiosum

N Engl J Med. 2009;361:2046-55

DOCK8 Deficiency



DOCK8 vs. STAT3 Hyper IgEs

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

IDBR INFECTIOUS DISEASE BOARD REVIEW COURSE Preview Question

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.

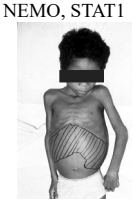
Going over the allotted 15 minutes you elicit points trying to establish whether she has hyper-IgE recurrent infection syndrome (Job's).

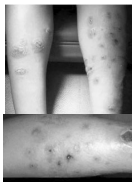
Which one of the following is <u>not</u> supportive of the diagnosis of Job's:

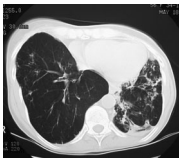
a) Pneumatoceles
b) Scoliosis
c) Severe warts
d) Retained baby teeth
e) Recurrent fractures

Clinical Spectrum of NTM Infections

Disseminated	Skin	Pulmonary
Severe, Young	Exposure	Chronic, Older
IFNγ/IL-12 defects	Inoculation	Bronchiectasis
NEMO, STAT1		Cystic fibrosis (CF)
		Ciliary dyskinesia (PCD)



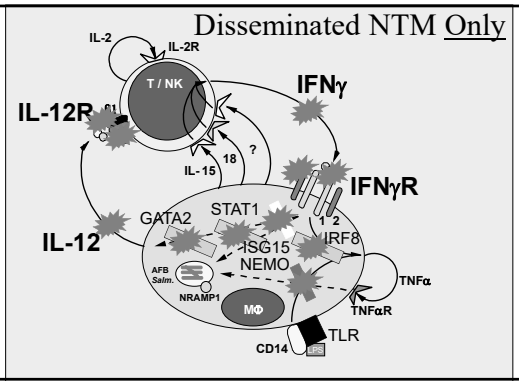




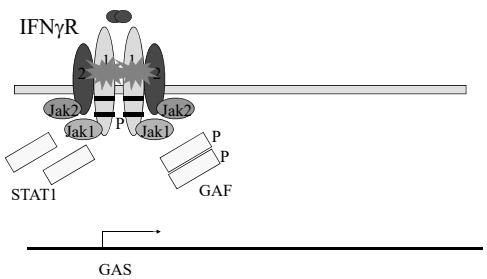
IMMUNE EXPOSURE EPITHELIAL

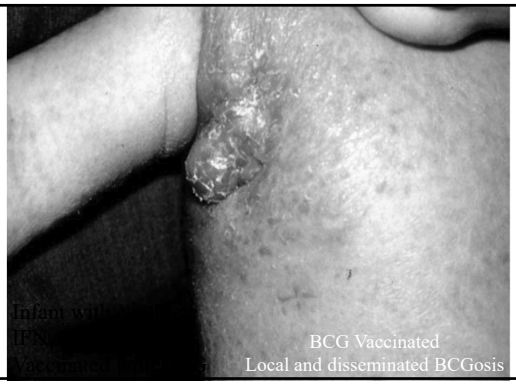
Lancet Infect Dis. 2015;15:968-80

Disseminated NTM <u>Only</u>

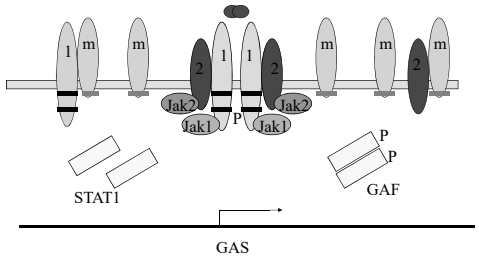


Autosomal Recessive IFNGR1 (both alleles)

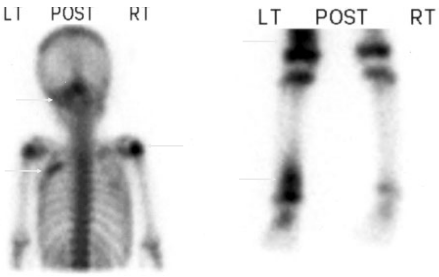




Autosomal Dominant IFNGR1 (one allele)



Mycobacterial Osteomyelitis in Dominant IFNγR1 Deficiency



Ann Allergy Asthma Immunol 2002;89:239-43.

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

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

Lancet. 2004;364:2113-21

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)

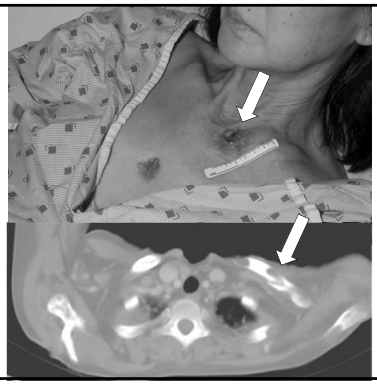
N Engl J Med. 2017;377:1077-1091.

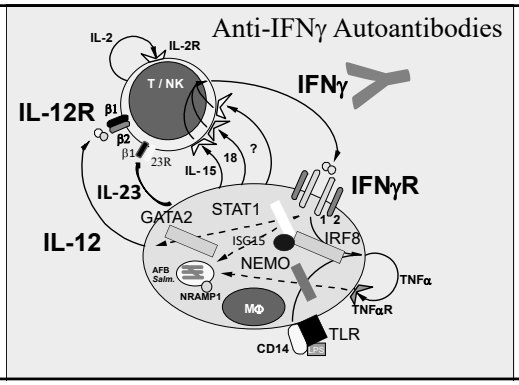
60 yo Vietnamese woman

USA 1970s

1 year recurring disseminated *M. avium* complex

Numerous fistulae





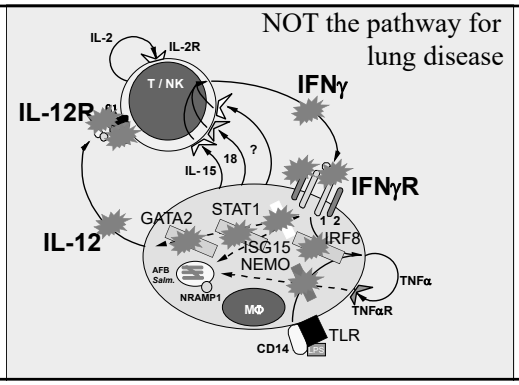
Anti-IFNγ autoantibody syndrome

Disseminated NTM later in life
also TB, *Talaromyces*, *Burkholderia*, VZV

Predominantly female, mostly East Asian

Dx- anti-IFNg autoantibody detection
Quantiferon is often INDETERMINATE
Rx- antimycobacterials, possibly rituximab

NEJM 2012;367:725



IDBR INFECTIOUS DISEASE BOARD REVIEW COURSE **Preview Question**

30 yo Thai woman with back pain

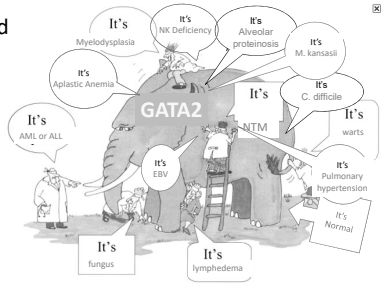
2 months pain and weight loss
HIV-, normal CBC and chemistries, normal CD4
Biopsy: osteomyelitis, MAC growing
Quantiferon indeterminate

You suspect that she has the anti-interferon gamma autoantibody syndrome

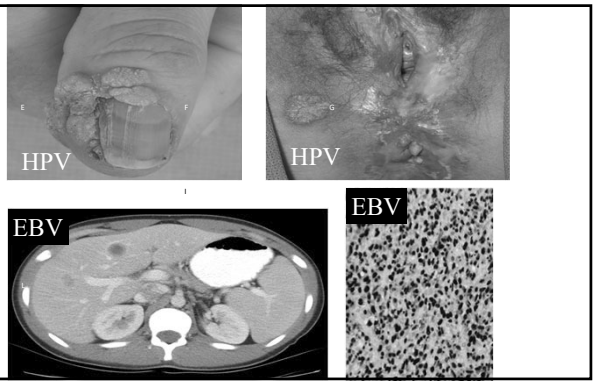
Supporting this diagnosis, you should:

a) Check complements and total IgG
b) Determine anti-IFNγ antibody levels
c) Determine anti-GM-CSF autoantibody levels
d) Determine anti-IFNα autoantibody levels
e) Determine her cellular response to IFNγ

The Blind



The Elephant



GATA2 Deficiency

Heterozygous mutations in GATA2, a critical hematopoietic gene
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: genetics, hypocellular marrow
Rx: antibiotics, BMT

Blood 2014; 123:809-21

Idiopathic CD4+ T-lymphocytopenia

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
  - surprisingly stable, consider incident cancers

Dx- determination of ICL (FACS)
- Often due to an underlying defect, so LOOK

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

N Engl J Med. 2023;388:1680-1691

Screening Laboratories

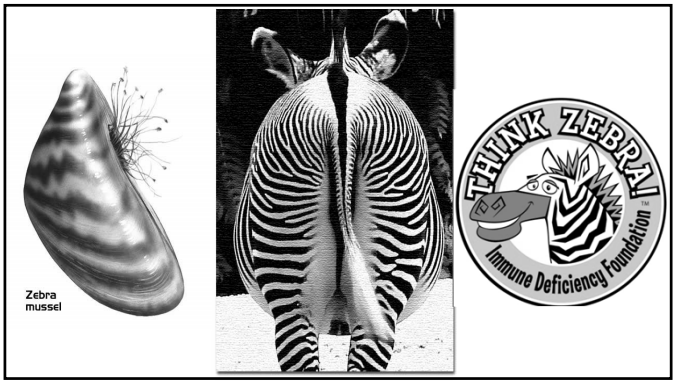
For Lymphocytes
- Ig levels
- immunization status (tetanus, pneumovax)
- CD4+ number
- *Genetics* (exome studies, panels)

Screening Laboratories

phagocytes
- DHR for CGD
- Genetics for everything else

complement
- CH_{50} (classical pathway)
- AH_{50} (alternative pathway)

Think about the gene involved!
Use Pubmed OMIM
Sequence is faster and cheaper than you think



04

Core Concepts: Antifungal Drugs

Dr. Barbara Alexander

4 – Core Concepts: Antifungal Drugs

Speaker: Barbara Alexander, MD

Core Concepts: Antifungal Drugs

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7/1/2024

Disclosures of Financial Relationships with Relevant Commercial Interests:

- **Consultant:** Scynexis, GSK, Astellas, Merck, HealthTrackRx, Basilea
- **Research Grant to My Institution:** Karius
- **Clinical Trials (Site PI/Study PI):** Scynexis, F2G
- **Royalties (Chapter Author):** UpToDate

Agenda

1. Review of Antifungals
   - Key points are underlined
2. Questions on antifungals with answers
3. New stuff (not on boards)

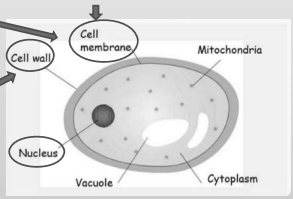
Antifungal Drugs

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



ANTIFUNGAL RESISTANCE Altered Target Ezymes

AZOLE RESISTANCE IN CANDIDA and ASPERGILLUS

- Fungus modifies the drug target, C14 ergosterol demethylase (gene cyp51A)
- Azoles no longer block synthesis of ergosterol, which is necessary for cytoplasmic membrane function
- Cross resistance varies with azole

ECHINOCANDIN RESISTANCE IN CANDIDA

- Fungus modifies the drug targets, glucan synthase, (genes fks1, fks2)
- Echinocandins no longer block synthesis of beta-D- glucan, which is necessary
- for cell wall synthesis
- Cross resistance between echinocandins is usual

Antifungal Resistant Species

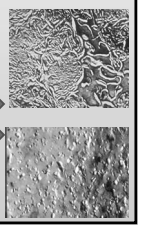
- Amphotericin B resistant: *Scedosporium apiospermum complex, Lomentosporum prolificans, Aspergillus terreus;* variable in *Candida lusitaniae, Candida auris, Fusarium species*
- Fluconazole resistant: All molds, *Rhodotorula species,Candida krusei, Candida auris, Candida haemulonii,* some *Candida glabrata*
- Voriconazole resistant: Mucorales; higher MIC's for cryptic *Aspergillus* species (lentulus, ustus, calidoustus)
- Posaconazole, Isavuconazole resistance: Similar to voricoazole, but more activity against Mucorales
- Echinocandin resistance: *Cryptococcus, Trichosporon, Rhodotorula*

CLSI. Epidemiological Cutoff Values for Antifungal Susceptibility testing. 4th ed. CLSI supplement M57S. Clinical and Laboratory Standards Institute; 2022.

Amphotericin B

Azotemia (less with saline loading), hypokalemia, renal tubular acidosis, anemia (erythropoietin loss)

- Amph B deoxycholate (conventional)
- Lipid formulations are less toxic
  - Ampho B Lipid Complex (ABLC) – flakes
  - Liposomal Ampho B (LAMB)- tiny particles



Azoles

All azoles teratogenic; CYP3A4 drug interactions

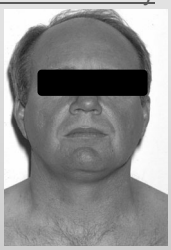
- Fluconazole: *Candida*, *Cryptococcus, Coccidioides*
  - Good concentration in urine
- Itraconazole: *Histoplasma, Blastomyces*, ringworm
  - Check blood levels
- Voriconazole: *Aspergillus,* molds other than *Mucorales*, *Candida*
  - Check blood levels
- Posaconazole: *Aspergillus,* variable *Mucorales*
  - Check blood levels
- Isavuconazole: *Aspergillus*, variable Mucorales
  - Fewer drug interactions, less QTc Prolongation than other azoles
  - Water soluable so no cyclodextrin (which can accumulate in renal dysfunction)

Voriconazole: THE FUNDAMENTALS

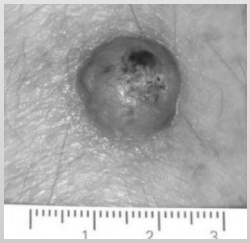
- Invasive *Candida;* Invasive *Aspergillus; Scedosporium apiospermum complex & Fusarium* in pts with refractory dz or intolerant of other therapy.
- Metabolism: Children are rapid metabolizers; Japanese 20% slower (2C19)
- Distribution: Good CSF levels, none in urine
- Formulations: IV contains sulphobutylether-B-cyclodextrin which accumulates in azotemia (use oral if CrCl <50 mL/min)
- Drug interactions: increases many other drug levels: cyclosporine, tacrolimus, serolimus, steroids (budesonide, fluticasone), etc.
- Side effects: hallucinations, hepatitis, photosensitivity, visual changes, peripheral neuropathy
  - After many months of Rx: skin cancer, periostitis

Voriconazole Side Effects

Photosensitivity:



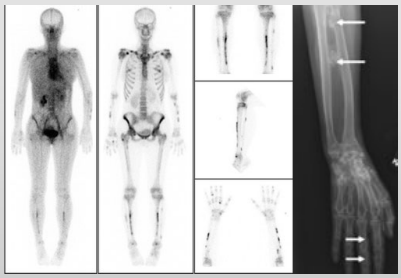
Skin cancer after months of sun:



Voriconazole Side Effects

Periostitis:

- Bone pain
- Months of Rx
- Alk phos high
- Plasma fluoride high (fluorosis)
- Bone scan
- Exostoses



Wermers, et al. CID 2011
Rossier, et al. Eur J Nuc Med Mol Imag 2011

Isavuconazole THE FUNDAMENTALS

- Approved for: Invasive Aspergillosis (noninferior to vori); Mucorales (use is controversial)
- **Inferior** to caspofungin for candidemia
- No good data on prophylaxis
- Distribution: no drug in CSF or urine; long half life (5.4 days)
- Drug interactions: fewer than vori or posa; teratogenic
- Isavuconazonium 372mg = isavuconazole 200 mg
- Load with 200 mg q8h X 6 doses then 200 mg qd, IV or PO
- No dose change for renal or moderate liver failure

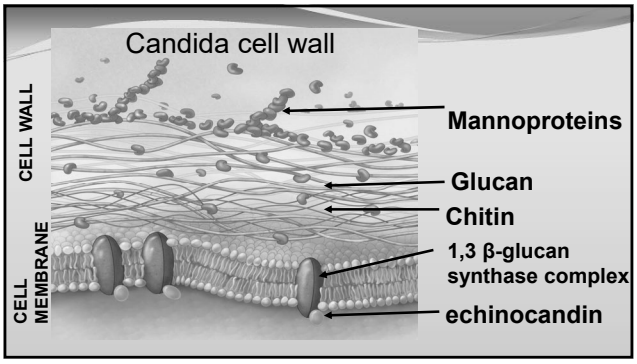
Posaconazole THE FUNDAMENTALS

- Approved for: prophylaxis in GVHD or prolonged neutropenia; oral thrush; Invasive Aspergillosis
  - Mucormycosis once patient has responded to amphotericin B
- Formulations:
  - Extended release tabs (three 100mg tablets twice daily on day 1, then 300mg daily)
  - IV same dose; contains cyclodextrin (use oral if CrCl <50 mL/min)
- Pharmacokinetics: 7-10 days for steady state; check trough levels (target usually 2-5 mcg/ml)
- Drug Interactions: increases some drug levels (CYP3A4)
- Side effects: Generally well-tolerated; hypertension, hypokalemia

FLUCONAZOLE THE FUNDAMENTALS

- Approved for: Candidiasis, Cryptococcosis, Prophylaxis in HSCT
- Also good for Coccidioidal meningitis, ringworm
- NO MOLD ACTIVITY
- Side Effects: Few; rarely dry skin, alopecia
- Distribution: Good penetration into urine and CSF
- Wide dose range; accumulated in renal dysfunction, requires adjustment
- Drug interactions: moderate CYP2C9 and CYP3A4
- TERATOGENIC

Echinocandins



Caspofungin, Micafungin, Anidulafungin, Rezafungin

- Indications: Invasive and Esophageal Candidiasis
  - Febrile neutropenia and refractory aspergillosis (caspofungin only)
  - Prophylaxis of *Candida* in HSCT (micafungin only)
- Resistance in *Candida* can arise during long therapy
- *Cryptococcus*, *Rhodotorula* & *Trichosporon* are intrinsically resistant
- *Aspergillus* and other mold activity is variable
- Formulations: IV only, once daily dosing.
  - Rezafungin with prolonged half-life; once weekly dosing
- Distribution: No drug in urine; protein binding high: poor penetration into CSF and vitreous humor of eye
- Drug interactions: none important

Flucytosine

- Indications: Used in combination wwith amphoB in cryptococcal meningitis and invasive candidiasis
- Distribution: Bioavailability 100%; good levels in CSF, eye, urine
- Side Effects: Accumulates in azotemia: bone marrow depression, hepatitis, colitis
- Measure blood levels/dose adjust
- Drug resistance arises during monotherapy

Now for a few questions

Question #1

PREVIEW QUESTION

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. Candida parapsilosis
B. Cryptococcus gattii
C. Candida auris
D. Candida krusei
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

The 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

PREVIEW QUESTION

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 (cont.)

PREVIEW QUESTION

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. rezafungin
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 count 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/Lomentosporum), Candida lusitaniae, or Asperillus terreus*
- Only ampho as first line for mucormycosis
- Fluconazole: not *Candida krusei , Candida auris; +/- Candida glabrata*
- Echinocandins: not *Trichosporon, Rhodotorula* or *Crypto*
- Know mechanisms of action: glucan, sterol, cell membrane, DNA synthesis
- Flucytosine: leuko- and thrombo-cytopenias, diarrhea, hepatitis

Take home, continued…

- Voriconazole: phototoxicity, periostitis, skin cancer hallucinations
- Azole interactions:
  - Increases other drug levels: cyclosporine, tacrolimus, serolimus, warfarin, midazolam, steroids, etc.
  - Decrease azole level: phenytoin, rifampin, etc

New oral antifungals approved for vulvovaginal candidiasis

Ibrexafungerp – novel glucan synthase inhibitor

- Acute infection: two 150 mg tabs 12 hours apart on same day
  Cost $ 475
- Recurrent infection: 300g bid q month for 6 months
  Cost $2,992

Otesaconazole – azole with long half life (drug persists about 2 years)

- FDA approval: recurrent infection in women not breastfeeding or capable of childbearing
- Start with one week of fluconazole or otesaconazole then otesaconazole once a week for 11 weeks.
  Cost $2,966

Investigational Antifungals in Clinical Trials

- **Olorofim**. Novel drug for *Aspergillus, Coccidioides*, some molds including *Scedosporium, Lomentospora* (not Mucorales or yeast). PO, ALT rises in 8%
- **Fosmanogepix**. In vitro activity against *Candida* (not *krusei*), *Aspergillus, Fusarium, Scedosporium*, (not Mucorales). PO, IV.
- **Encochleated amphotericin B**: PO. low absorption.
- **Opelconazole**: aerosol for chronic aspergillosis

Thank You

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BR1

Board Review Session 1

Drs. Pavia (Moderator), Alexander, Aronoff, Patel, and Thomas

BR1 –Board Review: Day 1

Moderator: Andrew Pavia, MD

Board Review: Day 1

Moderator: Andrew Pavia, MD
Faculty: Drs. Alexander, Aronoff, Patel, and Thomas

7/30/2024

BOARD REVIEW DAY 1 — INFECTIOUS DISEASE BOARD REVIEW 2024

#1 **You are caring for a 70-year-old man in 2024 with HIV (CD4 cell count 300, HIV RNA <20) and chronic obstructive pulmonary disease (COPD).**

He calls because he has fever and cough for 3 days, and his home rapid SARS CoV-2 test is positive.

He says he is not short of breath and his oxygen saturation is >95% (on home oximeter).

1 of 4

BOARD REVIEW DAY 1 — INFECTIOUS DISEASE BOARD REVIEW 2024

#1 **He takes darunavir, ritonavir, TAF/FTC for HIV infection.**

He takes inhaled corticosteroids for COPD.

His renal function is normal.

He received 2 doses of an mRNA Covid vaccine in 2021 but has not had a booster.

2 of 4

BOARD REVIEW DAY 1 — INFECTIOUS DISEASE BOARD REVIEW 2024

#1 **You recommend:**

A) Start nirmatrelvir/ritonavir (Paxlovid) and continue his other medications

B) Start nirmatrelvir/ritonavir and hold his other medications while he is taking nirmatrelvir/ritonavir

C) Start nirmatrelvir/ritonavir and hold or change darunavir, ritonavir, TAF/FTC while he is taking nirmatrelvir/ritonavir

D) Start molnupiravir

E) No need for Covid treatment

3 of 4

BOARD REVIEW DAY 1 — INFECTIOUS DISEASE BOARD REVIEW 2024

#2 **A 56-year-old male with underlying alcoholic cirrhosis underwent a deceased-donor orthotopic liver transplant 7 months ago.**

He now presents to the emergency department for a progressive non-productive cough and increasingly painful skin lesions. The skin lesions are multifocal but most concentrated on the right leg. He denies antecedent trauma including arthropod bites. His only antimicrobial prophylaxis is sulfamethoxazole-trimethoprim for *Pneumocystis jirovecii*.

1 of 5

BOARD REVIEW DAY 1 — INFECTIOUS DISEASE BOARD REVIEW 2024

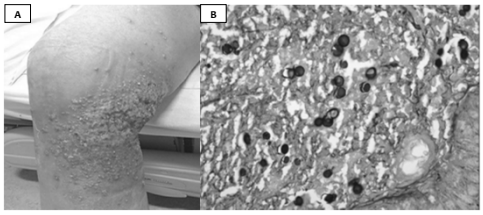
#2 **A peripheral pustular lesion is unroofed and PCR testing of this fluid is negative for varicella zoster and herpes simplex virus. Dermatopathology from a punch biopsy of the affected site demonstrates broad-based budding yeast measuring 8 to 15 microns in diameter (Figure B). Mucicarmine stains and serum cryptococcal antigen are negative.**

Cross-sectional imaging of the chest, abdomen, and pelvis demonstrates new multifocal pulmonary nodules.

2 of 5

BOARD REVIEW DAY 1 | INFECTIOUS DISEASE BOARD REVIEW 2024

#2



3 of 5

BOARD REVIEW DAY 1 | INFECTIOUS DISEASE BOARD REVIEW 2024

#2 **Which of the following would be the most appropriate INITIAL therapy?**

A) High dose intravenous sulfamethoxazole and trimethoprim

B) Amphotericin-B deoxycholate plus flucytosine

C) Oral terbinafine

D) Intravenous micafungin

E) Intravenous liposomal amphotericin

4 of 5

BOARD REVIEW DAY 1 | INFECTIOUS DISEASE BOARD REVIEW 2024

#3 **An 18-year-old male is admitted with diarrhea, fever, and abdominal pain. Six weeks previously, he was diagnosed with parotiditis, and prescribed clindamycin for 14 days.**

Approximately 2 weeks later, he developed onset of frequent non-bloody liquid stools. Clostridioides difficile PCR and antigen returned positive, and he completed a 10-day course of oral fidaxomicin.

He initially improved, but 5 days before admission started having recurrent liquid stools, decreased appetite, diffuse abdominal pain, and fever prompting hospital admission.

1 of 5

BOARD REVIEW DAY 1 | INFECTIOUS DISEASE BOARD REVIEW 2024

#3 **On exam he is a thin, uncomfortable appearing man. Temperature is 102.4 F, BP is 102/68, HR is 95 and O2 saturation is 98% on room air. Abdominal exam is notable for diffuse discomfort to palpation, but no peritoneal signs. Bowel sounds are hyperactive.**

Labs include:

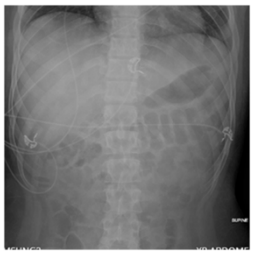
WBC=10.9, Cr=0.68

Stool C diff PCR and antigen are both positive.

2 of 5

BOARD REVIEW DAY 1 | INFECTIOUS DISEASE BOARD REVIEW 2024

#3 **Abdominal imaging shows dilated loops of bowel, but no evidence of ischemic colitis or megacolon:**



3 of 5

BOARD REVIEW DAY 1 | INFECTIOUS DISEASE BOARD REVIEW 2024

#3 **What is the best treatment option for this patient?**

A) Oral vancomycin and IV metronidazole

B) Fecal microbiota transplant

C) Oral vancomycin x 10 days followed by rifaximin for 20 days

D) Oral Metronidazole x 14 days

E) Fidaxomicin x 10 days

4 of 5

BOARD REVIEW DAY 1 INFECTIOUS DISEASE BOARD REVIEW 2024

#4 **As director of your institution's Infection Prevention and Control team, you are made aware of three patients in the surgical intensive care unit with Klebsiella pneumoniae bacteremia.**

The isolates are all KPC-positive, which is unusual at your institution. You ask the laboratory to type the associated isolates (to assess relatedness).

1 of 3

BOARD REVIEW DAY 1 INFECTIOUS DISEASE BOARD REVIEW 2024

#4 **What is the preferred typing method?**

A) Multiple locus variable-number tandem repeat analysis

B) Whole genome sequencing

C) Pulsed-field gel electrophoresis

D) Multilocus sequence typing

2 of 3

BOARD REVIEW DAY 1 INFECTIOUS DISEASE BOARD REVIEW 2024

#5 **A 56-year-old man with genotype 1 HCV infection is treated with 8 weeks of glecaprevir and pibrentasvir. Prior to treatment, liver elastography was 12.6 kPa.**

Your liver consultant suggests this elastography score indicates severe fibrosis.

1 of 4

BOARD REVIEW DAY 1 INFECTIOUS DISEASE BOARD REVIEW 2024

#5 **(Normal score is between 2 and 7 kPa. Scores of 7.2, 9.3, and 12.7 kPa indicate mild, moderate, and severe fibrosis.**

One year after treatment, a repeat liver elastography is 8.7 kPa. HCV RNA remains undetectable. ALT is 26 IU/L. At baseline and 6 months after treatment, liver ultrasounds were negative for hepatocellular carcinoma (HCC).

2 of 4

BOARD REVIEW DAY 1 INFECTIOUS DISEASE BOARD REVIEW 2024

#5 **What would you recommend?**

A) He should continue ultrasounds every 6 months for life for early detection of HCC

B) He can stop 6-monthly ultrasounds

C) Alpha fetoprotein blood levels should be monitored instead of ultrasounds

D) Liver biopsy is necessary to exclude cirrhosis before stopping HCC screening

3 of 4

BOARD REVIEW DAY 1 INFECTIOUS DISEASE BOARD REVIEW 2024

#6 **An 80-year-old woman with congestive heart failure and a recent hip fracture is admitted with confusion, hypoxemia and is found to have bilateral infiltrates on her chest x-ray.**

Blood cultures are negative, urine studies for Legionella and pneumococcal antigen are negative, and sputum studies are not diagnostic.

1 of 4

BOARD REVIEW DAY 1 INFECTIOUS DISEASE BOARD REVIEW 2024

#6 **Several other residents of her nursing home are ill with fever and cough.**

A nasopharyngeal swab PCR is positive for human metapneumovirus and negative for influenza and RSV.

2 of 4

BOARD REVIEW DAY 1 INFECTIOUS DISEASE BOARD REVIEW 2024

#6 **Which of the following therapies is most appropriate:**

A) Inhaled ribavirin

B) Azithromycin

C) Methylprednisone

D) Doxycycline

E) Supportive care only

3 of 4

BOARD REVIEW DAY 1 INFECTIOUS DISEASE BOARD REVIEW 2024

#7 **A 68-year-old man underwent heart transplant and is maintained on mycophenolate mofetil, tacrolimus, and prednisone, as well as valganciclovir, atovaquone and nystatin swish + swallow.**

He previously was diagnosed with invasive pulmonary aspergillosis. At the time of diagnosis, blood and BAL galactomannan were positive/above the upper limit of the assay, and 1,3 beta-D-glucan was >500 pg/ml positive.

1 of 5

BOARD REVIEW DAY 1 INFECTIOUS DISEASE BOARD REVIEW 2024

#7 **His pulmonary lesions improved, and he became afebrile on voriconazole.**

Three months later, while he was still on voriconazole, he became febrile, and a large new pulmonary lesion appeared on CT in a different location. The earlier lesion had nearly resolved.

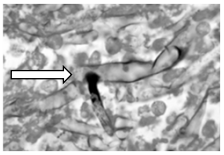
1,3 Beta D glucan had fallen to 216 pg/ml. His serum galactomannan is negative.

2 of 5

BOARD REVIEW DAY 1 INFECTIOUS DISEASE BOARD REVIEW 2024

#7 **His bronchoalveolar lavage was not diagnostic: the BAL galactomannan was negative.**

A biopsy of the new lung lesion is performed and the GMS stain is shown below.



Grocott-Gömöri methenamine silver (GMS) 400x

3 of 5

BOARD REVIEW DAY 1 INFECTIOUS DISEASE BOARD REVIEW 2024

#7 **What is the most likely pathogen?**

A) *Cryptococcus neoformans*

B) *Aspergillus terreus*

C) *Scedosporium apiospermum complex*

D) *Cunninghamella bertholletiae*

E) *Fusarium solani*

4 of 5

BOARD REVIEW DAY 1 INFECTIOUS DISEASE BOARD REVIEW 2024

#8 **A 56-year-old man is seen for low back pain that has been present for a month. He is afebrile and x-rays show abnormalities of the left sacroiliac joint suggestive of infection.**

Two months before his pain began, he spent a two-week vacation in Spain where he enjoyed eating local cheeses made from unpasteurized cow, goat, and sheep milk. He has had no gastrointestinal or genitourinary symptoms.

1 of 3

BOARD REVIEW DAY 1 INFECTIOUS DISEASE BOARD REVIEW 2024

#8 **Which one of the following is the most likely cause of his sacroiliitis?**

A) *Brucella*

B) *Listeria*

C) *Yersinia*

D) *Salmonella*

E) *Campylobacter*

2 of 3

BOARD REVIEW DAY 1 INFECTIOUS DISEASE BOARD REVIEW 2024

#9 **A 23-year-old presented with headache, fever, and confusion of two days' duration.**

Physical examination was notable for a petechial rash, nuchal rigidity, and a temperature of 39°C.

1 of 4

BOARD REVIEW DAY 1 INFECTIOUS DISEASE BOARD REVIEW 2024

#9 **Cerebrospinal fluid analysis revealed a protein of 137 mg/dL (15-45 mg/dL), glucose of 10 mg/dL and 500 leukocytes/µL, of which 95% were neutrophils and 5% lymphocytes.**

A multiplex PCR panel performed on cerebrospinal fluid detected Neisseria meningitidis and human herpes virus 6.

2 of 4

BOARD REVIEW DAY 1 INFECTIOUS DISEASE BOARD REVIEW 2024

#9 **Which of the following is the most appropriate therapy?**

A) Ceftriaxone

B) Ceftriaxone and acyclovir

C) Ceftriaxone and ganciclovir

D) Ceftriaxone and foscarnet

E) Ceftriaxone, vancomycin, and acyclovir

3 of 4

BOARD REVIEW DAY 1 INFECTIOUS DISEASE BOARD REVIEW 2024

#10 **A 68-year-old woman is referred because her internist responded to an EPIC prompt and performed HBV serologic testing. Her results were as follows:**

HBsAg – neg

Anti-HBc IgM – neg

Anti-HBc IgG – positive

Anti-Hbs Ab – positive

HBV DNA – negative

ALT – 26 IU/L

1 of 3

BOARD REVIEW DAY 1 INFECTIOUS DISEASE BOARD REVIEW 2024

#10 **What is the best diagnosis to give the woman?**

A) Occult hepatitis B
B) Prior hepatitis B
C) False positive anti-HBc IgG
D) HBV vaccination
E) Chronic hepatitis B

2 of 3

BOARD REVIEW DAY 1 INFECTIOUS DISEASE BOARD REVIEW 2024

#11 **A 63-year-old male underwent allogeneic stem cell transplant for chronic myelogenous leukemia 120 days ago.**

He has had multiple episodes of acute graft-versus-host disease, for which he received multiple pulses of corticosteroids and remains on maintenance cyclosporine.

His absolute neutrophil count hovers between 750 and 1000 cell/μL. He is receiving prophylactic doses of trimethoprim-sulfamethoxazole.

1 of 5

BOARD REVIEW DAY 1 INFECTIOUS DISEASE BOARD REVIEW 2024

#11 **The patient developed a fever, patchy pulmonary infiltrates, and hypoxia. He is intubated and undergoes bronchoscopy.**

The micro lab reports that branched hyphae are present on wet mount of the BAL.

No pneumocystis was seen. PCR on the BAL is positive for CMV.

Liposomal amphotericin (5 mg/kg/day) is started.

2 of 5

BOARD REVIEW DAY 1 INFECTIOUS DISEASE BOARD REVIEW 2024

#11 **Five days later, the lab reports that the BAL culture is growing *Scedosporium apiospermum*.**

PCR of peripheral blood for CMV is undetectable.

The patient is still febrile, and the pulmonary status has deteriorated.

3 of 5

BOARD REVIEW DAY 1 INFECTIOUS DISEASE BOARD REVIEW 2024

#11 **At this point, you would recommend:**

A) Raise the dose of liposome amphotericin B to 10 mg/kg
B) Add ganciclovir
C) Switch to fluconazole
D) Switch to voriconazole
E) Add caspofungin

4 of 5

BOARD REVIEW DAY 1 INFECTIOUS DISEASE BOARD REVIEW 2024

#12 **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 bismuth subsalicylate, metronidazole, a proton pump inhibitor, and tetracycline.

1 of 3

BOARD REVIEW DAY 1 INFECTIOUS DISEASE BOARD REVIEW 2024

#12 **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

2 of 3

BOARD REVIEW DAY 1 INFECTIOUS DISEASE BOARD REVIEW 2024

#13 **You are treating a 56-year-old Asian woman for chronic hepatitis B.**

She wants to know if it is ok to stop her entecavir. She is tired of taking it as her only medicine, and it has become expensive in her health plan.

1 of 4

BOARD REVIEW DAY 1 INFECTIOUS DISEASE BOARD REVIEW 2024

#13 **Her HBV DNA has been suppressed for more than 8 years and you witnessed an e antigen conversion (HBeAg positive to negative with anti-HBe) four years ago.**

Her ALT has been normal, and she does not have cirrhosis. She is HIV negative.

2 of 4

BOARD REVIEW DAY 1 INFECTIOUS DISEASE BOARD REVIEW 2024

#13 **Which is most appropriate?**

A) Continue entecavir

B) Check quantitative HBV core antigen

C) Discontinue entecavir and monitor

D) Check anti-HBs

3 of 4

05

Core Concepts: Antiviral Drugs

Dr. Andrew Pavia

5 – Core Concepts: Antiviral Drugs

Speaker: Andrew T. Pavia, MD

IDBR INFECTIOUS DISEASE BOARD REVIEW AUGUST 17-21, 2024

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

7/1/2024

IDBR INFECTIOUS DISEASE BOARD REVIEW AUGUST 17-21, 2024

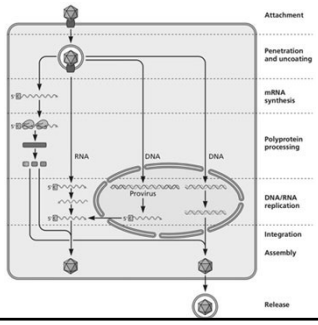
Disclosures of Financial Relationships with Relevant Commercial Interests

- Commercial Interests: Antimicrobial Therapy Inc, WebMD, Sanofi

What you need to know

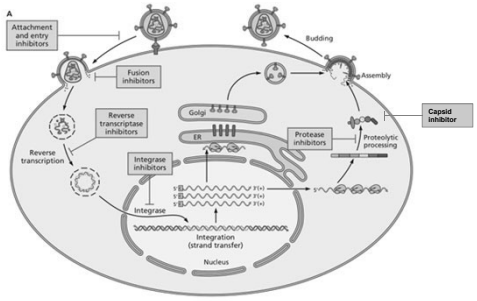
- Common basic mechanism e.g. target and drug type
  - Target: Polymerases (including reverse transcriptase)
    - Types: nucleoside/nucleotide analogs, NNRTI's, mutagens
  - Target: Entry
  - Target: Uncoating
  - Target: Integration
  - Target: Budding or release
- Clinically important resistance mechanisms and cross resistance – most testable
- It is possible that remdesivir, Paxlovid, or molnupiravir will be on the exam by mechanism

Antiviral mechanisms of action



Attachment	Influenza, HIV
Penetration and uncoating	Influenza, HIV
mRNA synthesis	
Polyprotein processing	HIV, SARS-CoV-2, Hepatitis C
DNA/RNA replication	HSV, CMV, influenza, Hepatitis B, Hep C, SARS-CoV-2
Integration	HIV
Assembly	HIV, CMV (Letermovir)
Release	Influenza, HIV

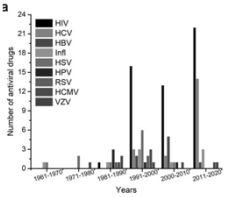
1. HIV antiretroviral targets in the life cycle



Limited Antivirals, limited targets

DNA Viruses
- Herpes Viruses
  - HSV
  - CMV
- Smallpox, mPox
- Hepatitis B
- Adenovirus

RNA viruses
- HIV
- Hepatitis C
- Influenza
- SARS-CoV-2
- Ebola, Lassa



Int J Biol Macromol. 2021 Mar 1:172

5 – Core Concepts: Antiviral Drugs

Speaker: Andrew T. Pavia, MD

General concepts

- Viruses use host mechanisms for part of their life cycle
- Need to inhibit a viral target without inhibiting host cellular target
- For acute infections, window of efficacy is generally short
- If replication is not completely inhibited, resistant mutants are likely to be selected
- The longer the duration of replication with drug exposure and the less effective the host response, the greater the risk of resistance. Combination therapy proven in chronic viral infections
- Pre-exposure prophylaxis important for HIV, CMV, and to a lesser extent influenza

QUESTION

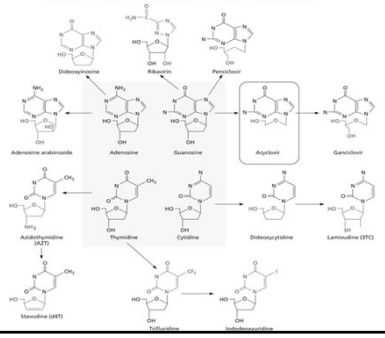
A patient with HIV infection (CD4 count of 15 cells/μL, VL 2 million) has a 3-year history of a recurrent perianal herpes simplex that had previously responded to acyclovir or valacyclovir. On this occasion, the painful ulcers has not responded to a 10-day course of acyclovir 400 mg TID followed by a 10-day course of valacyclovir 1g bid. The patient has been adherent to his regimens.

The best therapeutic option would be:

1. Intravenous ganciclovir
2. Intravenous acyclovir
3. Intravenous foscarnet
4. Valganciclovir
5. Famciclovir

Herpes Viruses

Nucleoside and nucleotide analogs



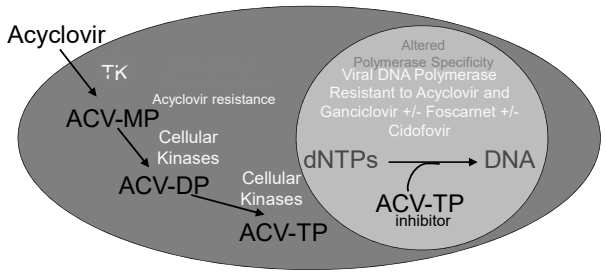
Acyclovir and Valacyclovir

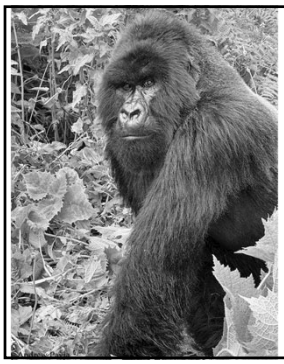
- Acyclic guanosine nucleoside analogs, act as chain terminators
- Must be phosphorylated to tri-phosphate
- Therapeutic uses:
  - HSV-1, HSV-2, VZV but NOT CMV or EBV
- Resistance occurs almost exclusively in immunosuppressed hosts (especially HSCT recipients and advanced HIV)
  - More common with HSV than VZV
  - When acyclovir resistant HSV or VZV disease is successfully treated, usually with foscarnet, 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 and Valacyclovir

- 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



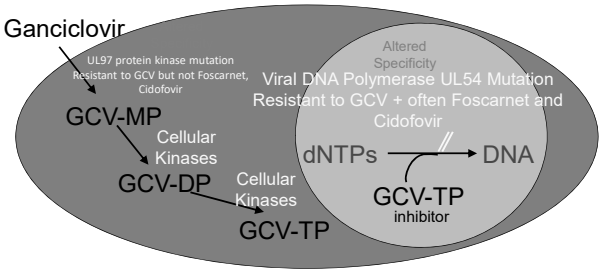


CMV

Ganciclovir and Valganciclovir

- Guanosine analog
  - Active against **CMV, HSV-1, HSV-2, VZV, +/- HHV-6**
- 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, marabavir
  - 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, HHV-6A, HHV-6B
  - Active against resistant HSV, UL 97 mutant 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
  - Unclear efficacy for adenovirus, polyoma viruses
- Resistance
  - Viral DNA polymerase mutations (not UL 97)
- Use with caution
  - Significant renal toxicity

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
  - Limited data on treatment
- Drug Interactions
  - Cytochrome p450 3A inhibitor: increases cyclosporine, tacrolimus, sirolimus and decreases voriconazole
- Resistance
  - Emerges on therapy; de novo resistance rare
  - Not likely testable: UL56 gene of terminase complex. No cross resistance

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)
    - Relatively common in patients chronically treated with lamivudine monotherapy
- Tenofovir (TDF and TAF)
  - 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
  - Entecavir can induce M184V mutation in HIV

Resistance Concerns if Patient Has HBV/HIV Coinfection

- Emtricitabine (FTC), lamivudine (3TC), and tenofovir (TDF) have activity against both HIV and HBV
  - When HBV and HIV treatment is needed, ART should be initiated with the combination of TDF + FTC or TDF + 3TC as the (NRTI) backbone of antiretroviral (ARV) regimen.
- If HBV treatment is needed and TDF cannot safely be used, entecavir is recommended in addition to a fully suppressive ARV regimen
- Entecavir has activity against HIV
  - Use without ARV in HIV/HBV co-infected patients may select for M184V mutation that confers HIV resistance to 3TC and FTC.
- If ART needs to be modified due to HIV virologic failure and the patient has adequate HBV suppression, ARV drugs active against HBV should be continued for HBV treatment in combination with suitable HIV regimen

Red = testable

Influenza

QUESTION

A 65 year old man in on the hematology oncology ward receiving conditioning prior to HSCT. He develops fever and an oxygen need. A PCR is positive for influenza A H1N1

Which of the following regimens is appropriate and least likely to lead to the emergence of resistance?

A) Rimantidine
B) Oseltamivir
C) Baloxavir marboxil
D) Rimantidine and Zanamivir
E) Letermovir

5 – Core Concepts: Antiviral Drugs

Speaker: Andrew T. Pavia, MD

Influenza Therapy

- Adamantanes (Rimantidine, Amantadine)
  - Mechanisms of action
    - M2 protein
  - Activity
    - Influenza A only
  - Not recommended because resistance is widespread and stable
- Neuraminidase Inhibitors (Oseltamivir, Zanamivir, Peramivir)
  - Mechanisms of action
    - Inhibits release of new virions from surface of infected cell
  - Activity
    - Influenza A and B
  - 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

SARS-CoV-2

SARS-CoV-2

- Remdesivir
  - Mechanism
    - Acts as adenosine 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)
- Nirmaltrevir/ritonavir (Paxlovid)
  - Inhibits Mpro (main protease)
  - Drug-Drug interactions
  - Several mutations identified in Mpro that confer resistance but at fitness cost
  - Clinical importance of mutations remains under investigation
- Molnupiravir
  - Mechanism
    - Acts as cytidine nucleoside analog
    - Causes "catastrophic errors" in replication

See Antiviral Resistance Primer online
Good Luck on the Exam!
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06

Respiratory Viral Infections Including Influenza, Immunocompetent, and Immunocompromised Patients

Dr. Andrew Pavia

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

Speaker: Andrew T. Pavia, MD

IDBR INFECTIOUS DISEASE BOARD REVIEW AUGUST 17-21, 2024

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

7/1/2024

IDBR INFECTIOUS DISEASE BOARD REVIEW AUGUST 17-21, 2024

Disclosures of Financial Relationships with Relevant Commercial Interests

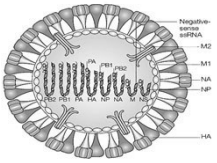
- Commercial Interests: Antimicrobial Therapy Inc, WebMD, Sanofi

What you need to know for the boards

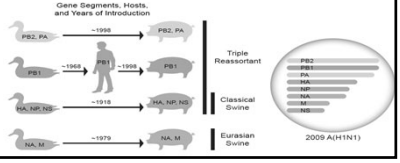
- Minimal virology
- Epidemiology including avian influenza
- Diagnosis
- Complications
- Antivirals
- Vaccines

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



Reassortment of genes leads to pandemic shifts
e.g. A/California/7/2009 (H1N1)pdm09, the virus formerly known as swine flu



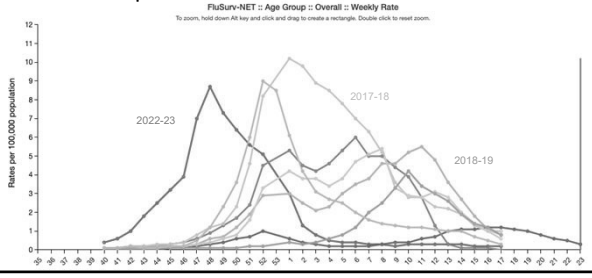
Clinical findings of influenza

- Fever, malaise, cough, sore throat, myalgia, chills, eye pain, headache
- Sudden onset is typical
- During an epidemic, fever with cough has high predictive value
- Fever may be absent in the elderly, immunocompromised, very young

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

Speaker: Andrew T. Pavia, MD

Winter but variable timing and intensity; hospitalization rates from FluSurv-NET



Groups at Risk for Complications of Influenza

Group	Example/Comment
Children <5 yrs	Highest hospitalization rate children <2 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	May also be increased in other disadvantaged groups

Influenza Transmission

- Incubation period: 1-4 days (average: 2 days)
- Shedding:
  - Adults: 1 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
- Large droplets (up to 6 feet) most important.
- Fomite and small droplet (true airborne) likely contribute.
- Standard plus droplet precautions recommended
- "Use caution" for aerosol generating procedures
- Monitor and manage ill health care personnel

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

What makes a human influenza strain?

- Use of α2-6-linked receptors. PB2 adaptation
- 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. Current strain causing severe outbreak in birds with recent spill over in mammals**
- H7N9: Caused >130 cases of severe disease 2013; >200 in second wave; decreasing
- H7N3: Isolated cases in farm workers
- H7N7: H7 viruses associated with conjunctivitis
- H9N2: Sporadic cases associated with poultry
- H10N3: First human case 2021

* Currently causing human disease

H5N1 High pathogenicity Avian influenza

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

Speaker: Andrew T. Pavia, MD

HPAI H5N1 influenza

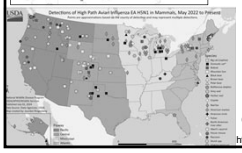
- Initially identified in goose in Guangdong in 1996
- 18 human cases/6 deaths Hong Kong 1997
- Re-emerged in 2003 with large poultry outbreaks and sporadic human cases – high mortality
- In 2020, reassortment led to emergence of Eurasian clade of HPAI H5N1 Clade 2.3.4.4b
- Large outbreaks among commercial and backyard poultry and wild birds around the world
- ~ 90 million birds culled in US in since 2020
- 909 human cases to date; 13 of clade 2.3.4.4b

Photo: Mads Claus Rasmussen

Photo: NBC News

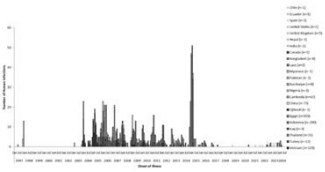
Human and other mammalian cases of H5N1 (Not testable)

Cattle herds



Other mammals

Epidemic Curve of Human cases, 1997-2024 by country



https://www.cdc.gov/flu/avianflu/spotlights/2023-2024/h5n1-technical-report_april-2024.htm

Question #1

PREVIEW QUESTION

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 #1 (Cont.)

PREVIEW QUESTION

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

Mild complications of influenza

Complication	Comment
Otitis media	
Sinusitis	
Parotitis	Newly described
Asthma exacerbation	Antibiotics not indicated
Croup	Young children
Bronchiolitis/Bronchitis	

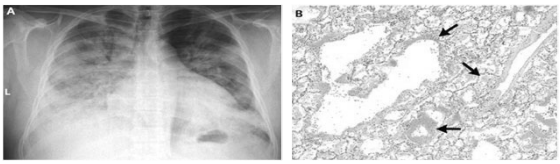
Severe cardiopulmonary complications of influenza

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

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

Speaker: Andrew T. Pavia, MD

Influenza associated hemorrhagic pneumonitis



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
Other	Stroke, ADEM, Reyes Syndrome
Musculoskeletal	
Myositis, Rhabdomyolysis	Can be severe and lead to AKI
Cardiac	
Pericarditis	
Myocarditis	see also Uyeki Ann Intern Med 274:9 Nov 2021

Question #2

- 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 #2 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

Diagnosis

Photo: ©Andrew Pavia

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 (pre-Covid)
- Rapid influenza detection tests have low-moderate sensitivity 10-70%; reasonably specific
- Positive antigen test in peak season high PPV; negative test should not be used for decisions
- PCR/NAAT recommended by IDSA Guidelines, rapid platforms NAAT expanding. When flu is circulating, test for both SARS-COV-2 and flu
- Serology has no role

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

Speaker: Andrew T. Pavia, MD

Influenza in transplant pearls

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

Question #3

PREVIEW QUESTION

- 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 #3 (Cont.)

PREVIEW QUESTION

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 2024

- Antiviral treatment is recommended for patients with confirmed or suspected influenza as soon as possible for:
  - Who are hospitalized regardless of duration of symptoms
  - 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
  - Consider for otherwise healthy outpatients within 48 hrs of symptom onset

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

ACIP Guidelines for Antiviral Use 2024 (con't.)

- Recommended medications for outpatients:
  - Oseltamivir, baloxavir, inhaled zanamivir and IV peramivir
- Recommended medications for inpatients:
  - Oseltamivir

https://www.cdc.gov/flu/professionals/antivirals/summary-clinicians.htm

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 therapy.
- Treatment duration
  - NAIs: 5 days
  - Baloxavir: single dose
- Initiating treatment within 2 days of symptoms results in improved outcomes
  - Substantial reduction in morbidity and mortality in hospitalized patients up to 5 days after sx

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

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

Speaker: Andrew T. Pavia, MD

Baloxavir

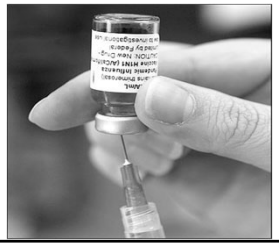
- Cap-dependent polymerase inhibitor
- Non inferior to oseltamivir in two phase 3 studies
- Superior for influenza B in patients with risk factors
- Shorter duration of shedding
- Resistance mutations emerge on treatment in 10-20%

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
- **PEP is recommended to control influenza outbreaks in nursing homes**
- Prophylaxis may increase selection of resistant viruses
- 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

Vaccines



ACIP Recommendations for Influenza vaccination 2024-25

- Routine influenza vaccination is recommended for all persons aged 6 months and older.
- All vaccines will be trivalent!!! (TIIV = Trivalent inactivated influenza vaccine) H1N1, H3N2, B Victoria
- Enhanced vaccines recommended for those >65
  - High dose inactivated, adjuvanted, recombinant
- Consider HD or adjuvanted for solid organ recipients

https://www.cdc.gov/flu/season/faq-flu-season-2024-2025.htm

Vaccine pearls (con't.)

- All influenza vaccines can be given to those with egg allergy.
- For those with anaphylaxis to egg, consultation with allergist no longer recommended. Anaphylaxis to flu vaccine is still a contraindication

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
- Egg adaptation may lower efficacy

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

Speaker: Andrew T. Pavia, MD

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. If a vaccine other than ccIIV4 or RIV4 is used, the selected vaccine should be administered in an inpatient or outpatient medical setting (including but not necessarily limited to hospitals, clinics, health departments, and physician offices).
- A previous severe allergic reaction to flu vaccine, regardless of the component suspected of being responsible for the reaction, is a contraindication to future receipt of the vaccine.

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

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

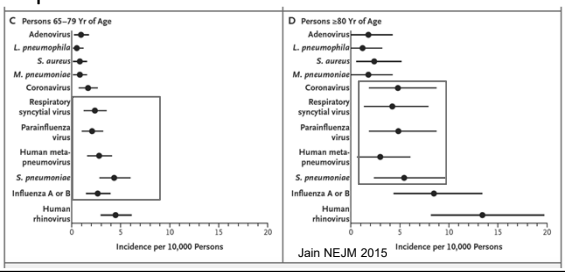
Photograph by Adam Clark

What you may be tested on

- Focus on lower respiratory tract disease in compromised hosts, *including* older adults
- RSV, adenoviruses, hMPV are fair game
- Parainfluenza viruses possibly
- Coronaviruses including MERS (possible) and SARS-1 (unlikely) possibly SARS-CoV-2
- Hantavirus pulmonary syndrome is a popular zebra

Photo: ©Andrew Pavia

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	Consolidation, 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 and transplant patients with respiratory symptoms
- Consider testing in hospitalized elderly

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

Speaker: Andrew T. Pavia, MD

Respiratory Viruses in HSC Transplant Patients

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

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

Question #4

- 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 or effusion

Question #4 Continued

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

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

Question #5

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

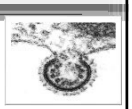
A. RSV is an incidental finding which might cause URI symptoms
B. RSV likely accounts for infiltrate. He should be immediately started on palivizumab (Synagis) and ribavirin
C. RSV likely accounts for infiltrate. Supportive care is appropriate
D. He has high risk CAP and should be started on vancomycin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

Risk factors for RSV hospitalization among adults

- Age
- CHF
- CAD
- COPD
- Diabetes mellitus
- Immune compromise, especially hematopoietic stem cell transplant and solid organ transplant
- Asthma
- Morbid obesity

Anderson et al, Diagn Microbiol Infect Dis (2016): https://doi.org/10.1016/j.diagmicrobio.2016.02.025
Prasad et al, Clin Infect Dis (2020): https://doi.org/10.1093/cid/ciaa730
Kujawski et al, Plos One (2022): https://doi.org/10.1371/journal.pone.0264890
Branche et al, Clin Infect Dis (2022): https://doi.org/10.1093/cid/ciab595

RSV

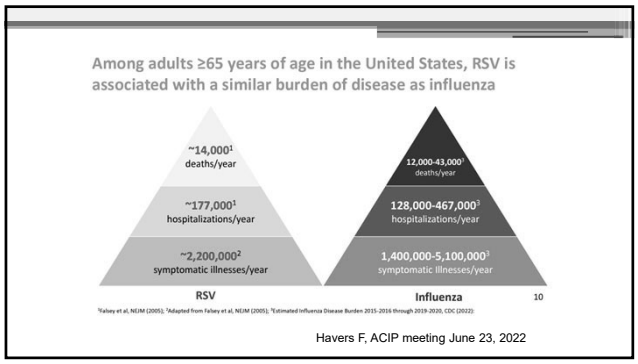


- Most common cause of LRTI in children
- Common cause of URI with rhinitis in adults.
- AE-COPD, worsened CHF, asthma exacerbation and pneumonia in elderly and immunocompromised
- Transmitted by large droplet and contact; Late fall to spring (usually December- April)
- Similar rates of hospitalization to influenza among those> 65
- COPD, CAD, CHF risk factors for hospitalization

Falsey NEJM 2005, Widmer 2012
Brance Clin Infect Dis 2022

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

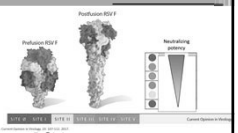
Speaker: Andrew T. Pavia, MD



RSV

- Long incubation period 2-8 days
- Diagnosis by PCR
- No indications for palivizumab (Synagis) or nirsevimab 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, much less expensive

RSV Prevention!



- Three licensed vaccines for those > 60
  - Protein >80% effective at preventing severe RSV
  - Target pre-fusion F protein
    - GSK adjuvanted single dose
    - Pfizer un-adjuvanted single dose
    - Moderna mRNA single dose
- Pfizer licensed for pregnant women to protect infant ~ 70% effective
- New long acting monoclonal Ab nirsevimab for infants

Case

- A 20 year old soldier undergoing advanced infantry training presents in March with several days of fever, cough, chest pain, tachypnea, hypoxia and conjunctivitis with this CXR.
- No travel, tick bites, animal exposures
- WBC 3.0, platelets 160, CRP 2.5, AST 85, ALT 80

Question #6

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 #6

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

Speaker: Andrew T. Pavia, MD

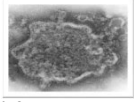
Adenovirus

- DS DNA; 7 species, >50 serotypes
- Associated with URI, pharyngitis, conjunctivitis, otitis, pneumonia, myocarditis, hemorrhagic cystitis; hepatitis, disseminated disease in compromised hosts
- Adenovirus species F type 40/41 associated with gastroenteritis; unclear association with pediatric liver failure
- Outbreaks of pneumonia in day care, closed settings, stressed populations e.g. military barracks
- No real seasonality

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; HLH
- Diagnosis by PCR of **respiratory secretions, blood**, pathology of organ biopsy
- Cidofovir, Brincidofovir have been used for Rx

Human Metapneumovirus



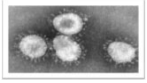
- "Discovered' in the last decades
- Nonsegmented, single stranded, negative sense RNA virus: Paramyxoviridae family, Pneumovirinae subfamily
- Causes URI, bronchiolitis, pneumonia similar to RSV
- Winter/Spring in temperate climates
- In younger adults, URI common with sore throat, hoarseness, wheezing,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

Falsey J Ped Inf Dis 2008
Walter Inf Dis Clin North America 2017

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



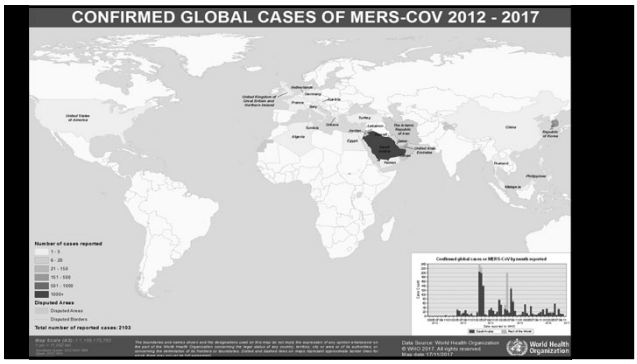
- HuCoV 229e, HuCoV OC43
  - "Older" associated predominantly with URI
- HuCoV HKU1, HuCoV NL63
  - Recently described using molecular techniques. Associated with URI and some pediatric and adult pneumonia
- May be detected on newer multiplex platforms (Luminex, FilmArray). Do not cross react with SARS-CoV-2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

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

Speaker: Andrew T. Pavia, MD



Question #7

- 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 #7 (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

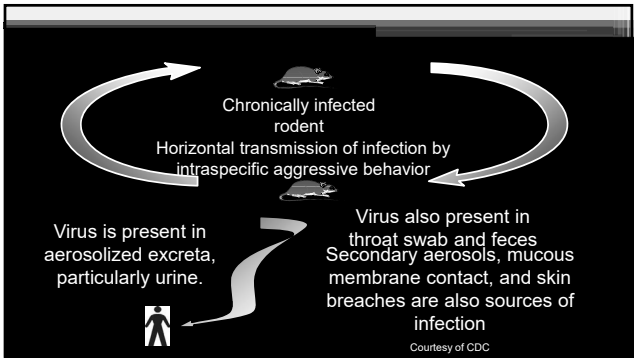
Question #7 (con't)

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

A. Adenovirus
B. Influenza
C. Anthrax
D. Coxiella burnetii
E. Sin Nombre virus (Hantavirus Pulmonary Syndrome)

Hantavirus Pulmonary Syndrome HPS

- First described in a 1993 outbreak in the 4 Corners
- Outbreak in 2012 Yosemite. Endemic cases of HPS in much of US, Chile, Argentina
- Caused by specific North American and Latin American hantaviruses – member of Bunyaviridae 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



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

Speaker: Andrew T. Pavia, MD

Stages of Hantavirus Pulmonary Syndrome (HPS)

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

HPS-Cardiopulmonary Phase

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

HPS-Cardiopulmonary Phase

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

Respiratory viruses: Take home

- RSV, hMPV, Parainfluenza viruses are common causes of CAP and exacerbation of underlying cardiopulmonary disease 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
- HPS has distinct epidemiologic risks and recognizable lab abnormalities

Good Luck on the Exam!

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@AndrewPaviaMD

07

Nocardia, Actinomycosis, Rhodococcus, and Melioidosis

Dr. David Aronoff

7 – Nocardia, Actinomycosis, Rhodococcus, and Melioidosis

Speaker: David M. Aronoff, MD

IDBR INFECTIOUS DISEASE BOARD REVIEW AUGUST 17-21, 2024

Nocardia, Actinomycosis, Rhodococcus, & Meliodosis

David M. Aronoff, MD, FIDSA, FAAM
John B. Hickam Professor of Medicine
Chair, Department of Medicine
Indiana University School of Medicine
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7/15/2024

IDBR INFECTIOUS DISEASE BOARD REVIEW AUGUST 17-21, 2024

- **Disclosures of Financial Relationships with Relevant Commercial Interests**

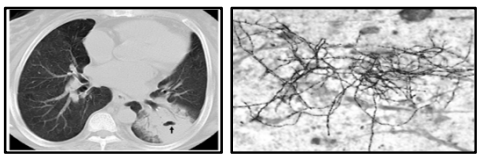
  - None

Case

PREVIEW QUESTION

54 year old man with 4 weeks of cough, low grade fevers, & left-sided chest pain. Received a liver transplant 11 months ago, complicated by rejection, requiring high dose steroids 4 months ago. He receives TMP/SMX three times a week. On exam, he is stable, chronically-ill appearing, febrile (101.1ºF), has clear lungs and benign abdomen. Labs reveal a normal white blood cell count, slight anemia, & normal creatinine. Chest radiograph reveals hazy opacity in left lower lung zone. Chest CT reveals nodular air-space consolidation in the left lower lobe with central cavitation (image). Gram strain of bronchoalveolar lavage fluid reveals beaded gram positive filamentous organisms (image).

PREVIEW QUESTION



CT Image from J. Bargehr, *et al. Clinical Radiology*, 2013-05-01, Volume 68, Issue 5, Pages e266-e271.
Gram stain image from Murray, *et al.* Medical Microbiology, 7E. 2013 Saunders, Elsevier.

PREVIEW QUESTION

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

A. Cryptococcus neoformans
B. Histoplasma capsulatum
C. Actinomyces israellii
D. Nocardia farcinica
E. Aspergillus fumigatus

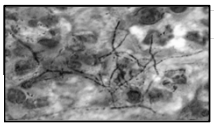
What are the most appropriate next steps in this patient's care?

A. Initiate therapy with intravenous TMP/SMX
B. Obtain a needle biopsy of the lung nodule to confirm the diagnosis
C. Obtain a brain MRI & start amikacin & TMP/SMX
D. Defer therapy until antimicrobial susceptibilities return

7 – Nocardia, Actinomycosis, Rhodococcus, and Melioidosis

Speaker: David M. Aronoff, MD

Nocardia Infections



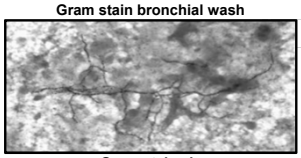
- **Microbiology:**
  - Beaded & branching gram-positive rods
  - Partially acid-fast
  - Aerobic (unlike anaerobic *Actinomyces*)
  - More than 80 species & >40 cause disease in humans
    - New phylogeny based on DNA sequence (*formerly*, *N. asteroides* complex): **species names are *lookups***.
- **Pathogenesis:**
  - **Inhalation** (most common)
  - **Direct inoculation** through the skin

Photo: http://path.upmc.edu/cases/case226/dx.html; Good reference: Restrepo A & Clark NM. *Clinical Transplantation*. 2019:e13509.

Images of *Nocardia*

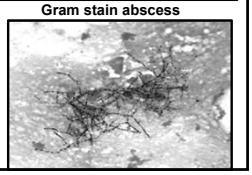
- **Beaded**
- **Branching**
- **Gram positive**
- **Partially acid-fast**

Gram stain bronchial wash



Partially acid-fast

Gram stain abscess



Images from http://thunderhouse4.wordpress.com/2010/06/nocardia-species.html

Clinical Features of *Nocardia*

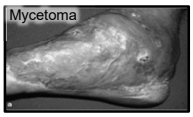
- **Immunocompromised**
  - **Glucocorticoid use, solid organ transplant**, hematopoietic transplant, alcoholism, diabetes, CGD, CF, autoantibodies against GM-CSF (seen in autoimmune pulmonary alveolar proteinosis), anti-TNF therapy, ectopic ACTH syndrome, AIDS (less common)
    - *PJP prophylaxis may not prevent nocardiosis* (& does not predict TMP/SMX resistance)
  - Months to years after transplantation
- **90%**: **slowly progressive pneumonia** with cough, dyspnea, & fever
  - *Aspergillus* similar; co-infections occur
  - Similar to cryptococcal disease & actinomycosis
  - Can disseminate to any organ (**brain** in particular: **get MRI;** can be asymptomatic!)

Margalit I, *et al. Clinical Microbiology and Infection* (2021).

Clinical Features of *Nocardia*

- **10%**: Skin infections from direct inoculation:
  - Immunocompetent host in tropical region (*N. brasiliensis*)
  - Immunocompromised patient who gardens or walks barefoot
  - **Sporotrichoid** lesions
  - **Mycetomas**: chronic, progressive, lower limbs, draining sinuses (similar to Actinomycetes & eumycetoma). "Madura foot"

Sporotrichoid lesions



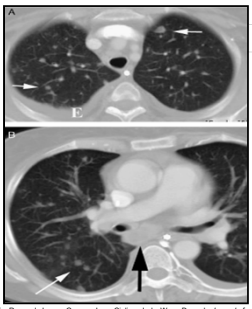
Mycetoma

Baradkar V P, *et al. Indian J Pathol Microbiol* 2008;51:432-4 Sharma NL, *et al. Indian J Dermatol Venereol Leprol* 2008;74:635-40

Nocardia Diagnosis

- **Diagnosis**:
  - Suggestive **radiology**
    - Chest imaging: **nodules**, cavities, infiltrates with consolidation, effusions, ground-glass opacities
    - MRI brain: single or multiple **abscesses**
  - Blood **culture**, BAL, biopsy
    - Gram stain, **modified acid-fast stain**, culture
  - Species identification with nucleic acid sequencing or MALDI: **predictive of drug susceptibility**

- 56-year-old woman post kidney-pancreas transplant & *N. brasilienses*
- Small lung nodules (white arrows), small right pleural effusion & subcarinal lymphadenopathy (black arrow)

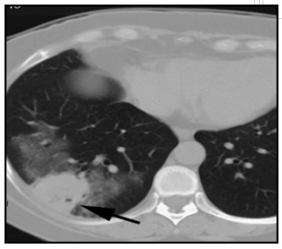


Pulmonary Nocardiosis: Computed Tomography Features at Diagnosis. Blackmon, Kevin; Ravenel, James; Gomez, Juan; Ciolino, Jody; Wray, Dannah. *Journal of Thoracic Imaging*. 26(3):224-229, August 2011. DOI: 10.1097/RTI.0b013e3181f45dd5

7 – Nocardia, Actinomycosis, Rhodococcus, and Melioidosis

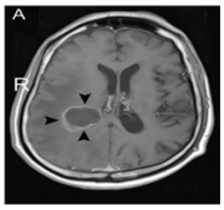
Speaker: David M. Aronoff, MD

- 55-year-old woman with acute myelogenous leukemia & *N. nova*
- Axial CT image without contrast = solitary RLL **mass** with single focus of **cavitation** (arrow) & surrounding **ground-glass opacity**



Pulmonary Nocardiosis: Computed Tomography Features at Diagnosis. Blackmon, Kevin; Ravenel, James; Gomez, Juan; Ciolino, Jody; Wray, Dannah. *Journal of Thoracic Imaging*. 26(3):224-229, August 2011. DOI: 10.1097/RTI.0b013e3181f465d5

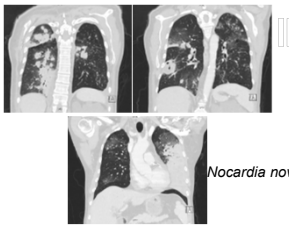
- Right frontoparietal subcortical ring lesion with a central dark signal & bright **ring enhancement** (black arrowheads) in postcontrast T1-weighted image.



Nandhagopal, Ramachandiran, Zakariya Al-Muharrmi, and Abdullah Balkhair. "Nocardia brain abscess." *QJM* 107.12 (2014): 1041-1042.

Case

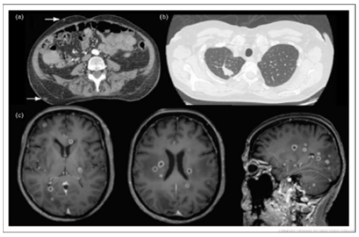
- 60 YO s/p kidney transplant on immunosuppression with 3 week of cough, fevers, dyspnea & malaise
- SARSCoV2 negative
- MRI head negative



Nocardia nova

1. Severe bilateral pneumonia with scattered areas of ground glass attenuation, consolidation, soft tissue nodules & tree-in-bud micronodules throughout
2. L>R pleural effusions & small pericardial effusion

Case



Nocardia cerradoensis

Total body CT & brain MRI of a **solid organ transplant recipient** with disseminated nocardiosis. (A) Sub-cutaneous nodules (white arrow) on CT-scan. (B) Nodule in the R upper lung seen on CT-scan. (C) Multiple round-shaped, contrast-enhanced lesions on gadolinium-enhanced T1-weighted brain MRI.

Lebeaux D, *et al. Current Opinion in Infectious Diseases* 34(6):611-618, December 2021.

Nocardia Treatment

- **Susceptibility testing is a must**
  - Important because of drug resistance
- **TMP/SMX** is mainstay (skin = monotherapy; LZD/TZD alternatives)
- Empiric 2-drug combination therapy:
  - TMP/SMX + one of these:
    - Amikacin, imipenem/meropenem >> ceftriaxone/cefotaxime
    - Linezolid/tedizolid ± imipenem/ceftriaxone/cefotaxime as alternate agents
- Empiric 3-drug combination therapy for CNS (TMP/SMX + IMI + Ami)
- Desensitize for sulfa allergy
- 2-6 weeks induction followed by 6+ months of oral TMP/SMX monotherapy

Restrepo A & Clark NM. *Clinical Transplantation*. 2019;e13509
Margalit I, *et al*. "How do I manage nocardiosis?." *Clinical Microbiology and Infection* (2021).
Traxler RM, *et al. CMR*. 2022

Nocardia Treatment

Antibiotics **2022**, *11*, 612

Table 3. Therapeutic management of nocardiosis according to clinical presentation.

Localization	Empiric Induction Treatment *,‡	Maintenance Oral Therapy ‡	Duration
Primary skin Pulmonary stable	TMP/SMX orally Linezolid orally	TMP/SMXM Minocycline Amoxicillin/clavulanate	6–12 months
Pulmonary moderate/severe	TMP/SMX iv + imipenem OR amikacin TMP/SMX iv + ceftriaxone ± linezolid Linezolid+ ceftriaxone OR imipenem	TMP/SMX Minocycline Amoxicillin/clavulanate	6–12 months
CNS involvement	TMP/SMX iv + imipenem ± amikacin TMP/SMX iv + imipenem + linezolid Linezolid + imipenem Imipenem + amikacin	TMP/SMX	9–12 months
Disseminated (>two organs without CNS involvement)	TMP/SMX iv + imipenem OR amikacin TMP/SMX iv + linezolid + imipenem OR amikacin Imipenem + amikacin	TMP/SMX Minocycline Amoxicillin/clavulanate	6–12 months

TMP/SMX: trimethoprim/sulfamethoxazole; CNS: central nervous system. * Continue multi-drug parenteral therapy for two to six weeks and adjust based on susceptibility test. ‡ Antibiotic dosing: TMP/SMX 15 mg/kg (divided in three to four doses), linezolid 600 mg q12h, imipenem 500 mg q6h, minocycline 100–300 q12h, amikacin 20–30 mg/kg/day, ceftriaxone 2 g q24h.

★ van den Bogaart L & Manuel O. *Antibiotics* (2022)

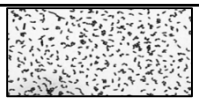
7 – Nocardia, Actinomycosis, Rhodococcus, and Melioidosis

Speaker: David M. Aronoff, MD

Nocardia Buzzwords

- **B**eaded
- **B**ranching
- **B**rain (+ lung)
- **B**actrim

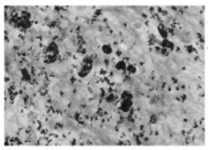
Rhodococcus



- **Clinical findings**:
  - Indolent pneumonia (80%) in **immunocompromised** host
  - **Fever, cough, hemoptysis**, fatigue, subacute, pleuritic CP
  - Nodules, thick-walled **cavities**, infiltrates, effusions possible
  - Extrapulmonary dissemination possible (**skin & brain**)
  - Mimic of TB, NTM, *Aspergillus*, *Nocardia*

Photo: microbe canvas

Rhodococcus



- **Typical patient**:
  - T cell immunosuppressed
    - PLWHA & CD4<100; organ transplant
  - Inhalation or ingestion
  - Farm, soil, manure or horse exposure in some patients
- **Microbiology**: *R. equi* is the most common
  - Gram positive, **aerobe**, **coccobacillary**
  - Colonies can be **salmon pink**
  - **Weakly acid fast**: can be mistaken for *Nocardia* but **no branching**

Image from W.V. Lin *et al. / Clinical Microbiology and Infection* (2019)

Rhodococcus

33 year-old male PLWHA (CD4 = 20) who lived on a cattle & horse farm

Presented to hospital with 1 month of fever, dry cough, 13# weight loss, sweats & anorexia

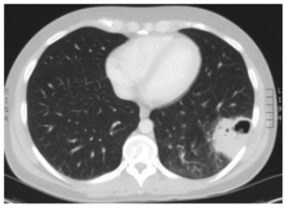


Image from Stewart A., *et al. IDCases.* (2019)

Rhodococcus

- **Diagnosis:**
  - **Culture** followed by 16S rRNA, MALDI-TOF
  - Tissue: gram stain, **necrotizing granulomatous** reaction; microabscess
  - Blood cultures may be positive (>25%)
- **Treatment:**
  - Combination therapy is recommended
  - **Macrolide or fluoroquinolone** in combination with **rifampin** or in combination with 2 of the following: vancomycin, imipenem, linezolid, or an aminoglycoside x 2-3 wks then 2 drugs until clinical response complete (macrolide or FQ + a second agent)

Lin WV, *et al. Clin Micro Infect* (2019), Stewart A., *et al. IDCases.* (2019)
Kotton CN, *Uptodate* (2023)

Rhodococcus Buzzwords

- **Short** Gram positive rod (coccobacillus)
- **Cavitary** pneumonia (hemoptysis)
- **Salmon pink** colonies
- Advanced **HIV/AIDS**
- **Horse** / manure exposure

Case

PREVIEW QUESTION

A 62 yr old sheep rancher from Northern Australia referred hospitalized for refractory pneumonia that failed to respond completely to multiple, prolonged courses of antibiotics over 3 months, leaving him with continued low-grade fever, productive cough & asthenia.

Gram negative rods noted in moderate abundance on sputum Gram stain & in sputum culture. Identification by automated system failed & isolate sent to referral lab.

Question

PREVIEW QUESTION

- Which of the following would have been a likely source of this infection?

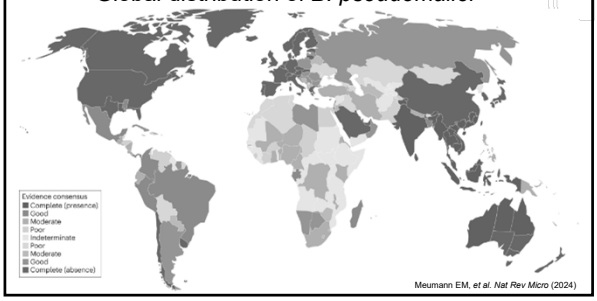
A. Hospital nebulizer while hospitalized in Australia (nosocomial superinfection)
B. Water or soil from his ranch
C. Coughing worker on his ranch
D. Sick sheep on his ranch.

Melioidosis Microbiology & Epidemiology

- Microbiology lab:
  - Facultative intracellular GNR, *Burkholderia pseudomallei*
  - Oxidase positive, non-fermenting GNR
  - Characteristic **bipolar staining** with a "safety pin" appearance
- Melioidosis is highly endemic in Southeast Asia & northern Australia
  - *Esp.* Northeastern Thailand & northern Australia

Chakravorty A, Heath CH. *Australian Journal of General Practice* (2019)
Meumann EM, *et al. Nat Rev Micro* (2024)

Global distribution of *B. pseudomallei*



Meumann EM, *et al. Nat Rev Micro* (2024)

AN ASIDE:

If I Say Non-Fermenting GNR You Think of

- Mfln·lf~ f¡afl#anfi·tv¡ffla
- %jv¡n#fiaj#nf#a·~a¡¡w
- -·fi|uf}lnfiajn«ajva#-#«fln·lf~a}hv
- Q#n¡f#f«uf~f¡afl#-a}#f«uv}a
- Q«uv¡tf~f¡afl«a·jv-fiv}fl

Melioidosis Clinical Syndromes

- **Clinical findings:**
  - Acute infection can present with **pneumonia, bacteremia & septic shock**
  - Metastatic abscesses: skin ulcers or abscesses more common than bone, spleen, brain, prostate
  - Chronic infection presents like TB (cough, hemoptysis, night sweats)
  - Can become latent & reactivate like TB (rare)

Wiersinga WJ, *et al. Nat Rev Dis Primers* (2018); Kottarathil M, *et al. Indian J Tuberculosis* (2024)

7 – Nocardia, Actinomycosis, Rhodococcus, and Melioidosis

Speaker: David M. Aronoff, MD

Melioidosis Clinical Syndromes

- **Risk Factors:**
  - Infection occurs from exposure to contaminated soil or water by percutaneous inoculation, **inhalation**, or ingestion
  - Risk factors = **diabetes**, **alcohol use disorder**, chronic renal & lung disease, corticosteroid therapy, malignancy, & thalassemia
  - Acute infection more common than chronic infection

Chakravorty A, Heath CH. *Australian Journal of General Practice* (2019)
https://www.cdc.gov/melioidosis/health-care-workers/

Melioidosis in the US

- In the United States
  - Rare: about 10-15 cases a year & usually from exposure elsewhere
  - 4 recent cases in the US linked to imported aromatherapy products & also 3 recent autochthonous cases with exposure in the southern US

Gee JE, *et al. NEJM* (2022) Petras JK, *et al. NEJM* (2023)

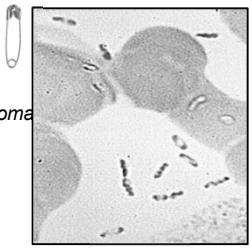
Melioidosis in the US

- 2 unrelated people living in the **Gulf Coast region** of the southern US became sick with melioidosis two years apart—in 2020 & 2022
- Three samples from soil & puddle water in 2022 tested positive at CDC for *B. pseudomallei*

https://www.cdc.gov/media/releases/2022/p0727-Melioidosis.html

Bacteria with "safety pin" appearance

- *Yersinia pestis*
- *Vibrio parahemolyticus*
- *Burkholderia mallei & pseudoma*
- *Haemophilus ducreyi*
- *Klebsiella granulomatis* (granuloma inguinale)
- *Pasteurella multocida*



Y. pestis

Melioidosis Diagnosis & Rx

- **Diagnosis: Culture on Ashdown Medium**
  - **Alert the lab you are concerned about this pathogen!**
  - Indirect immunofluorescence, lateral flow immunoassays & nucleic acid amplification tests have been developed; none have sufficient sensitivity to replace culture assays
- **Treatment: Treat all cases**
  - Mild disease: initial intensive **IV therapy for two weeks** followed by eradication therapy **orally for 3-6 months**
  - *B. pseudomallei* **resistant** to penicillin, ampicillin, 1st/2nd generation cephalosporins, polymyxin, aminoglycosides
  - TMP/SMX for **postexposure prophylaxis**
  - **Meropenem or ceftazidime** then **tmp/smx for 3-6 months**

Wiersinga WJ, *et al. Nat Rev Dis Primers* (2018); Hemarajata P, *et al. JCM* (2016)
Peacock SJ, *et al. EID* (2008), Meumann EM, *et al. Nat Rev Micro* (2024)

For the most up-to-date recommendations by the International Melioidosis Society: http://www.melioidosis.info

Melioidosis: **Buzzwords**

- **SE Asia** (Thailand)/Australia
- **Soil/water exposure** (inhalation/inoculation/rainy season; post-tsunami injury)
- Pneumonia + **severe sepsis**/shock or multiple abscesses
- Can be **years after exposure** (not usually)
- **Safety pins** on methylene blue or Wright's stain; Gram negative rods
- **Ashdown media**

Le Tohic, s., *et al. European Journal of Clinical Microbiology & Infectious Diseases* (2019)

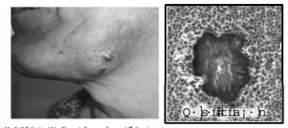
Glanders

- Caused by *Burkholderia mallei* & is rare in humans
- Requires close contact w/ infected animals (horses, donkeys, mules)
- Bacteria enter through the eyes, nose, mouth, or skin wounds
- *B. mallei* is an obligate mammalian pathogen & must cause the disease to be transmitted between hosts
- Africa, Asia, Middle East, Central America, South America
- Similar presentation to melioidosis

Smith ME, Gossman WG. Glanders And Melioidosis. [Updated 2017 Oct 6]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2018 Jan.

Actinomyces Take-Aways

- Microbiology lab:
  - Gram-positive, **anaerobic**, non–spore-forming bacteria
  - Part of the normal mucosal flora of the oral, gastrointestinal, respiratory, & genital tracts
  - *Actinomyces israelii* most common species
  - Produce **sulfur granules**
- Typical patient:
  - Recent dental procedures
  - Aspiration (thoracic)
  - IUD (pelvic)

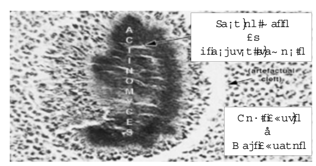


Actinomyces Take-Aways

- Clinical findings:
  - Oral-cervicofacial more common>abdominal & thoracic infection
  - **Lumpy jaw**
  - Slow growing mass, **ignores tissue planes**, can pus-out (necessitate), form sinuses, fistulas
  - DDx: Cancer, TB, *Nocardia*
- Diagnosis:
  - Culture, histopathology (sulfur granules)
- Treatment:
  - **Penicillins** (PCN, ampicillin) x weeks to months

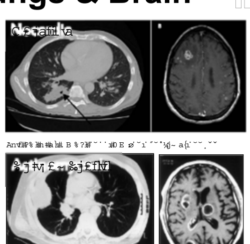
Actinomyces: **Buzzwords**

- **Sulfur granules**
- **Dental work**
- **IUD**
- **Erosive mass**
- **Filamentous anaerobe**



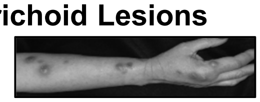
Lesions in the **Lungs & Brain**

- Actinomycosis
- *Aspergillus, Zygomycetes*
- *Blastomyces, Coccidioides, Cryptococcus, Histoplasma*
- *Mycobacterium tuberculosis*
- *Nocardia*
- Infectious emboli (SBE)
- Lemierre syndrome (*Fusobacterium*)
- *Toxoplasma*
- Tumors



Causes of Sporotrichoid Lesions

Nodular lymphangitis



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Tirado-Sanchez, *et al. J.Fungi*; 2018,4,56;doi:10.3390/jof4020056, Photo: eScholarship

7 – Nocardia, Actinomycosis, Rhodococcus, and Melioidosis

Speaker: David M. Aronoff, MD

08

Acute Hepatitis

Dr. David Thomas

8 – Acute Hepatitis

Speaker: David Thomas, MD

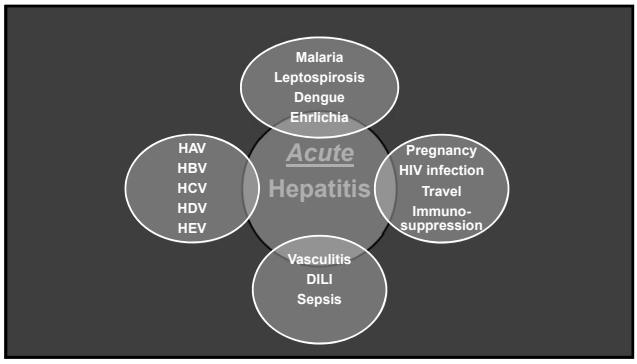
Acute Hepatitis

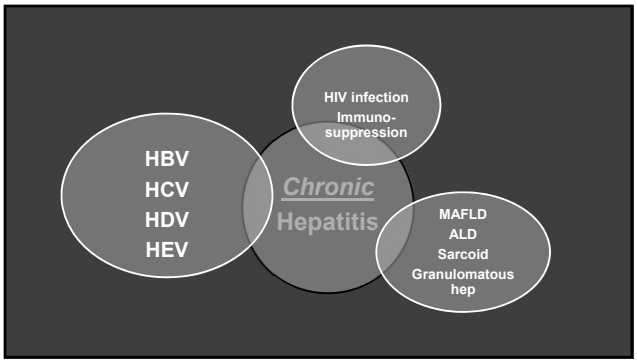
David Thomas, MD
Stanhope Bayne Jones Professor of Medicine
Johns Hopkins University

7/1/2024

Disclosures of Financial Relationships with Relevant Commercial Interests

- Data and Safety Monitoring Board: Merck
- Advisory Board: Merck, Excision Bio





18 year-old with jaundice

- 18 y/o presents with 5d of headache, fever, diarrhea, vomiting, chest pain
- PMH – Open fractures of all R metatarsals with pins x 3mo
- SH – home tattoos; lives with parents and pregnant girlfriend; dogs and rats; swam in freshwater dam 1 wk before symptom onset; cuts grass; multiple tick bites; Maryland

Courtesy E Prochaska, MD

18 year-old with jaundice, con't

- T 39.4; BP 118/62 (then on pressors); P 91; 97% RA
- Icteric, non-injected, no murmurs
- Diffuse petechial rash; purple macules on ankle
- WBC 11,740 (92.4 P, 0.8B, 2% L); Hb 14.2; Plt 47,000
- Creatinine 0.9-3.4; CRP 10.1; Tbili 4.1 (direct 3.7); ALT/AST 26/53; CK 887
- HIV Ab neg; SARS-CoV-2 PCR neg; Monospot - neg

Courtesy E Prochaska, MD

18 year old with jaundice

The cause of his illness is:

A. **Acute hepatitis A**
B. **Babesia microti**
C. **Tularemia**
D. **Leptospira icterohaemorrhagiae**
E. **HSV**

Courtesy E Prochaska, MD

Leptospirosis

1. **Exposure to fresh water (eg rafting in Hawaii/Costa Rico or triathlon) OR rats (Baltimore)**

Leptospirosis

2. **Bilirubin fold change > ALT**

Leptospirosis

3. **Biphasic possible and systemic findings** **(conjunctival suffusion, kidney, skin, muscle, lungs, liver)**

ddx: liver (ALT) and muscle (CPK): **lepto, flu, adeno, EBV, HIV, malaria, Rickettsia/Ehrlichiosis, tularemia, TSS, coxsackie, vasculitis**

Leptospirosis

4. **Diagnosis:**
   - **PCR most useful (urine pos longer)**
   - **serology late**

PREVIEW QUESTION

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.**

8 – Acute Hepatitis

Speaker: David Thomas, MD

Acute hepatitis in Uganda PREVIEW QUESTION

Which test result is most likely positive?

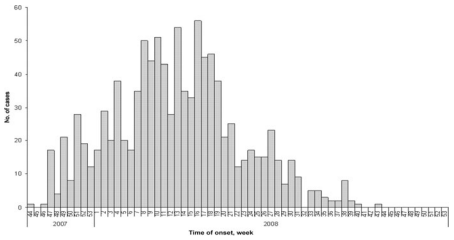
A. Ebola PCR
B. IgM anti-HEV
C. IgM anti-HAV
D. Schistosomiasis "liver" antigen
E. 16S RNA for Rickettsial organism

1. Vaccination works to prevent hepatitis A *up to 14d after* exposure in healthy young adults

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; Al-Shimari BMC Public Health 2023

3. Hepatitis E: Epidemiologic Clues

- –Outbreaks – contaminated water in Asia/Africa
- –Sporadic - undercooked meat (BOAR, deer, etc)
- –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**
- –**Vaccine: not USA (not boards)**

PREVIEW QUESTION

Acute Hepatitis at ID Week

- **42 year old homeless male approaches a group of ID fellows attending ID Week in San Diego**
- **One fellow noticed jaundice and suggested he seek medical testing. With what diagnosis was the fellow most concerned?**

8 – Acute Hepatitis

Speaker: David Thomas, MD

Acute hepatitis at ID week PREVIEW QUESTION

Fellow worried about what?

A. HAV

B. HBV

C. Delta

D. HCV

E. HEV

1. Hepatitis A: Key Epidemiologic Clues – People, Places and Foods

Homelessness and Hepatitis A—San Diego County, 2016–2018

Corey M. Peak, Sarah S. Stous, Jessica M. Healy, Megan G. Hofmeister, Yulin Lin, Sumathi Ramachandran, Monique A. Foster, Annie Kao, and Eric C. McDonald

Morbidity and Mortality Weekly Report (*MMWR*)

Notes from the Field: Increase in Reported Hepatitis A Infections Among Men Who Have Sex with Men — New York City, January–August 2017

1. Hepatitis A: Key Epidemiologic Clues – People, Places and Foods

Multistate Outbreak of Hepatitis A Linked to Frozen Strawberries - Current Case Count Map and Table

Case Count as of December 13, 2016

State	Case Count
Arkansas	1
California	1
Maryland	12
New York	5
North Carolina	4
Oregon	1
Virginia	109
West Virginia	7
Wisconsin	3
Grand Total	143

Outbreak of hepatitis A in Hawaii linked to raw scallops

Outbreak

The Hawaii Department of Health (HDOH) is investigating an outbreak of hepatitis A in its state. For the latest case count and investigation findings, visit the HDOH outbreak investigation website. On August 15, 2016, HDOH identified raw scallops served at Genki Sushi restaurants on the islands of Oahu and Kauai as a likely source of the ongoing outbreak.

CDC and the U.S. Food and Drug Administration (FDA) are assisting HDOH with its investigation. At this time, CDC is not aware of any hepatitis A virus infections in other states linked to the Hawaii outbreak. CDC continues to monitor for illnesses in other states.

2. Hepatitis A: Key Clinical Clues

- **There are outbreaks all over the world**
- **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: All children 1-18 yrs receive hepatitis A vaccine (since 2006)**
  - **HIV, HCV or HBV positive persons/chronic liver disease/homeless/MSM/PWID/Travelers/adoptee exposure**
- ***Post-exposure:*** **vaccinate or possibly IG if**
  - **> 40 years or immunosuppressed then IG is 'preferred'**

Victor NEJM 2007; MMWR July 3 2020; MMWR October 19, 2007 / 56(41);1080-1084

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 (antibodies for routine screen)**

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, modest ALT, and especially low platelets**

8 – Acute Hepatitis

Speaker: David Thomas, MD

Hepatitis with bacterial infections

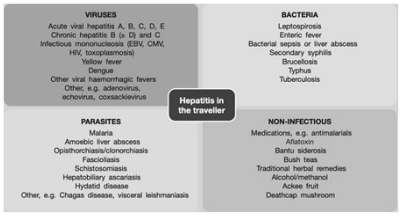
2. Coxiella burnetti and spirochetes (syphilis and lepto) also in ddx with liver, lung, renal, skin, CNS disease but tend to be cholestatic vs Rickettsia/Ehrlichia

Hepatitis with bacterial infections

3. Hepatitis F or G are always WRONG answers

Hepatitis with travel to developing country

There is a broad differential



Jones Medicine 2017

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

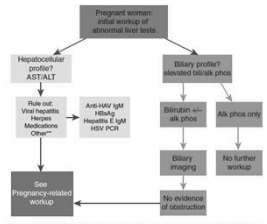


Figure 1. Workup of abnormal liver test in pregnant woman. **Other differential diagnosis to consider if clinically appropriate: AIH, Wilson disease.

ACOG 2016

8 – Acute Hepatitis

Speaker: David Thomas, MD

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 Summary

- **Acute A: vaccine effective**
- **HEV: chronic in transplant and/or boar**
- **HIV: acute HCV in MSM**
- **Low plt: Ehrlichial or rickettsial**
- **Find the lepto case (jaundice>hepatitis)**

Thanks and good luck on the test!

Questions:

Dave Thomas

–dthomas@jhmi.edu

8 – Acute Hepatitis

Speaker: David Thomas, MD

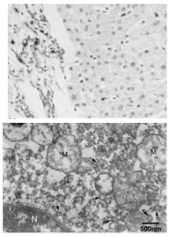
BREAK
SLIDES BEYOND THIS ARE FOR THE PRESENTER'S RECORDS; NOT TO BE DISTRIBUTED OR SHOWN

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)
≥0.8$\times 10^9$/L	654 (83.0)
<0.8$\times 10^9$/L	134 (17.0)
Platelets, $\times 10^9$/L	181 (147-221)
≥100$\times 10^9$/L	761 (96.6)
<100$\times 10^9$/L	27 (3.4)
Hemoglobin, g/L	138.0 (127.0-151.0)
International normalized ratio	1.02 (0.97-1.09)
Albumin, g/L	41.4 (38.3-43.8)
Alanine aminotransferase, U/L	21.1 (15.0-33.0)
Aspartate aminotransferase, U/L	25.0 (19.6-33.0)

Hao Am J Gastro 2020



Wang J Hepatol 2020

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

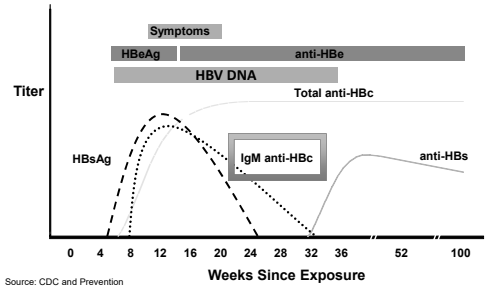
- 27 year old male presents with fatigue and dark urine. Hx recent sexual exposures with other men.
- No fever, vitals normal. Mild icteric. ALT 1945 IU/ml; AST 1239 IU/ml; TB 4.2 mg/dl; WBC 3.2k nl diff.
- Total HAV pos; HAV IgM neg; HCV RNA neg; IgM anti-HBc pos; HBsAg pos; RPR neg; HIV 4th gen neg
- 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



Source: CDC and Prevention

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

Acute hepatitis in HIV

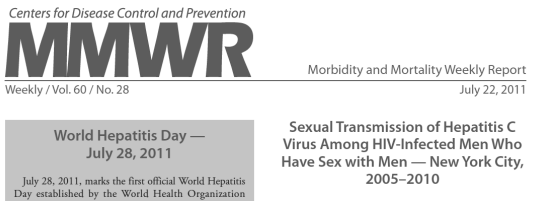
46 y/o HIV pos male, CD4+ lymphocyte 235/ml^3, HIV RNA undetect; HBsAg pos; no symptoms on TDF/FTC/RAL. Liver enzymes increased from ALT of 46 to 1041 IU/L. TB was 2.3. He has a long history of various ART regimens. He is sexually active with other men.

Acute hepatitis in HIV

Which of the following is the most likely cause of hepatitis:

A. toxicity from the RAL
B. acute HCV infection
C. IRIS
D. resistant HBV
E. HDV

Recognize acute HCV in HIV POS MSM


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

8 – Acute Hepatitis

Speaker: David Thomas, MD

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

09

Zoonoses

Dr. David Aronoff

9 – Zoonoses
Speaker: David M. Aronoff, MD

Zoonoses

David M. Aronoff, MD, FIDSA, FAAM
John B. Hickam Professor of Medicine
Chair, Department of Medicine
Indiana University School of Medicine
aronoff@iu.edu

7/18/2024

- **Disclosures of Financial Relationships with Relevant Commercial Interests**

  - None

Zoonoses: Important!

- Most recent epidemics & pandemics have been caused by zoonotic pathogens
- Emerging coronaviruses, hemorrhagic fever viruses, arboviruses, influenza A viruses & bacteria have caused recent major zoonotic epidemics

Case

A 38-year-old healthy man in western Canada, presented with 5-days of fever, chills, night sweats, diffuse myalgias, & arthralgias. Months earlier, he had killed a black bear & froze meat. 2 days before symptom onset, he & 4 household members ingested bear meat that had been thawed & cooked as meatballs. Three other household members also fell ill in the same time frame, but with milder symptoms. The meatballs had not been thoroughly cooked. 2 days after ingestion, the patient noted vague abdominal discomfort & nausea. 8 days after ingestion, he reported intense fever & chills, mild headache, severe prostration, myalgia in proximal limb muscles, transient abdominal pain, & pink-tinged urine. He denied vomiting, diarrhea, chest pain, shortness of breath, adenopathy, or rash. The fever lasted for 9 days total primarily at night.

Case

P/E: VS & exam findings normal

Labs: mildly increased WBC count ($10.4*10^9$/L), with hypereosinophilia ($3.3*10^9$/L; normal <0.50). AST = 61U/L (normal 15 to 45), creatine kinase (762 U/L; normal 55 to 170), & CRP (64.6 mg/L; normal <10).

Bilirubin, creatinine, & INR normal.

HIV screening & blood cultures at 5 days of incubation negative.

Trichinella serology on a sample 1 week after ingestion of bear meat was **negative**.

Question #1

Which of the following is the most likely infectious diagnosis?

A. Acute trichinellosis from ingestion of viable *Trichinella* larvae
B. *Coxiella burnetii* infection (Q fever) from ingesting raw bear meat
C. Bacteremic *Streptobacillus moniliformis* from inadvertent cutaneous inoculation while preparing bear meat
D. Acute *Necator americanus* infection

Case Continued

Given the clinical suspicion for *Trichinella* infection, empirical treatment with mebendazole (400 mg po TID) was initiated on day 12 of illness, for a total of 13 days

The diagnosis of acute trichinellosis was subsequently confirmed with repeat serological testing performed 6 weeks after having consumed the bear meat

Remember *Trichinella* organisms not killed by freezing or drying/curing. Cooking thoroughly is important

Table 1. Zoonotic pathogens causing recent epidemics

Zoonotic pathogen	Reservoir host/Vector	Disease (key syndromes)	Major recent epidemics
SARS-CoV	Likely bats	SARS (pneumonia)	Global (2002–2003)
MERS-CoV	Dromedary camels	MERS (pneumonia)	Saudi Arabia, South Korea (2012–2019)
SARS-CoV-2	Unknown	COVID-19 (pneumonia)	Global (2020–present)
Ebola virus	Likely bats	Ebola virus disease (haemorrhagic fever)	West Africa (2013–2016) DRC (2018–2020)
Lassa virus	Multimammate rat	Lassa fever (haemorrhagic fever)	Nigeria (2018)
Rift valley fever virus	*Aedes* and *Culex* mosquitoes	Rift valley fever (haemorrhagic fever)	East Africa (2006–2007)
Zika virus	*Aedes* mosquitoes	Zika virus disease (arthralgia/myalgia, rash)	Brazil, Americas (2015–2016)
Chikungunya virus	*Aedes* mosquitoes	Chikungunya fever (arthralgia/myalgia, rash)	Indian Ocean Islands, India (2004–2007)
Dengue virus	*Aedes* mosquitoes	Dengue fever (arthralgia/myalgia, rash, haemorrhage)	Americas (2010)
West Nile virus	Birds/*Culex* mosquitoes	West Nile disease (meningitis/encephalitis, paralysis)	United States (2002)
Influenza A viruses	Waterfowl, Poultry, Pigs	Influenza (pneumonia)	Global (2009)
Yersinia pestis	Rats/Fleas	Plague (sepsis, pneumonia)	Madagascar (2017)
Brucella spp.	Cattle, sheep, goats	Brucellosis (undulant fever, endocarditis)	China (2020)
Coxiella burnetii	Cattle, sheep, goats	Q fever (pneumonia, hepatitis)	Netherlands (2007)

THERE ARE MANY

TABLE 1. Bacterial zoonoses by transmission mechanism and causative agent(s)

Bacterial zoonoses transmitted by direct contact with animals or infected animal materials	Causative agent(s)
Anthrax	*Bacillus anthracis*
Brucellosis	*Brucella* spp.
Cat scratch disease	*Bartonella* spp.
Erysipelothrix infections	*Erysipelothrix rhusiopathiae*
Glanders and melioidosis	*Burkholderia mallei* and *Burkholderia pseudomallei*
Leptospirosis	*Leptospira interrogans* spp.
Mycobacterioses	*Mycobacteria* spp.
Q fever	*Coxiella burnetii*
Bacterial zoonoses transmitted principally by animal bites or scratches	
Pasteurellosis	*Pasteurella multocida* and other spp.
Capnocytophaga infections	*Capnocytophaga canimorsus*
Cat scratch disease	*Bartonella henselae*
Rat bite fever	*Spirillum minus* and *Streptobacillus moniliformis*
Vector-borne bacterial zoonoses	
Lyme borreliosis	*Borrelia burgdorferi* sensu lato (incl. *Borrelia garinii*, *Borrelia afzelii*)
Tick- and louse-borne relapsing fever borreliosis	*Borrelia recurrentis*, *Borrelia turicatae*, *Borrelia hemsii*, 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***
- *Yersinia pestis*
- *Francisella tularensis*

BIRDS
- ***Chlamydophila psitacci***
- *Chlamydia*

FARM ANIMALS (sheep, cows, horses, goats, chicken, *etc*)
- ***Bacillus anthracis***
- ***Brucella***
- ***Coxiella burnetii***
- ***Campylobacter***
- ***E. coli* (Shiga toxin+)**
- ***Erysipelothrix rhusiopathiae***
- ***Hepatitis E***
- ***Leptospira***
- ***Parapoxviruses (orf, etc)***
- ***Rhodococcus***
- ***Salmonella***
- ***Trichinella***

FISH
- ***Erysipelothrix rhusiopathiae***
- ***Mycobacterium marinum***
- ***Streptococcus iniae***
- *Vibrio*

DOGS
- ***Pasteurella multocida***
- ***Capnocytophaga canimorsus***
- *Campylobacter*
- *Leptospira*
- *Staph intermedius/pseudintermedius*

LEECHES
- ***Aeromonas hydrophila***

RABBITS
- ***Francisella tularensis***

REPTILES
- ***Salmonella***

BEARS
- ***Trichinella spiralis***

RODENTS
- ***Leptospira***
- ***Monkeypox***
- ***Salmonella***
- ***Spirillum minus***
- ***Streptobacillus moniliformis***
- ***Yersinia pestis***

CAMELS
- **MERS-CoV**

BATS
- ***Rabies***
- ***Nipah virus***

Zoonoses: Various Routes of Infection

- **Direct contact with animal or animal tissue**
  - Cat scratch disease, anthrax, tularemia, brucellosis
- **Contact with insect vector**
  - Tularemia, plague
- **Intact skin contact with animal urine**
  - Leptospirosis
- **Ingestion of animal product**
  - Brucellosis, hepatitis E
- **Inhalation of animal product**
  - Q Fever

Case

PREVIEW QUESTION

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

PREVIEW QUESTION

Most likely dx:

A.Bartonella henselae
B.Treponema pallidum
C.Haemophilus ducreyi
D.Francisella tularensis
E.Klebsiella (Calymmatobacterium) granulomatis

Purulent Inguinal Node

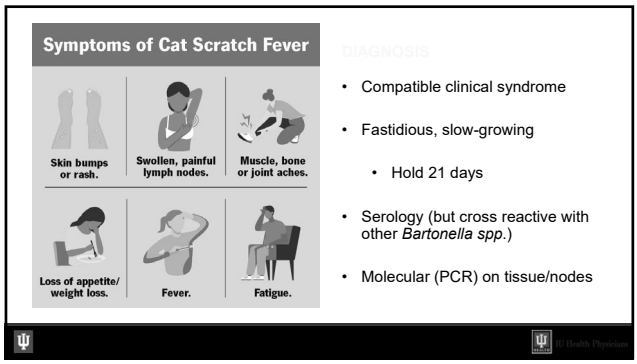
- *Bartonella henselae*: young cats
  - **Stellate abscess** on bx. **Warthin Starry** stain positive early
  - Dx: serology, PCR, or DFA on pus
- Tick borne tularemia ("glandular"): this case *could be* tularemia
  - Exposure to wild animals or their ticks
  - Gram stain, routine culture negative
  - Patient should be **systemically ill** (fevers, chills, malaise common)
  - **Uncommon**: 100-200 cases per year in the USA
- Chancroid: painful genital ulcer with adenopathy (can be purulent)
- No suppurative lymph nodes in syphilis or granuloma inguinale (*Klebsiella granulomatis*) (painless ulcers)

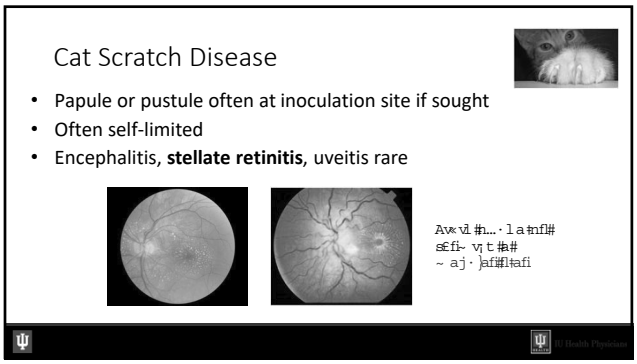
Purulent Inguinal Node (continued)

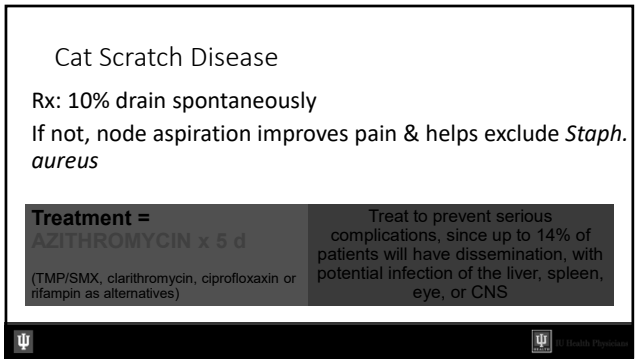
- *Staphylococcus aureus*. Gram stain of pus & culture positive. Distal lesion may be present.
- Lymphogranuloma venereum (LGV)-
  - Sexually transmitted (no history in this case)
  - *Chlamydia trachomatis* L1-L3: genital lesion usually inapparent
  - Painful inguinal &/or femoral lymphadenopathy. "Groove sign"
  - Can form "Stellate abscesses" on bx
  - (+) Nucleic acid amplification test on urine, rectal swab, or wound

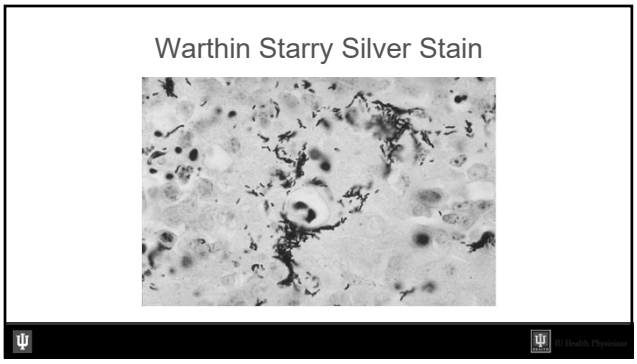
Cat Scratch Disease

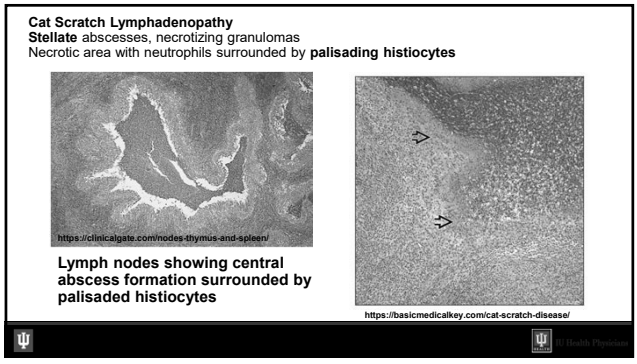
- *B. henselae* causes most cases
- >13,000 cases in the USA per year[1]
- 80% <21 yrs old
- Clinical findings:
  - Acute suppurative lymphadenitis proximal to bite, scratch, lick of young cat
  - Fever, headache, poor appetite, & exhaustion
  - Cats have chronic bacteremia but seem healthy
- Cat fleas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

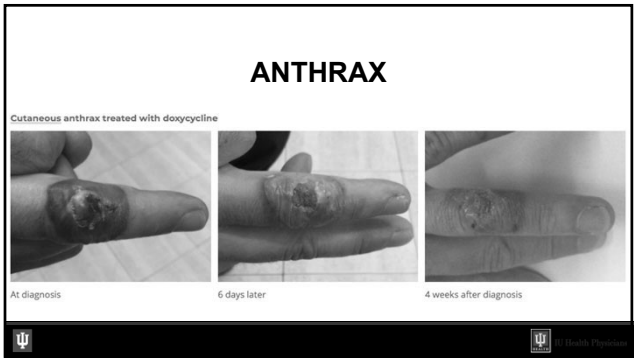






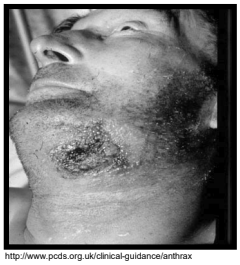






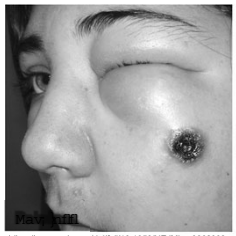
ANTHRAX

- 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 (alert the lab!)
- RX: Penicillin but "weaponized" strains resistant to multiple antibiotics
- Inhalation (**5%**), ingestion (<1%)
- Anthrax rare in USA



http://www.pcds.org.uk/clinical-guidance/anthrax

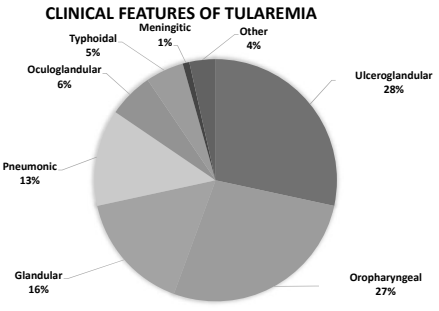
Edema
Vesicles
Necrotic ulcer

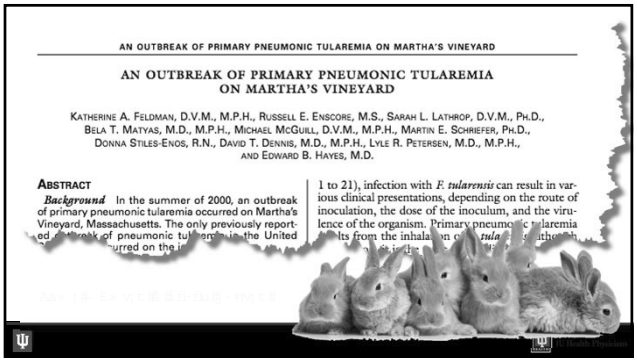


https://www.nejm.org/doi/full/10.1056/NEJMicm0802093

TULAREMIA

- Highly infectious gram-negative **coccobacillus** *Francisella tularensis*
- Vectors = **Ticks** (*Dermacentor variabilis* > *Amblyomma americanum*) & **Deerflies**
- Direct inoculation = rabbits, squirrels, muskrats, beavers, cats (bites)
- Hunters **skinning animals** (old days); farmers, veterinarians
- Red tender local lymph node inoculation site may form ulcer
- **Ulceroglandular** is the most common manifestation
- Risk of bioweaponization





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 States occurred on the

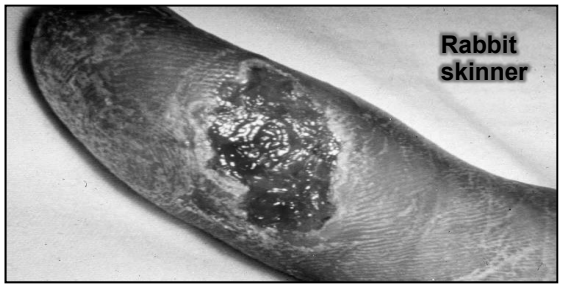
1 to 21), infection with *F. tularensis* can result in various clinical presentations, depending on the route of inoculation, the dose of the inoculum, and the virulence of the organism. Primary pneumonic tularemia results from the inhalation of

TULAREMIA

- Incubation period: 3-5 days but up to 3 weeks
- DX: Serology; PCR
- Culture of *F. tularensis* is lab hazard. Notify the lab!
- Neg routine culture, needs chocolate agar or BCYE (like *Legionella*)
- RX: **gentamicin** (or streptomycin), FQ, **doxycycline**
- Prophylaxis (bioterrorism) doxycycline

Maurin & Gyuranecz. *Lancet* (2016)
Nelson CA, *et al. CID* (2024)

BCYE – buffered charcoal yeast extract



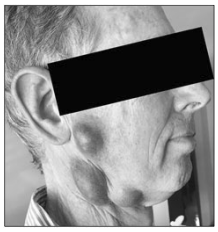
Glandular Tularemia

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



August, 2023

SUPPLEMENT
Volume 78, Issue Supplement_1, 15 February 2024
Tularemia: Update on Treatment and Clinical Findings

Volume 78, Issue Supplement_1
15 February 2024

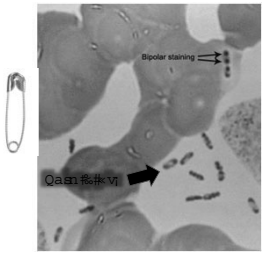
PLAGUE

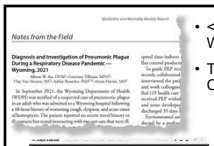
PLAGUE

- *Yersinia pestis*
- Exists in the USA
  - Rodent **flea bite**
  - **Prairie dogs, cats (outdoor/indoor)**
- Fever, nausea & swollen, painful lymph nodes
- Sepsis, pneumonia-hematogenous or aerosol in crowded conditions

PLAGUE

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



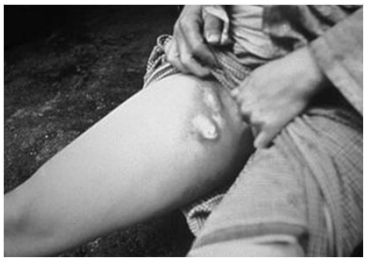


- <10 cases of human plague per year in USA, mostly rural West
- Typically, in northern New Mexico, northern Arizona, southern Colorado, California, southern Oregon & western Nevada
  - Humans usually exposed from the **bites of fleas** carrying *Y. pestis*
  - **Household pets can get infected** if they hunt rodents infected with plague or are bitten by an infected flea
  - Pets can transfer the infection to humans via tissue or bodily fluids (*e.g.*, respiratory droplets from cough or sneezes) or can carry home fleas that in turn bite humans

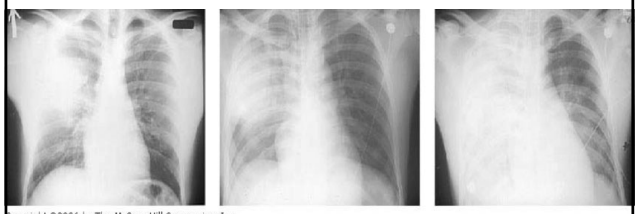
Plague Map USA

1 dot placed in state of residence for each reported plague case

1970-2020



Wikipedia image



Pneumonic form: Rapid Progression of Pneumonic Plague on CXR over 13 Hours

Question #3

- 28 yr old male presents with temp 39°C, 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

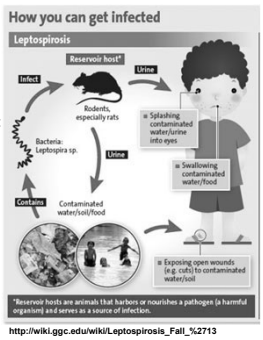
O · nfl‡v€ ¡ #î °

Most likely diagnosis:

A. Malaria
B. Dengue
C. Ehrlichiosis
D. Leptospirosis
E. Zika

LEPTOSPIROSIS

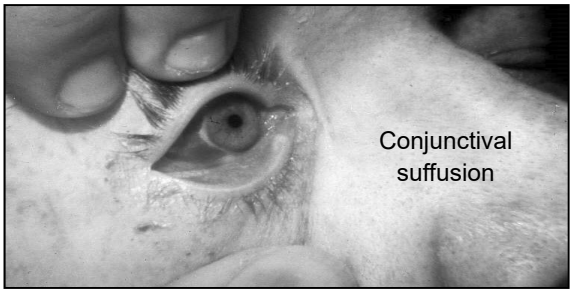
- Spirochetes excreted in urine of infected host & able to survive in wet environment
- Exposed intact skin to animal urine in water: veterinarians, farmers, loggers, triathletes, white water rafting, trapping
- Urine from cows, pigs, dogs, raccoons, rats, mice.
  - Summer & early Fall



http://wiki.ggc.edu/wiki/Leptospirosis_Fall_%2713

LEPTOSPIROSIS

- Fever, myalgia, headache (aseptic meningitis late in course)
- Conjunctival suffusion, +/- rash
- In severe cases: jaundice (Weil syndrome), azotemia, pulm. hemorrhage
  - Jaundice: *bilirubin is high out of proportion to transaminase elevation*
- Lab: serology by agglutination test, culture urine in Fletcher's medium
  - PCR & sequencing emerging
- Rx: **doxycycline** for outpatients, IV penicillin for inpatients
  - Jarisch-Herxheimer in first 2 hr



Question #4

A 41 year old car salesperson from Baltimore was admitted for a febrile illness & found to have *Brucella melitensis* in their blood culture. They 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, they had bought some lamb & beef at a farmer's market outside Baltimore.

Question #4

The most likely source of the 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

- Brucellosis is primarily transmitted through **direct contact** with infected animals or their bodily fluids, including vaginal discharges, aborted materials & semen
- Brucellosis can also be transmitted through the **ingestion** of raw or unpasteurized dairy products from infected animals, including milk & cheese (unpasteurized)
- Those who work closely with livestock, such as farmers, veterinarians & livestock handlers, are at a heightened risk

Qureshi KA, *et al. Ann Med* (2023)

BRUCELLOSIS

- An illness characterized by acute or insidious onset of fever & one or more of the following: fever, night sweats, arthralgia, headache, fatigue, anorexia, myalgia, weight loss, arthritis/spondylitis, meningitis, or focal organ involvement (endocarditis, orchitis/epididymitis, hepatomegaly, splenomegaly).
- Nodes, liver, spleen may be enlarged
- Rare in the US, with 80–120 cases reported annually; most of these are associated with *Brucella* exposures abroad

Animal Sources of *Brucella*

DOGS	CATTLE	SHEEP & GOATS
• *Brucella canis*	• *Brucella abortis*	• *Brucella melitensis*
SHEEP	**PIGS**	**RATS**
• *Brucella ovis*	• *Brucella suis*	• *Brucella neotomae*

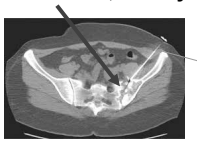
Qureshi KA, *et al. Ann Med* (2023)

BRUCELLOSIS

Later onset lesions in bone, liver

Epididymo-orchitis[1], endocarditis

sacroiliitis, tenosynovitis, meningitis



Biopsy needle

Malodorous perspiration

BRUCELLOSIS (con't)

- WBC normal or low, anemia, plt can be low
- DX: Bone marrow/blood/tissue culture, serology, PCR
  - ***LET THE LAB KNOW YOU ARE WORRIED ABOUT BRUCELLA*** *(lab safety issue!)*
- RX: Doxy plus rifampin or strep/gent
  - TMP-SMX in pregnant or young children

Qureshi KA, *et al. Ann Med* (2023)

Question #5

This common cause of acute hepatitis is acquired via fecal-oral transmission or from undercooked meats, especially pig/wild boar. It is particularly severe in pregnant patients, causing stillbirths & maternal mortality.

A. Epstein Barr virus
B. Cytomegalovirus
C. Hepatitis E virus
D. Hepatitis A virus

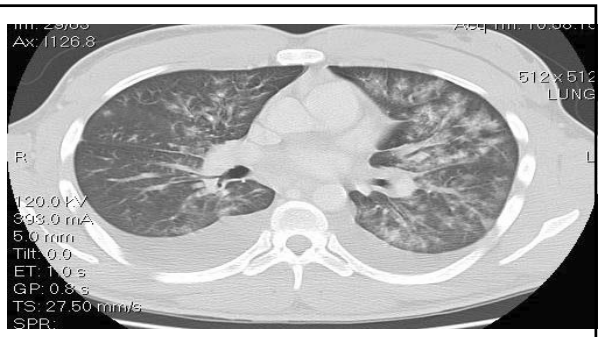
Inhalation of animal products

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 102ºF
- 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 #6

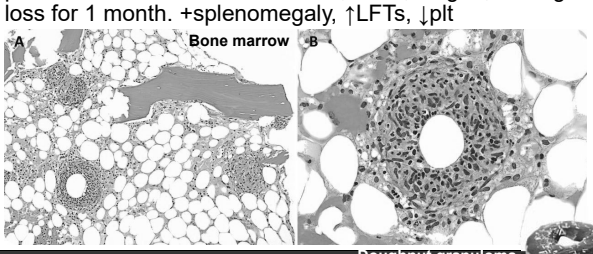
Which of the following is the most likely diagnosis?

A. Brucellosis
B. Anthrax
C. Leptospirosis
D. Q fever
E. Visceral leishmaniasis

Q FEVER

- *Coxiella burnetii*: tiny cocco baccilus
  - Infects cows, sheep, goats, cats, etc.
- Spores survive in straw, manure, meat, *parturient tissue* for months.
  - Aerosol, ingest raw milk
- Acute pneumonia (in half cases), fever, headache, hepatosplenomegaly
- **Chronic endocarditis** on native or prosthetic valves
- **Granulomatous hepatitis**
  - **Doughnut granulomas**
- DX: serology, valve PCR; specific tissue stain; hard to culture
- RX: acute: Doxycycline or levofloxacin or azithromycin
- Chronic: doxycycline plus hydroxychloroquine

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



Grant Herndon, and Heesun J. Rogers *Blood* 2013;122:3099

Doughnut granuloma

The End

Thank you!

aronoff@iu.edu

@DMAronoff (Twitter, Bluesky)
david.aronoff (Insta, Threads)

10

Chronic Hepatitis

Dr. David Thomas

10 – Chronic Hepatitis

Speaker: David Thomas, MD

IDBR INFECTIOUS DISEASE BOARD REVIEW AUGUST 17-21, 2024

Chronic Hepatitis

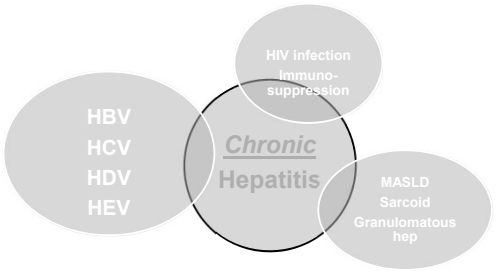
David Thomas, MD
Stanhope Bayne Jones Professor of Medicine
Johns Hopkins University

7/1/2024

IDBR INFECTIOUS DISEASE BOARD REVIEW AUGUST 17-21, 2024

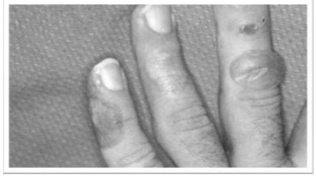
Disclosures of Financial Relationships with Relevant Commercial Interests

- Data and Safety Monitoring Board: Merck
- Advisory Board: Merck, Excision Bio



Case: Hepatitis C and a rash PREVIEW QUESTION

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

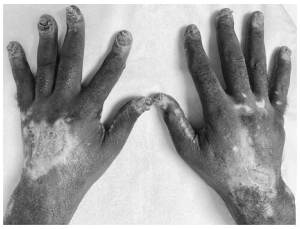
Question: HCV with a rash PREVIEW QUESTION

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

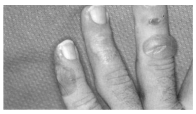
Tejesh S. Patel, M.D., and Evgeniya Teterina Mohammed, M.D.



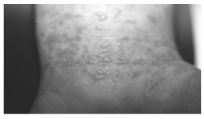
June 10, 2021
N Engl J Med 2021; 384:e86

Compare

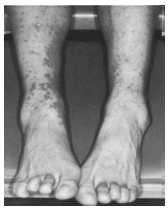
Porphyria cutanea tarda



Lichen planus



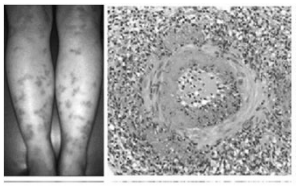
Cryoglobulin vasculitis



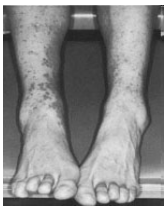
blogspot.com; OConnor Mayo Clin Proc 1998

Compare

HBV: Polyarteritis nodosa



HCV: Cryoglobulin vasculitis



blogspot.com; OConnor Mayo Clin Proc 1998; Chen Rheum 2014

Question: What is true regarding testing for HCV antibodies?

A. **Testing indicated only for those with risk**
B. **New 4th generation antibody/ag test sensitive for acute infection**
C. **Indicated for pregnant women**
D. **Repeat after cure if new exposures**
E. **Often falsely negative in persons with HIV**

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 or older.	I, B
One-time HCV testing should be performed for all persons less than 18 years old with activities, exposures, or conditions or circumstances associated with an increased risk of HCV infection (see below).	I, B
Prenatal HCV testing as part of routine prenatal care is recommended with each pregnancy.	I, B
Periodic repeat HCV testing should be offered to all persons with activities, 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, for HIV-infected men who have unprotected sex with men, and men who have sex with men taking pre-exposure prophylaxis (PrEP).	IIa, C

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 routine screen by primary. RNA also pos; moderate ETOH; otherwise well. CMP and CBC were normal.

Question: 54 y/o with HCV antibodies and RNA

Which of is most necessary before treatment:

A. **HCV genotype**
B. **HCV 1a resistance test**
C. **Elastography**
D. **HBsAg**
E. **Repeat in 6 month to be sure chronic**

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

Staging is needed to assess for cirrhosis (but not urgent)

Accepted staging methods	Not for routine staging
1. Liver biopsy	1. Viral load
2. Blood markers	2. HCV genotype
3. Elastography	3. Ultrasound
4. Combinations of 1-3	4. CT scan or MRI

Hcvguidelines.org

HCV NS5 RAS testing is uncommonly recommended

Regimen-Specific Recommendations for Use of RAS Testing in Clinical Practice

RECOMMENDED	RATING
Elbasvir/grazoprevir NS5A RAS testing is recommended for genotype 1a-infected, treatment-naive or -experienced patients being considered for elbasvir/grazoprevir. If present, a different regimen should be considered.	I, A
Ledipasvir/sofosbuvir NS5A RAS testing can be considered for genotype 1a-infected, treatment-experienced patients with and without cirrhosis being considered for ledipasvir/sofosbuvir. If clinically important* resistance is present, a different recommended therapy should be used.	I, A
Sofosbuvir/velpatasvir NS5A RAS testing is recommended for genotype 3-infected, treatment-naive patients with cirrhosis and treatment-experienced patients (without cirrhosis) being considered for 12 weeks of sofosbuvir/velpatasvir. If Y93H is present, weight-based ribavirin should be added or another recommended regimen should be used.	I, A

* Clinically important = ≥100-fold shift in the in vitro EC_{50} to ledipasvir

NB: no PI resistance testing
Clinically sig is >100-fold in vitro

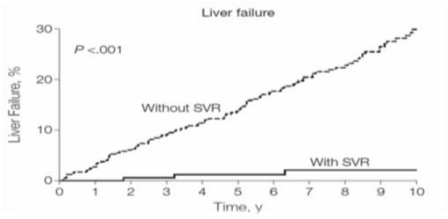
Wyles, HCVguidelines.org

Case con't: 54 year old with HCV

Elastography (17.3 kPa) and Fib-4 (5.5) consistent with cirrhosis. Genotype 1a; HBsAg neg; Ultrasound and UGI are ok. Which can you NOT say is true of treatment?

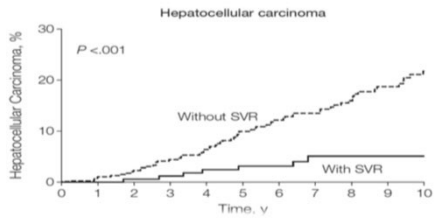
A. reduces risk of reinfection
B. reduces risk of death
C. reduces risk of HCC
D. reduces risk of liver failure

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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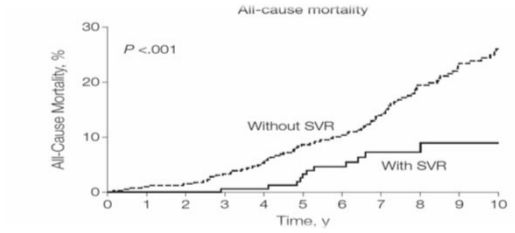
SVR reduces clinical outcomes



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.

54 year old with HCV

Which is true of initial HCV treatment?

A. **Avoid sofosbuvir if renal insufficiency**
B. **Avoid glecaprevir (PI) if on atorvastatin**
C. **Avoid sofosbuvir/ledipasvir if genotype 1**
D. **Prolong treatment if person also has HIV**

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

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 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)[b]	8 weeks	I, B

[a] For decompensated cirrhosis, please refer to the appropriate section.
[b] Dosing is 3 coformulated tablets (glecaprevir [100 mg]/pibrentasvir [40 mg]) taken once daily. Please refer to the prescribing information. For patients with HIV/HCV coinfection, a treatment duration of 12 weeks is recommended.

HCV-HIV ART drug interactions

www.hcvguidelines.com

Slide 22 of 44

		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	
	Cabotegravir	ND	ND	ND	ND	ND
	Cobicistat-boosted elvitegravir	C	C			C
	Dolutegravir					ND
	Raltegravir					ND
Entry Inhibitors	Fostemsavir	ND	ND	ND	ND	ND
	Ibalizumab-uiyk	ND	ND	ND	ND	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
	Tenofovir alafenamide	D	D	ND		D

HCV treatment summary

- **Test and treat (and stage)**
- **Two pangenotypic regimens: SOF/VEL and G/P**
- **Watch for HBV relapse at week 8 if HBsAg pos**
- **No change for HIV (avoid drug interactions), renal insufficiency, acute infection**
- **Compensated cirrhosis same for G/P and SOF-based except GT3 with resistance**

Hepatitis B: 2023 Testing Recs for USA

Universal hepatitis B virus (HBV) screening
- HBV screening at least once during a lifetime for adults aged ≥18 years (new recommendation)
- During screening, test for hepatitis B surface antigen (HBsAg), antibody to HBsAg, and total antibody to HBcAg (total anti-HBc) (new recommendation)

Screening pregnant persons
- HBV screening for all pregnant persons during each pregnancy, preferably in the first trimester, regardless of vaccination status or history of testing*
- Pregnant persons with a history of appropriately timed triple panel screening and without subsequent risk for exposure to HBV (i.e., no new HBV exposures since triple panel screening) only need HBsAg screening

Risk-based testing
- Testing for all persons with a history of increased risk for HBV infection, regardless of age, if they might have been susceptible during the period of increased risk†
- Periodic testing for susceptible persons, regardless of age, with ongoing risk for exposures, while risk for exposures persists†

MMWR March 10, 2023

After HBV testing, which requires treatment

1. **41 yr male in China HBsAg pos, HBeAg neg, anti-HBe pos, ALT 78 IU/ml, AST 86 IU/ml, HBV DNA 5,600**
2. **51 yr male HBsAg neg, anti-HBc pos, HBeAg neg, anti-HBe pos, ALT 48 IU/ml, AST 36 IU/ml, HBV DNA neg**
3. **21 yr woman born in Viet Nam HBsAg pos, HBeAg pos, anti-HBe neg, ALT 18 IU/ml, AST 16 IU/ml, HBV DNA 8.2 mil**
4. **62 yr woman about to start hydroxychloroquine for SLE anti-HBc pos, HBsAg neg, HBeAg neg, anti-HBe pos, DNA neg, ALT 34 IU/ml, AST 28 IU/ml**
5. **19 yr man about to start college anti-HBs pos, HBsAg neg, HBeAg neg, DNA neg, ALT 18 IU/ml, AST 12 IU/ml**

After HBV testing, which requires treatment

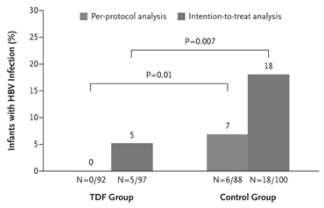
Age (yrs)	DNA (IU/ml)	ALT (IU/ml)	Issue/interpretation
41	5600	78	Chronic HBV with replication and inflammation
51	Neg	48	Isolated core/possible occult HB. Probable MASLD
21	8,200,000	18	High replication without inflammation (immunotolerant)
62	Neg	34	Isolated core/possible occult. Mild immunosuppression
19	Neg	18	Vaccinated

Treatment of chronic hepatitis B (HBsAg pos)

- **Disease (ALT and/or biopsy and/or elastography) + Replication (HBV DNA > 2,000 IU/ml)**
- **Cirrhosis- treat all**
- **HIV – treat all**
- **Pregnancy- treat if HBV DNA > 200,000 IU/ml**

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

Evaluation of persons with CHB

- **HIV, HBV DNA, anti-HDV, HBeAg**
- **Genotype if IFN considered; q HBsAg if 'covered'**
- **Stage (liver enzymes and/or elastography or biopsy)**
- **Renal status**
- **US to r/o HCC**
  - **Cirrhosis: all**
  - **Asian: male 40; female 50**
  - **African: 25-30**

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

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

HIV/HBV coinfected need treatment for both

- **All are treated and tested for both**
- **HBV-active ART**
- **Entecavir less effective if LAM exposure**
- **Watch switch from TAF- or TDF-containing regimen**

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**
- **(Newer practice is to use quantitative HBsAg and stop only when low (eg <100))**

PREVIEW QUESTION

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.

PREVIEW QUESTION

What do you recommend?

A. Hold rituximab
B. Hold prednisone
C. Entecavir 0.5 mg
D. HCV PCR

Rituximab, high-dose prednisone, and BM transplant high risk for HBV reactivation

- **If HBsAg pos, prophylaxis *always* recommended**
- **If anti-HBc pos but HBsAg neg, prophylaxis still recommended with high-risk exposures (anti-CD20, high dose Pred, BM tx)**
- **Use TAF or ETV for 6-12 mo after dc immunosuppression (12 for anti-CD20)**

AASLD Terrault Hepatology 2018

Chronic hepatitis in a 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.

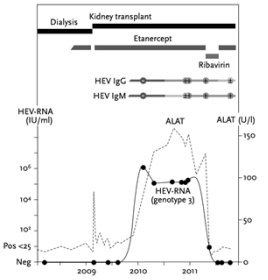
Barrague Medicine 2017

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

Chronic Hepatitis for the Boards Summary

- **HCV-associated conditions: PCT or cryoglobulinemia**
- **HCV: HBV relapse or drug interaction**
- **HBV: relapse post rituximab**
- **HEV: chronic in transplant patient**
- **Guess b and good luck**

Thanks and good luck on the test!

Questions:

Dave Thomas

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11

Helicobacter and Clostridioides Difficile

Dr. David Aronoff

11 – Helicobacter and Clostridium Difficile

Speaker: David Aronoff, MD

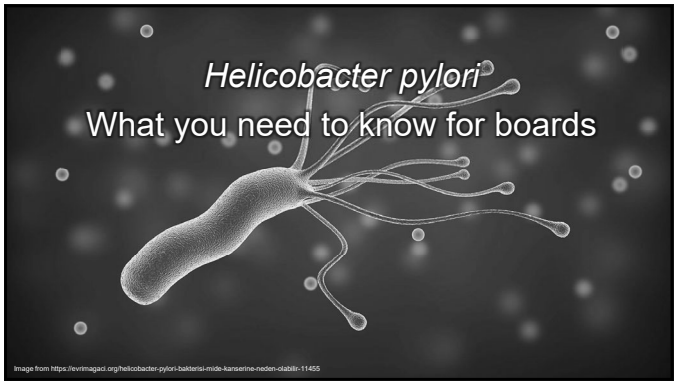
Helicobacter* and *Clostridioides difficile

David M. Aronoff, MD, FIDSA, FAAM
John B. Hickam Professor of Medicine
Chair, Department of Medicine
Indiana University School of Medicine
aronoff@iu.edu

7/25/2024

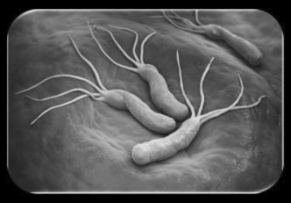
- **Disclosures of Financial Relationships with Relevant Commercial Interests**

  - None



Helicobacter pylori Microbiology

- Spiral-shaped, Gram-negative rod
- Flagellated
- Non-invasive
- Catalase +, oxidase +
- Grows best at pH 6-8



Urease + → **Survival, Colonization, Diagnosis**

Urea → CO_2 + NH_3 → ↑**pH**

Image from https://www.news-medical.net/life-sciences/Helicobacter-pylori-Life-Cycle.aspx

Helicobacter pylori: Take Home Points

- Hp causes peptic ulcer disease (PUD), chronic gastritis, gastric adenocarcinoma, & gastric mucosa associated lymphoid tissue (MALT) lymphoma
- Hp does **not** cause reflux/GERD
- Test for Hp if h/o MALT lymphoma, active PUD, early gastric cancer
- Consider testing: Pts <60 years of age with dyspepsia & w/o alarm features, chronic NSAID use, unexplained iron deficiency, immune thrombocytopenia

Helicobacter pylori: Take Home Points

- Test after stopping PPI (2 wks) & antibiotics (4 wks)
  - Urea breath test, stool antigen, or biopsy can diagnos Hp
  - NEVER TEST WITH SEROLOGY
- Endoscopy for diagnosis if alarm symptoms

ALARM SYMPTOMS
- **Unexplained iron-def anemia**
- **GI bleeding**
- **Unintentional weight Loss**
- **Palpable mass**
- **Severe abdominal pain**
- **Persistent vomiting**
- **Progressive dysphagia / odynophagia**

Helicobacter pylori: Take Home Points

- All patients with active infection should be offered treatment
- Initial antibiotic regimen guided by the presence of risk factors for macrolide resistance & presence of a penicillin allergy
  - In the **USA** macrolide resistance is generally >15% so **avoid macrolides**
  - **Bismuth quadruple therapy** = bismuth/metronidazole/tetracycline/PPI (double dose PPI)
  - Treat for **14 days**

Helicobacter pylori: Take Home Points

- **Test of cure** to confirm eradication must be performed in all patients treated for Hp at least 4 weeks after treatment
  - PPI therapy should be withheld for 1-2 weeks before testing because of bacteriostatic effects of PPI on Hp

Saniee P, *et al. Helicobacter.* 2016 Apr;21(2):143-52. doi: 10.1111/hel.12246

Question #1

A young woman undergoes upper endoscopy for unexplained nausea & vomiting. The stomach appears normal. Surveillance biopsies are taken & the gastric biopsy urease test is positive. The biopsies are most likely to show:

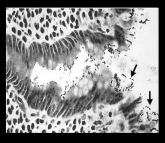
A. Hp organisms, but no gastric or esophageal inflammation.
B. Hp organisms plus gastric inflammation (gastritis).
C. Hp organisms plus esophagitis.
D. Neither Hp organisms, nor inflammation because the urease test is often false positive with a normal endoscopy.

Question #2

What is the most likely source for humans to acquire *H. pylori* infection?

A. Perinatally from mother
B. Ingestion of raw vegetables
C. Ingestion of undercooked meat
D. Ingested tap water from a municipal source
E. Contact with infected secretions from another human

Helicobacter pylori



- Humans are the only natural Hp host
- Infects > 50% of the world's population
  - US ~20-40%*
- A leading chronic infection in humans
- Majority are asymptomatic but **all have chronic active gastritis**
- Severity of gastritis varies depending on the Hp strain & the host

*At greater risk: indigenous Americans, Black/AA, Hispanic, & immigrants from high-cancer-risk countries like Japan, Korea, Taiwan & China

Lee Y, *et al. Annu Rev Med* (2022)
Crowe SE, *NEJM* (2019)

Helicobacter pylori & Cancer

Hp is a carcinogen that causes an inflammation-driven cancer

- 1-3% of infected individuals will develop cancer
- Hp causes 15% of the total cancer burden globally
- Up to 89% of all gastric cancer is attributable to Hp

Chronic active gastritis
↓
Atrophic gastritis
↓
Epithelial metaplasia
↓
Intraepithelial neoplasia
↓
Invasive carcinoma

Lee Y, *et al. Annu Rev Med* (2022)
Shah SC, *et al Gastroenterology* (2021)

11 – Helicobacter and Clostridium Difficile

Speaker: David Aronoff, MD

Transmission of *H. pylori*

- Transmission likely **fecal-oral** or **oral-oral**
- Intrafamilial spread very common
  - Person-to-person, esp. mother-to-child but not during pregnancy
- Low socioeconomic status, poor sanitation, crowding associated with ↑transmission

JAMA 282:2240, 1999 & *Crowe SE, UpToDate* (2018)
Zhou XZ, *et al. Gut.* (2023) May;72(5):855-869. doi: 10.1136/gutjnl-2022-328965. PMID: 36690433

Disease Paths for *Helicobacter pylori* Infection

• Asymptomatic gastritis	85-90%
• Peptic ulcer (DU, GU)	1-17%
• Gastric cancer	0.1-3%
• MALT lymphoma	<0.01%

DU, duodenal ulcer
GU, gastric ulcer
MALT, mucosal-associated lymphoid tissue

Lee Y, *et al. Annu Rev Med* (2022)
NEJM 347: 1175, 2002
Gut 66:6, 2017

H. pylori: Disease Associations

- #1 cause of chronic gastritis
- PUD: 90% of DU, 80% of GU
- MALT lymphomas (72 – 98%)
- Gastric Cancer (60 – 90%)

Hp causal

H. pylori is a World Health Organization-designated carcinogen & the strongest known risk factor for non-cardia gastric adenocarcinoma

- Iron deficiency anemia, B12 deficiency, ITP
- Eradication of 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;160:1831–184

Question #3

PREVIEW QUESTION

A 25-year-old 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

Who Should Be **Tested** for Hp?

Patients with:

Do Not Test for GERD Symptoms

- Suspected Hp infection (e.g., active DU)
- Current or past GU or DU
- Uninvestigated dyspepsia
- Gastric MALT lymphoma
- Family members in same household of pt w/ proven, active Hp infection
- Family hx of PUD or gastric cancer
- 1st generation immigrants from high-prevalence areas
- Higher prevalence groups (Latino, Black/AA, indigenous populations)
- Regular user of NSAIDs
- Long-term PPI use
- Fe deficiency anemia (unexplained)
- ITP (low evidence base)

Lee Y, *et al. Annu Rev Med* (2022)

Diagnosis of Hp Infection

NO:

Noninvasive (global)	Sensitivity	Specificity	
Urea Breath Test UBT (^{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

Serology is not useful. UBT considered 'best test'. Antigen test is usually less expensive.
Use only monoclonal stool Ag tests.
Histology requires 10^4 organisms to visualize

Lee Y, *et al. Annu Rev Med* (2022)

Testing Limitations for Hp

PPI
Antibiotics
Bismuth
Bleeding
} Interfere with all Hp tests because they reduce bacterial load

False negatives due to decreased Hp burden
Recommend delay diagnostic testing until:

- PPI stopped for > 2 weeks (**OTC antacids & H2RA do not affect UBT/SA testing**)
- Antibiotics, bismuth stopped for > 4 weeks
- Bleeding stopped for 4-8 weeks

Lee Y, et al. Annu Rev Med (2022)
Crowe SE, UpToDate (2018)
Crowe SE, NEJM 380:1158-65 (2019)

Initial Diagnosis of *H. pylori* with Dyspepsia

MOST = NONINVASIVE

- Stool antigen test (SAT)
- Urea Breath Test (UBT)

- Endoscopy mandatory if ≥60 years old or '**alarm symptoms** or signs':
  - Unexplained iron-def anemia
  - GI bleeding
  - Unintentional weight Loss
  - Palpable mass
  - Severe abdominal pain
  - Persistent vomiting
  - Progressive dysphagia / odynophagia

Crowe SE, UpToDate (2018)
Crowe SE, NEJM 380:1158-65 (2019)

Question #4

- Which of the following is the most appropriate next step for evaluating a 29-year-old previously healthy but overweight male patient with typical retrosternal heartburn symptoms?
  - A. Stool antigen test for *H. pylori*
  - B. Urea breath test for *H. pylori*
  - C. No testing for *H. pylori*
  - D. Serological testing for *H. pylori*
  - E. Empiric therapy for *H. pylori* regardless of testing

Explanation for Q#4

- Hp is not implicated as an etiological factor in gastroesophageal reflux disease (GERD)
- Treatment for (eradication of Hp) can **increase** the risk for Barrett's esophagus & esophageal adenocarcinoma
- Serology is **not** a recommended test for *H. pylori*

Siddique O, *et al. AJM* 2018

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,[1,2] John Y. Kao,[3] Fasiha Kanwal,[1,2,3] Mark Gilger,[3,4] Frank LoVecchio,[5] Steven F. Moss,[6] Sheila Crowe,[7] Adam Elfant,[7] Thomas Haas,[8] Ronald J. Hapke,[4,9] and David Y. Graham[10,11]

- "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*

Treatment of Hp

- Cure rates of most Hp therapies are **relatively low** (<80%)
- Antibiotic resistance is a HUGE challenge, provoking quadruple therapies
- **Ask about prior antibiotic exposure** hx (especially clarithromycin & fluoroquinolones)
- Discuss the critical importance of **adherence to treatment**
- Use **high dose PPI** (BID dose; increase gastric pH>4-5)
  - Hp grows optimally at pH 6-8 & low pH hinders stability & activity of macrolides, amoxicillin
  - Fast metabolizers of PPIs (CYP2C19 genotypes) reduce levels of omeprazole/lansoprazole
  - Vonoprazan: new potassium-competitive acid blocker appears promising

Lee YC, Annu Rev Med (2022)

Treatment of Hp

- 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: results are inferior)
  - 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
Lee YC, *Annu Rev Med*: 2022

Treatment of Hp Continued…

- Consider antibiotic susceptibility testing after multiple relapses
  - Culture-based & non-culture-based (NGS) techniques can determine resistance
- Success should always be confirmed by a **test of cure** after treatment of every patient (*e.g.*, UBT performed 4 or more weeks after therapy)

Lee YC, Annu Rev Med (2022)

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

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
- For salvage; not amazing

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)
Smith SM, *et al. European Journal of Gastroenterology & Hepatology* (2024)

Question #6

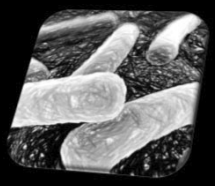
After treatment of this patient for Hp gastritis, the *H. pylori* stool antigen test should be repeated:

A. On the final day of *H. pylori* therapy
B. Two weeks after completion of *H. pylori* therapy
C. Four weeks after completion of *H. pylori* therapy
D. The test should not be repeated to assess cure

11 – Helicobacter and Clostridium Difficile

Speaker: David Aronoff, MD

CLOSTRIDIOIDES DIFFICILE



Clostridioides difficile: Take Home Points

- Community-onset disease increasingly common
- Diagnosis of *C. difficile* infection (CDI) relies on combination of appropriate clinical syndrome plus evidence of toxin B
- Not all *C. difficile* organisms are toxigenic/disease-causing
- Severe disease is based on leukocytosis &/or renal injuf‰

Clostridioides difficile: Take Home Points

- Fidaxomicin is a favored first-line option, & oral vanco is good (more recurrences, but often more available/less $)
- Metronidazole is no longer a preferred option
- Recurrence is a major challenge
- Recurrence risk reduced by stopping other antibiotics, using fidaxomicin, bezlotoxumab, live biotherapeutic products, or FMT
- No test of cure should be performed

Facts about *C. difficile* infection (CDI)

- Not all antibiotic-associated diarrhrea (AAD) is due to *C. difficile* (probably <40%)
- Nearly all AA **colitis** is CDI
- ~500,000 cases & ~30,000 deaths per year in the US
- Healthcare-associated CDI rates are declining
- Community-associated CDI rates are increasing
- Recurrent CDI (rCDI) is a major problem, accounting for 75,000-175,000 cases of CDI each year in the US

Feuerstadt P, *et al. BMC Infectious Diseases* (2023) 23:132
Selvaraj V & Alsamman MA. Antibiotic-Associated Diarrhea Beyond *C. Difficile*: A Scoping Review. *Brown Hospital Medicine*. 2022

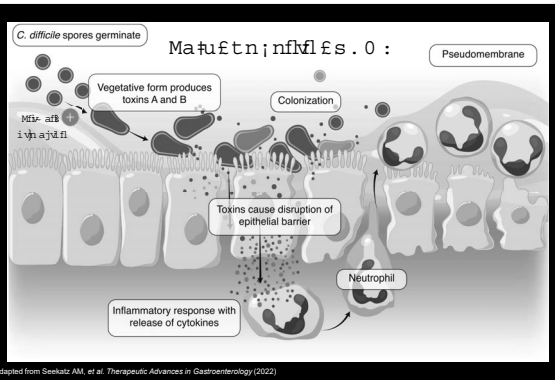
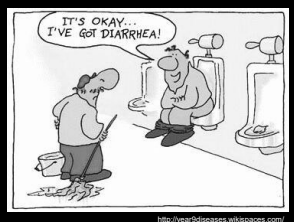


Figure adapted from Seekatz AM, *et al. Therapeutic Advances in Gastroenterology* (2022)

Common Clinical Manifestations

- Watery & mucousy diarrhea up to 10 - 15 times daily
- Lower abdominal pain & cramping
- Low grade fever (15%+)
- Leukocytosis (> 15,000 cells/ml = severe)
- Nausea
- Anorexia
- Malaise



http://year9diseases.wikispaces.com/

11 – Helicobacter and Clostridium Difficile

Speaker: David Aronoff, MD

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 (board exam vs. real world caveat)
- 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 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**
- **Can't differentiate colonization *vs* 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**

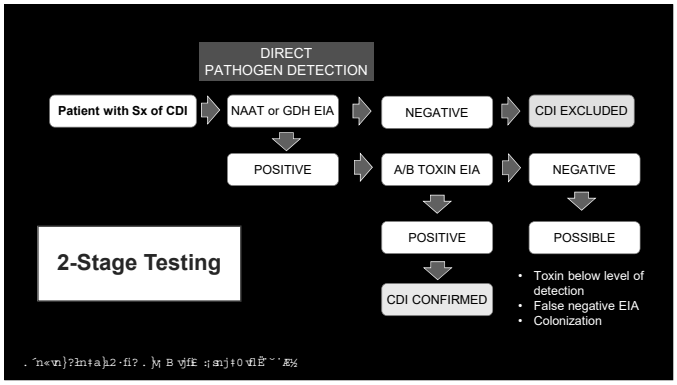
Disadvantages

- **Poor sensitivity**
- **False positives possible**

Usually used in a 2-step protocol with N%%S£fi809

11 – Helicobacter and Clostridium Difficile

Speaker: David Aronoff, MD



Question #7

PREVIEW QUESTION

- 67 year old woman develops diarrhea while hospitalized for community acquired pneumonia. She is afebrile, WBC count is 12,000/ml, 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?
  a. Metronidazole 500 mg po TID x 10 days
  b. Vancomycin 500 mg PO qid x 10 days
  c. Fidaxomicin 200 mg PO BID x 10 days
  d. Bezlotoxumab + vancomycin x 10 days
  e. Fidaxomicin 200 mg PO BID + metronidazole 500 mg PO TID x 10 days

Table 1. Treatment Strategies for CDI.

	IDEA/SHEA	ACG	ESCMID
Preferred Regimens for an Initial CDI Episode			
Non-severe	Fidaxomicin	Fidaxomicin or vancomycin (metronidazole for low-risk only)	Fidaxomicin
Severe	Fidaxomicin	Fidaxomicin or vancomycin	Fidaxomicin or vancomycin
Fulminant/complicated	High-dose vancomycin + IV metronidazole	High-dose vancomycin ± IV metronidazole	Vancomycin or fidaxomicin
Preferred Regimens for Recurrent CDI Episodes			
First recurrence	Fidaxomicin	Fidaxomicin or tapered/pulsed vancomycin	First-line: Fidaxomicin or the addition of bezlotoxumab (tailored based on treatment regimen for the initial episode)
Second recurrence	Fidaxomicin, vancomycin tapered and pulsed regimen, vancomycin followed by rifaximin, FMT	Not specifically addressed	FMT or standard regimens and bezlotoxumab, if not used previously (tailored based on past treatment regimens)

Table from Bainum TB, *et al. Microorganisms* (2023)

Recurrent CDI

Treatment	Contents	Dose/route	Recurrence rate (active treatment)	Recurrence rate (placebo)	Absolute risk reduction	FDA Approval	Ref.
Bezlotoxumab (ZINPLAVA®)	Monoclonal Ab	10 mg/kg IV x 1	15.7-17.4%[a]	25.7-27.6%[a]	**10.0-10.2%**	YES	(1)
SER-109 (VOWST®)	Feces	4 caps QD PO x 3 d	12.4%[b]	39.8%[b]	**27.4%**	YES	(2)
RBX2660 (REBYOTA®)	Feces	150 mL PR enema x 1	29.4%[b]	42.5%[b]	**13.1%**	YES	(3)
VE303	8 Clostridia strains	10 caps QD x 14 d	13.8%[b]	45.5%[b]	**31.7%**	NO	(4)*
FMT#	Feces	Various	32.3%	56.6%	**23.3%**	With pt. consent	(5)

1. Package Insert; 2. Package Insert; 3. Package Insert; 4. Louie T, *et al. JAMA* (2023); 5. Tariq R, *et al. CID* (2019)

Recurrence rates are shown for (a) 12 or (b) 8 weeks post treatment
*Phase II study data only
#FMT more effective with > 1 dose

Therapy of CDI with drug doses

TABLE 1

Recommended Treatment Options for CDI

Presentation	Treatment options
Initial case	Preferred: Fidaxomicin (Dificid), 200 mg twice daily for 10 days Alternative: Vancomycin, 125 mg four times daily for 10 days Alternative for nonsevere CDI if above agents not available: Metronidazole (Flagyl), 500 mg three times daily for 10 to 14 days
First recurrence	Preferred: Fidaxomicin, 200 mg twice daily for 10 days or twice daily for five days followed by once every other day for 20 days Alternatives: Vancomycin in a tapered and pulsed regimen Vancomycin, 125 mg four times daily for 10 days Adjunct: Bezlotoxumab (Zinplava), 10 mg per kg given intravenously once
Subsequent recurrences	Preferred: Fidaxomicin, 200 mg twice daily for 10 days or twice daily for five days followed by once every other day for 20 days Alternatives: Vancomycin in a tapered and pulsed regimen Vancomycin, 125 mg four times daily for 10 days, followed by rifaximin (Xifaxan), 400 mg three times daily for 20 days Fecal microbiota transplantation Adjunct: Bezlotoxumab, 10 mg per kg given intravenously once
Fulminant CDI	Vancomycin, 500 mg four times daily; if ileus is present, consider adding rectal dosing of vancomycin Metronidazole, 500 mg intravenously every eight hours, administered with oral or rectal vancomycin, particularly if ileus is present

Table from Finke J, *Am Fam Physician*. 2022 Jun;105(6):678-679.

Therapy of CDI

TABLE 1

Recommended Treatment Options for CDI

Presentation	Treatment options	Additional information
Initial case	Preferred: Fidaxomicin (Dificid), 200 mg twice daily for 10 days Alternative: Vancomycin, 125 mg four times daily for 10 days Alternative for nonsevere CDI if above agents not available: Metronidazole (Flagyl), 500 mg three times daily for 10 to 14 days	Fidaxomicin: Caution for use in patients with congestive heart failure Diagnosis of nonsevere cases supported by: White blood cell count < 15,000 cells per μL (15×10^3 per L) Serum creatinine < 1.5 mg per dL (132.6 μmol per L)

No more metronidazole
(unless mild disease, in young person, +/- cost constraints)

Table from Finke J, *Am Fam Physician*. 2022 Jun;105(6):678-679.

Therapy of CDI

TABLE 1

Recommended Treatment Options for CDI

Presentation	Treatment options	Additional information
Fulminant CDI	Vancomycin, 500 mg four times daily; if ileus is present, consider adding rectal dosing of vancomycin Metronidazole, 500 mg intravenously every eight hours, administered with oral or rectal vancomycin, particularly if ileus is present	Definition of fulminant CDI is supported by: Hypotension or shock, ileus, megacolon

Table from Finke J, *Am Fam Physician*. 2022 Jun;105(6):678-679.

Therapy of CDI

TABLE 1

Recommended Treatment Options for CDI

Presentation	Treatment options	Additional information
First recurrence	Preferred: Fidaxomicin, 200 mg twice daily for 10 days or twice daily for five days followed by once every other day for 20 days Alternatives: Vancomycin in a tapered and pulsed regimen Vancomycin, 125 mg four times daily for 10 days Adjunct: Bezlotoxumab (Zinplava), 10 mg per kg given intravenously once	Tapered and pulsed vancomycin regimen example: 125 mg four times daily for 10 to 14 days, two times daily for seven days, once daily for seven days, and then every two to three days for two to eight weeks

Table from Finke J, *Am Fam Physician*. 2022 Jun;105(6):678-679.

Therapy of CDI

TABLE 1

Recommended Treatment Options for CDI

Presentation	Treatment options	Additional information
Subsequent recurrences	Preferred: Fidaxomicin, 200 mg twice daily for 10 days or twice daily for five days followed by once every other day for 20 days Alternatives: Vancomycin in a tapered and pulsed regimen Vancomycin, 125 mg four times daily for 10 days, followed by rifaximin (Xifaxan), 400 mg three times daily for 20 days Fecal microbiota transplantation Adjunct: Bezlotoxumab, 10 mg per kg given intravenously once	Infectious Diseases Society of America guideline panel recommends appropriate antibiotic treatments should be tried for at least two recurrences (i.e., three CDI episodes) before offering fecal microbiota transplantation

Table from Finke J, *Am Fam Physician*. 2022 Jun;105(6):678-679.

Thank you

aronoff@iu.edu
@DMAronoff (Twitter, Bluesky)
david.aronoff (Insta, Threads)

Agenda Day 2: Sunday, August 18, 2024

#	Start		End	Presentation	Faculty
AM Moderator: Henry Masur, MD					
QP2	**8:00 AM EDT**	**-**	**8:30 AM EDT**	**Daily Question Preview Day 2**	**Henry Masur, MD**
12	8:30 AM	-	8:45 AM	How to Prepare for the Certification and Recertification, Including the LKA	Helen Boucher, MD
13	8:45 AM	-	9:45 AM	Core Concepts: Antibacterial Drugs I Gram Negative Organisms	Pranita Tamma, MD
14	9:45 AM	-	10:45 AM	Core Concepts: Antibacterial Drugs II Gram Positive Organisms	Helen Boucher MD
FC4	**10:45 AM**	**-**	**11:00 AM**	**Faculty Q&A**	**Drs. Bennett (Moderator), Boucher, Tamma**
15	11:00 AM	-	11:45 AM	CMV, EBV, HHV6 and HHV8 in Immunocompetent and Immunocompromised Patients	Camille Kotton, MD
	11:45 AM	-	12:15 PM	Lunch Break	
BR2	**12:15 PM**	**-**	**1:00 PM**	**Board Review Day 2**	**Drs. Alexander (Moderator), Boucher, Kotton, Platts-Mills, Saullo, Tamma, Trautner, and Whitley**
PM Moderator: Barbara Alexander, MD					
16	1:00 PM	-	2:00 PM	Infections in the Neutropenic Cancer Patient and Hematopoietic Stem Cell Recipients	Jennifer Saullo, MD
17	2:00 PM	-	3:00 PM	Infections in Solid Organ Transplantation	Barbara Alexander, MD
FC5	**3:00 PM**	**-**	**3:15 PM**	**Faculty Q&A**	**Drs. Alexander (Moderator) Kotton, and Saullo**
18	3:15 PM	-	3:45 PM	GI Infections Part 1	James Platts-Mills, MD
19	3:45 PM	-	4:30 PM	Skin and Soft Tissue Infections	Helen Boucher, MD
20	4:30 PM	-	5:00 PM	GI Infections Part 2	James Platts-Mills, MD
21	5:00 PM	-	5:45 PM	Infections of Upper and Lower Urinary Tract Infections	Barbara Trautner, MD
22	5:45 PM	-	6:15 PM	HSV and VZV in Immuno-competent and Immunocompromised Hosts	Richard Whitley, MD
FC6	**6:15 PM**	**-**	**6:30 PM**	**End of the Day Faculty Q&A**	**Drs. Alexander (Moderator), Boucher, Platts-Mills, Trautner, and Whitley**

QP2

Daily Question Preview 2

Dr. Henry Masur (Moderator)

QP2 – Question Preview: Day 2

Moderator: Henry Masur, MD

Daily Question Preview: Day 2

Moderator: Henry Masur, MD

7/1/2024`

PREVIEW QUESTION INFECTIOUS DISEASE BOARD REVIEW 2024

2.1

- **21-year-old female**
- **Renal transplant secondary to focal segmental glomerulosclerosis**
- **Dysuria, fevers, rigors, and hypotension**
- **Urine and blood cultures growing *Escherichia coli***
- **ICU to initiate vasopressors**
- **Susceptibilities shown on the next slide (note report in yellow)**

1 of 4

PREVIEW QUESTION INFECTIOUS DISEASE BOARD REVIEW 2024

2.1

Antibiotic	MIC	Interpretation
Amikacin	>8 µg/mL	S
Aztreonam	16 µg/mL	R
Cefazolin	>16 µg/mL	R
Cefotetan	2 µg/mL	S
Cefepime	4 µg/mL	R
Ceftazidime	>16 µg/mL	R
Ceftriaxone	32 µg/mL	R
Ciprofloxacin	1 µg/mL	R
Ertapenem	0.5 µg/mL	S
Gentamicin	2 µg/mL	R
Meropenem	0.5 µg/mL	S
Piperacillin/tazobactam	8/4 µg/mL	S
Tobramycin	2 µg/mL	S
Trimethoprim/sulfamethoxazole	0.5/4 µg/mL	S

2 of 4

PREVIEW QUESTION INFECTIOUS DISEASE BOARD REVIEW 2024

2.1 **Which one of the following antibiotics represents the most appropriate initial treatment?**

A) Cefepime

B) Trimethoprim-sulfamethoxazole

C) Meropenem

D) Piperacillin-tazobactam

3 of 4

PREVIEW QUESTION INFECTIOUS DISEASE BOARD REVIEW 2024

2.2

- **24-year-old male with acute myelogenous leukemia**
  - **Absolute neutrophil count = 0 cells/mL**
- **Acute onset fevers and respiratory distress**
- **Multifocal pneumonia**
- ***P. aeruginosa* recovered from bronchoalveolar lavage fluid**
- **Susceptibilities on next slide**

1 of 4

PREVIEW QUESTION INFECTIOUS DISEASE BOARD REVIEW 2024

2.2

Antibiotic	MIC	Interpretation
Amikacin	> 8 µg/mL	R
Aztreonam	> 16 µg/mL	R
Cefepime	> 16 µg/mL	R
Ceftazidime	> 16 µg/mL	R
Ciprofloxacin	> 2 µg/mL	R
Colistin	2 µg/mL	I
Gentamicin	> 8 µg/mL	R
Meropenem	16 µg/mL	R
Piperacillin/tazobactam	> 64/4 µg/mL	R
Tobramycin	> 8 µg/mL	R

***Pseudomonas aeruginosa* with "difficult-to-treat resistance" = resistance to all traditional beta-lactam and fluoroquinolone agents**

2 of 4

PREVIEW QUESTION

2.2 **Which one of the following antibiotics is <u>least</u> likely to be effective against DTR-*P. aeruginosa* infections?**

A) Ceftolozane-tazobactam

B) Ceftazidime-avibactam

C) Meropenem-vaborbactam

D) Imipenem-cilastatin-relebactam

3 of 4

PREVIEW QUESTION

2.3 **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

1 of 2

PREVIEW QUESTION

2.4 **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

1 of 2

PREVIEW QUESTION

2.5 **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.

1 of 3

PREVIEW QUESTION

2.5 **Which EBV-specific antibody profile would confirm a diagnosis of acute infectious mononucleosis?**

Response	VCA IgM	VCA IgG	EBNA IgG	EA IgG
A	+	+	+	+
B	+	+	-	+
C	-	+	+	+
D	-	-	+	-

2 of 3

PREVIEW QUESTION

2.6 **35 year old woman with AML, day 15 of induction therapy. Presentation - fever, chills, diffuse erythematous rash.**

Exam – 100/62, HR 120, grade 2 oral mucositis, diffuse, blanching, erythematous rash.

Cultures - Blood cultures with GPC in chains.

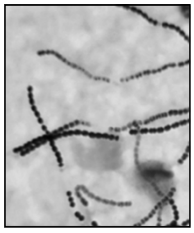
CXR - bilateral diffuse infiltrates.

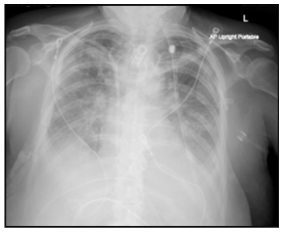
Prophylaxis - levofloxacin and acyclovir.

1 of 4

PREVIEW QUESTION

2.6





2 of 4

PREVIEW QUESTION

2.6 **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*

3 of 4

PREVIEW QUESTION

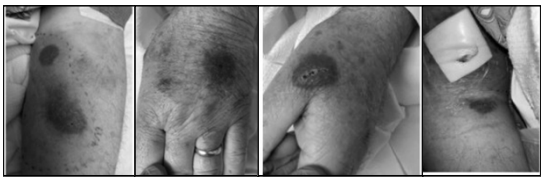
2.7 **70 year-old male with newly diagnosed AML developed erythematous, tender and edematous plaques over sites of trauma (blood draws, peripheral IV).**

He has been febrile to 38.7°C for the past several days.

1 of 4

PREVIEW QUESTION

2.7



2 of 4

PREVIEW QUESTION

2.7 **The most likely etiology is:**

A) *Candida albicans*

B) Sweet syndrome

C) *Aspergillus niger*

D) Varicella Zoster virus

E) *Pseudomonas aeruginosa*

3 of 4

PREVIEW QUESTION

2.8 **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.

1 of 3

PREVIEW QUESTION

2.8 **The most appropriate treatment for this condition is:**

A) Cidofovir
B) Ganciclovir
C) Acyclovir
D) Cyclophosphamide
E) Rituximab

2 of 3

PREVIEW QUESTION

2.9 **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.

1 of 3

PREVIEW QUESTION

2.9 **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

2 of 3

PREVIEW QUESTION

2.10 **A 50 year old female with alcohol substance abuse disorder 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

1 of 3

PREVIEW QUESTION

2.10 **Which one of the following is the most likely etiologic bacteria?**

A) *Pasteurella canis*
B) *Capnocytophaga canimorsus*
C) *Fusobacterium sp.*
D) *Bartonella henselae*

2 of 3

PREVIEW QUESTION

2.11 **A 45 year old USA male experiencing homelessness 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*

1 of 2

QP2 – Question Preview: Day 2

Moderator: Henry Masur, MD

PREVIEW QUESTION

2.12 A 24-year-old woman is evaluated for cystitis symptoms of 3 days' duration. She reports no fever, chills, flank pain, or vaginal discharge. She had similar symptoms three months ago and was treated with trimethoprim-sulfamethoxazole, with relief of symptoms.

On physical examination, vital signs and other findings are unremarkable.

On microscopic urinalysis, leukocytes are too numerous to count, erythrocyte count is 10/hpf, 4+ bacteria are present, and rare squamous epithelial cells are seen. Urine pregnancy test is negative.

hpf, high-powered field; TMP/SMX, trimethoprim/sulfamethoxazole

1 of 3

PREVIEW QUESTION

2.12 Which of the following is the most appropriate management?

A) Nitrofurantoin

B) TMP/SMX

C) Fosfomycin

D) Ciprofloxacin

E) Ibuprofen

2 of 3

PREVIEW QUESTION

2.13 A 38-year-old woman comes in for recurrent UTI. This is her 3rd episode of symptomatic, culture-proven cystitis in the past 12 months. The recurrent UTIs are very inconvenient to her. She notes that her UTI symptoms usually begin within 2 days of sexual intercourse.

You offer an antibiotic prescription to allow her to self-treat when she feels the cystitis symptoms developing, but she travels internationally and would rather completely avoid developing a UTI.

1 of 3

PREVIEW QUESTION

2.13 Which of the following is the most appropriate strategy to prevent recurrent UTI in this woman?

A) Nitrofurantoin daily for 24 months

B) Nitrofurantoin one dose after intercourse for 6 months

C) Ciprofloxacin daily for 6 months

D) Trimethoprim-sulfamethoxazole twice daily for 6 months

E) Cranberry tablets

2 of 3

PREVIEW QUESTION

2.14 A 30 year old heart transplant has received acyclovir for the past 60 days for 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

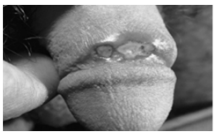
E) DNA polymerase

1 of 2

PREVIEW QUESTION

2.15 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.

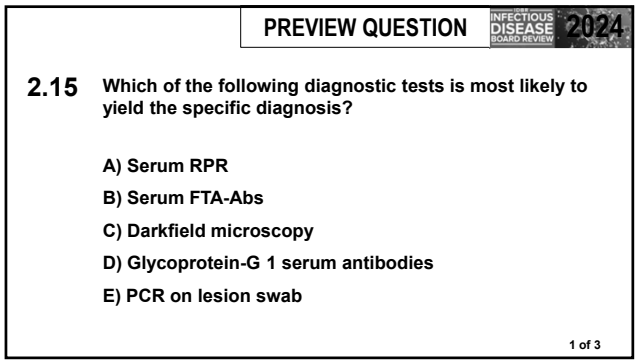
He had unprotected sexual intercourse with a female partner 2 weeks earlier. Neither he nor his partner has traveled outside the United States.



1 of 3

QP2 – Question Preview: Day 2

Moderator: Henry Masur, MD



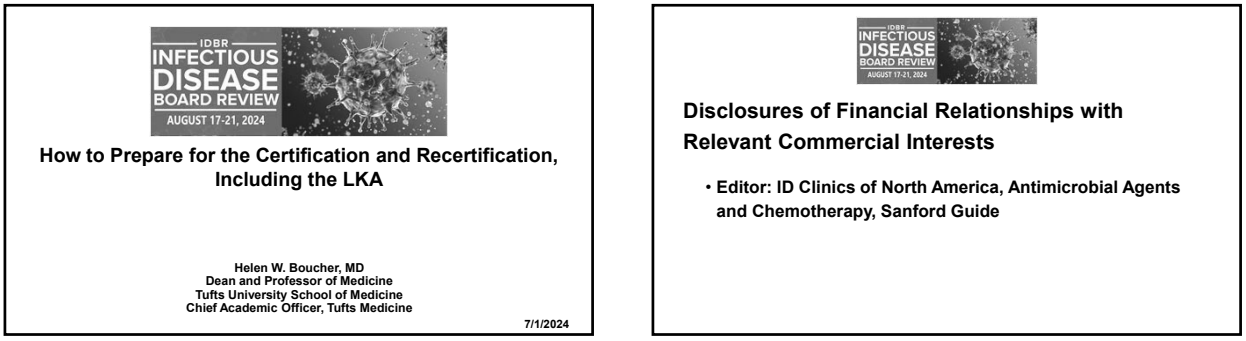
12

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

Dr. Helen Boucher

12 – How to Prepare for the Certification and Recertification Including the LKA

Speaker: Helen Boucher, MD



Website

www.abim.org

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

https://www.abim.org/Media/ut0j30zs/infectious-disease.pdf

3

Infectious Diseases Certification

- Initial Certification Exam
- Maintenance of Certification Options:
  - Every 10 year MOC exam
    - Offered 2x/year – Nov 13, 2024; Oct 21, 2025
  - Longitudinal Knowledge Assessment (LKA)
    - Began 2023

4

Certification Exams

- One day computer exam
- All questions: multiple choice, single best answer only

- Initial Certification:
  - Four 2-hour sessions: up to 60 questions each = 240
  - Time remaining for each session on computer screen
  - Message box will tell you when 5 minutes left in a session
  - Including registration, optional tutorial (up to 30 minutes), instructions, test, breaks ~ 10 hours

- Maintenance of Certification (formerly recertification): Four 2-hour exam sessions, up to 220 questions, ~ 10 hours
  - Open book: Up to Date allowed

5

New Option: Longitudinal Knowledge Assessment (LKA)

Current Plan (subject to change):

- 5 year recertification period - rolling
- 30 questions emailed every 3 months
  - Don't need to answer all at one time; can spread out over the quarter
- Four minutes to answer online
  - Open book
  - Correct answer and rationale provided
- Must answer 100 Q's per year (out of 120)
- Earn 0.2 MOC credits/correct answer
- After 5 years and at least 500 questions answered, ABIM provides pass/fail notification
- 500 correct answers fulfills required 100 MOC points

https://www.abim.org/lka/

6

12 – How to Prepare for the Certification and Recertification Including the LKA

Speaker: Helen Boucher, MD

Longitudinal Knowledge Assessment (LKA®) Quarterly Question Schedule (with deadlines)

Enrollment for the LKA **opens 12/1/23 and closes 6/30/24.**

QUARTER	OPENS	CLOSES
1	1/1	3/31 at 11:59 p.m. ET
2	4/1	6/30 at 11:59 p.m. ET
3	7/1	9/30 at 11:59 p.m. ET
4	10/1	12/31 at 11:59 p.m. ET

If you are planning to participate in the LKA, it is a good idea to start early so you don't miss any questions. Questions expire at the end of each quarter and you can't go back to answer them later. Any unopened questions will count against the 100 you can choose not to open over 5 years

https://www.abim.org/maintenance-of-certification/assessment-information/infectious-disease

7

https://www.abim.org/maintenance-of-certification/assessment-information/assessment-options/longitudinal-knowledge-assessment/

8

Exam

- **Can change answer until 60 question section over. Note ones unsure of and review them at end of session**
- **Roughly 20% of questions don't count = new questions being pretested**

9

Exam

- **Little less than two minutes per question**
- **Unanswered questions are marked wrong, so guess if you don't know**
- **Read the whole question!**
- **If question seems ambiguous, or seems to have two correct answers, you might be right. It may be a new question being tested for first time**
  Give your best answer and don't fret

10

Breaks

- **Breaks are optional. Take them!**
- **3 breaks during day: total 100 minutes**
- **1 break after each of first 3 test sessions**
- **Can use some or all of break time**
- **Amount of break time used after each session subtracted from total time**
  - **For example: if take 10 minute break after session one, amount of break time remaining for exam is 90 minutes**

Note: Proctors monitor entire space (test room, locker rooms, reception)

11

Exam

- **Confirmation email will specify appointment time and give driving directions to test center**
- **Check out site before exam:**
  - **Where is it? Where to park? Where to eat?**
- **Arrive ½ hour early**
- **Each testing center has 8 -25 workstations**
- **An administrator will be present**
- **At start of exam: see several screens reviewing instructions about taking exam, and asked to agree to a Pledge of Honesty**

12

12 – How to Prepare for the Certification and Recertification Including the LKA

Speaker: Helen Boucher, MD

Exam

- You will need personal ID (2 types):
  government-issued ID with photo and signature (driver's license, passport, etc.)
  And
  another form of ID with signature or photo (Social Security card, credit card, ATM card, etc.)
- Not allowed to take exam with expired ID
- Palm vein scan, security wanding, signature and photograph will be taken

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Exam

- Short orientation then taken to computer workstation
- May request left-handed mouse
- May request instructions adjust height and contrast of computer
- Erasable notepads provided and can type and save notes in pop-up box that accompanies each question
- Can request headphones or earplugs; cannot bring your own
- Any problem: Don't get up! Raise your hand
- Electronic fingerprint each time enter and exit testing room - allow 10 min to check back in

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Disabled Test Takers

- ABIM complies with the Americans with Disabilities Act (ADA)
  - They will make reasonable modifications to exam procedures as necessary, but there are limits
- Each request individually evaluated
- For more info see Forms of Accommodation on ABIM website

15

Not allowed in test room (small storage locker provided)

- Electronic devices: cell phone, PDA, pager, beeper
- Calculator, calipers, camera
- Watch – clock is in testing room
- Wallet, purse
- Briefcase, backpack
- Jacket, coat (sweater OK)
- Books, scratch paper, pens, pencils (noteboards provided)
- Medications require prior approval
  - "Contact us" feature on website
- Food and drink
  - Bring drinks for breaks to keep in locker; can bring lunch, but no refrigeration

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Questions about exam day

- Email: https://www.abim.org/contact.aspx
- Call ABIM 1-800-441-ABIM (2246)
  Mon-Fri: 8:30AM – 6PM

17

Exam Tutorial

- Examples of the exam question formats are available in a tutorial at the ABIM website:
  - https://www.abim.org/certification/exam-information/infectious-disease/exam-tutorial.aspx

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12 – How to Prepare for the Certification and Recertification Including the LKA

Speaker: Helen Boucher, MD

Exam Format

Exam is composed of multiple-choice questions with a single best answer, predominantly describing patient scenarios

- **Questions ask about the work done (that is, tasks performed) by physicians in the course of practice: making a diagnosis**
- **Ordering and interpreting results of tests**
- **Recommending treatment or other patient care**
- **Assessing risk, determining prognosis, and applying principles from epidemiologic studies**
- **Understanding the underlying pathophysiology of disease and basic science knowledge applicable to patient care**

19

- **>75% patient case presentations**
  - **not trying to trick you**
- **Normal lab values provided**
- **Pediatric questions not likely**
- **Very little basic science:**
  - **Mechanisms of resistance - ESBL, KPC**
- **Very little clinical microbiology (occasional clues):**
  - **Things you could do to help lab**
    - **e.g. oil on media for lipophilic yeast**
      Iron and 30º incubation for *M. haemophilum*

20

Exam Content

- **Exam content determined by a pre-established blueprint**
  - **Different for initial certification and MOC**
- **Primary medical content categories are ….**

21

2019 ID Exam Blueprint

Medical Content Category	% of Exam
Bacterial Diseases	27%
Human Immunodeficiency Virus (HIV) Infection	15%
Antimicrobial Therapy	9%
Viral Diseases	7%
Travel and Tropical Medicine	5%
Fungi	5%
Immunocompromised Host (Non-HIV Infection)	5%
Vaccinations	4%
Infection Prevention and Control	5%
General Internal Medicine, Critical Care, and Surgery	18%
	100%

22

Clinical Syndromes

- Pleuropulmonary infections
- Infections of the head and neck
- Infections and other complications in HIV/AIDS
- Cardiovascular infections
- Central nervous system infections
- Gastrointestinal and intra-abdominal infections
- Liver and biliary tract infections
- Skin and soft tissue infections
- Bone and joint infections

23

Clinical Syndromes (con't.)

- Infections of prosthetic devices
- Infections related to trauma
- Bloodstream infections and sepsis syndromes
- Nosocomial infections
- Urinary tract infections
- Sexually-transmitted diseases and reproductive tract infections
- Fever (infectious and non-infectious) and hyperthermia

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12 – How to Prepare for the Certification and Recertification Including the LKA

Speaker: Helen Boucher, MD

Patient Populations

- Patients who are neutropenic
- Patients with:
  - Leukemia, Lymphoma, or other malignancies
- Patients following solid organ or bone marrow transplantation/HSCT
- Patients with HIV/AIDS or patients immunocompromised by other disease or medical therapies
- Pregnant women
- Travelers and immigrants

25

• Note:

I recommend you take a look at the website and review the lists.

……..as an example

26

Rickettsia (2.5%)

- **R. rickettsii (Rocky Mountain Spotted Fever)**
- **R. akari (rickettsial pox)**
- **R. prowazekii (epidemic typhus)**
- **R. typhi**
- **Orientia tsutsugamushi (scrub typhus)**
- **R. conorii**
- **R. parkeri**
- **R. africae**
- **Coxiella burnetii**

27

Exam

- **Takes couple of years for new question to appear on exam and count. So, new developments in last 2 years less likely to be on exam and count**
  - **e.g. COVID-19, new Ebola treatment**
- **Things that were hot and now not, are unlikely to appear:**
  - **Anthrax**
- **Effort made not to have "look up" questions:**
  - **e.g. Treatments for uncommon parasitic diseases**
    - **Malaria - yes**
    - **Filariasis – no**

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Pass rates 1st-time Takers-Initial certification

Year	# of Examinees	Pass Rate
2010	359	91%
2011	348	96%
2012	342	95%
2013	364	87%
2014	361	86%
2015	347	94%
2016	348	98%
2017	339	97%
2018	338	98%
2019	362	98%
2020	364	94%
2021	372	92%
2022	379	94%
2023	407	96%

https://www.abim.org/Media/yeqiumdc/certification-pass-rates.pdf

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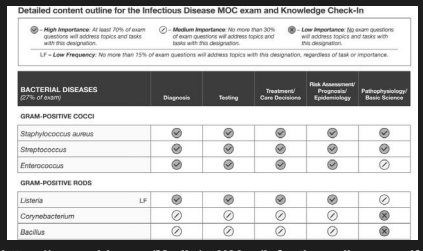
How is MOC Content Different?


Detailed content outline for the Infectious Disease MOC exam and Knowledge Check-In

✓ - *High Importance:* At least 70% of exam questions will address topics and tasks with this designation.

✓ - *Medium Importance:* No more than 30% of exam questions will address topics and tasks with this designation.

✓ - *Low Importance:* No exam questions will address topics and tasks with this designation.

LF – *Low Frequency:* No more than 15% of exam questions will address topics with this designation, regardless of task or importance.

BACTERIAL DISEASES (27% of exam)		Diagnosis	Testing	Treatment/ Care Decisions	Risk Assessment/ Prognosis/ Epidemiology	Pathophysiology/ Basic Science
GRAM-POSITIVE COCCI						
Staphylococcus aureus		✓	✓	✓	✓	✓
Streptococcus		✓	✓	✓	✓	✓
Enterococcus		✓	✓	✓	✓	✓
GRAM-POSITIVE RODS						
Listeria	LF	✓	✓	✓	✓	✓
Corynebacterium		✓	✓	✓	✓	✗
Bacillus		✓	✓	✓	✓	✗

https://www.abim.org/Media/ut0j30zs/infectious-disease.pdf

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12 – How to Prepare for the Certification and Recertification Including the LKA

Speaker: Helen Boucher, MD

Infectious Diseases MOC Pass rate

Year	#Examinees	Pass Rate (%)
2015	301	89%
2016	467	94%
2017	350	90%
2018	367	93%
2019	296	91%
2020	216	89%
2021	265	93%
2022	328	95%
2023	263	92%

https://www.abim.org/Media/cqyhgyeo/maintenance-of-certification-pass-rates.pdf

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What to do from now to exam

- Start Early!
  - Make notes of items to review just before the exam
- Know that this Board Review Course is excellent preparation
- Review questions and images from IDBR website to identify areas needing further study
- Go to ABIM website (www.abim.org) and:
  - Take the tutorial
  - Read about Exam Day: What to expect
  - See details about ID exam (blueprints, etc.)

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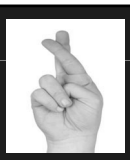
What to do from now to exam

- From binders/on line presentations for this course, pull out the "handouts" covering your weak areas and make a little "binder" (e.g. parasites, fungi, mimic syndromes)
- Review your "little binder" just before exam

33

Thank You: Jack Bennett & Bennett Lorber

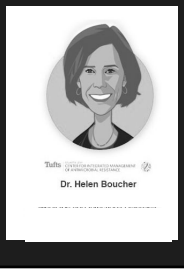


Good Luck
To You All !

34

Questions, Comments?

- @hboucher3
- Helen.boucher@tuftsmedicine.org



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13

Core Concepts: Antibacterial Drugs I: Gram Negative Organisms

Dr. Pranita Tamma

13 – Core Concepts: Antibacterial Drugs I Gram Negative Organisms

Speaker: Pranita Tamma, MD

Core Concepts: Antibacterial Drugs I Gram-Negative Organisms

Pranita D. Tamma, MD, MHS
Johns Hopkins University School of Medicine
Associate Professor, Pediatrics

7/24/2024

- **Disclosures of Financial Relationships with Relevant Commercial Interests**

  - None

Objectives

- Review antibiotic treatment options for infections caused by:
  - Extended-spectrum beta-lactamase producing Enterobacterales **(ESBL-E)**
  - Amp-C producing Enterobacterales **(AmpC-E)**
  - *Pseudomonas aeruginosa* with difficult-to-treat resistance **(DTR *P. aeruginosa*)**
  - Carbapenem-resistant Enterobacterales **(CRE)**
  - Carbapenem-resistant *Acinetobacter baumannii* **(CRAB)**

ESBL-E Infections

PREVIEW QUESTION

Clinical Case

- 21-year-old female
- Renal transplant secondary to focal segmental glomerulosclerosis
- Dysuria, fevers, rigors, and hypotension
- Urine and blood cultures growing *Escherichia coli*
- ICU to initiate vasopressors

PREVIEW QUESTION

Antibiotic	MIC	Interpretation
Amikacin	>8 µg/mL	S
Aztreonam	16 µg/mL	R
Cefazolin	>16 µg/mL	R
Cefotetan	2 µg/mL	S
Cefepime	4 µg/mL	R
Ceftazidime	>16 µg/mL	R
Ceftriaxone	32 µg/mL	R
Ciprofloxacin	1 µg/mL	R
Ertapenem	0.5 µg/mL	S
Gentamicin	2 µg/mL	R
Meropenem	0.5 µg/mL	S
Piperacillin/tazobactam	8/4 µg/mL	S
Tobramycin	2 µg/mL	S
Trimethoprim/sulfamethoxazole	0.5/4 µg/mL	S

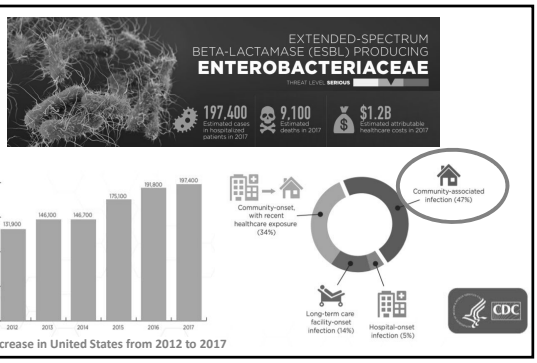
PREVIEW QUESTION

Antibiotic	MIC	Interpretation
Amikacin	>8 µg/mL	S
Aztreonam	16 µg/mL	R
Cefazolin	>16 µg/mL	R
Cefotetan	2 µg/mL	S
Cefepime	4 µg/mL	R
Ceftazidime	>16 µg/mL	R
Ceftriaxone	32 µg/mL	R
Ciprofloxacin	1 µg/mL	R
Ertapenem	0.5 µg/mL	S
Gentamicin	2 µg/mL	R
Meropenem	0.5 µg/mL	S
Piperacillin/tazobactam	8/4 µg/mL	S
Tobramycin	2 µg/mL	S
Trimethoprim/sulfamethoxazole	0.5/4 µg/mL	S

PREVIEW QUESTION

Which one of the following antibiotics represents the most appropriate initial treatment?

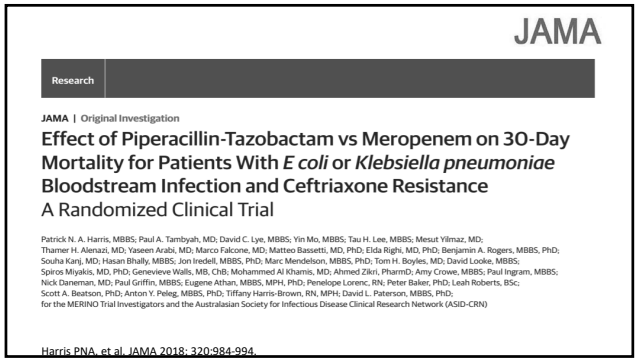
1. Cefepime
2. Trimethoprim-sulfamethoxazole
3. Meropenem
4. Piperacillin-tazobactam



53% increase in United States from 2012 to 2017

A Primer on ESBL-E

- Hydrolyze penicillins, cephalosporins, and aztreonam
- *E. coli*, *Klebsiella pneumoniae*, *Klebsiella oxytoca*, and *Proteus mirabilis*
- CTX-M enzymes are the most common ESBLs
- Ceftriaxone-resistant *E. coli*, *K. pneumoniae*, *K. oxytoca*, or *P. mirabilis* = think ESBL production


JAMA

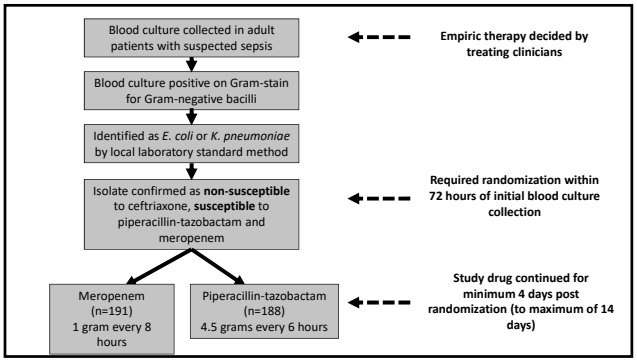
Research

JAMA | Original Investigation

Effect of Piperacillin-Tazobactam vs Meropenem on 30-Day Mortality for Patients With *E coli* or *Klebsiella pneumoniae* Bloodstream Infection and Ceftriaxone Resistance
A Randomized Clinical Trial

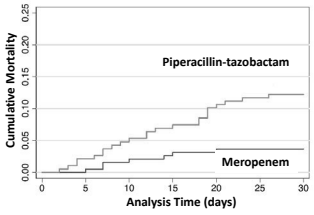
Patrick N. A. Harris, MBBS; Paul A. Tambyah, MD; David C. Lye, MBBS; Yin Mo, MBBS; Tau H. Lee, MBBS; Mesut Yilmaz, MD; Thamer H. Alenazi, MD; Yaseen Arabi, MD; Marco Falcone, MD; Matteo Bassetti, MD, PhD; Elda Righi, MD, PhD; Benjamin A. Rogers, MBBS, PhD; Souha Kanj, MD; Hasan Bhally, MBBS; Jon Iredell, MBBS, PhD; Marc Mendelson, MBBS, PhD; Tom H. Boyles, MD; David Looke, MBBS; Spiros Miyakis, MD, PhD; Genevieve Walls, MB, ChB; Mohammed Al Khamis, MD; Ahmed Zikri, PharmD; Amy Crowe, MBBS; Paul Ingram, MBBS; Nick Daneman, MD; Paul Griffin, MBBS; Eugene Athan, MBBS, MPH, PhD; Penelope Lorenc, RN; Peter Baker, PhD; Leah Roberts, BSc; Scott A. Beatson, PhD; Anton Y. Peleg, MBBS, PhD; Tiffany Harris-Brown, RN, MPH; David L. Paterson, MBBS, PhD; for the MERINO Trial Investigators and the Australasian Society for Infectious Disease Clinical Research Network (ASID-CRN)

Harris PNA, et al. JAMA 2018; 320:984-994.



Results

- 30-day mortality
  - Piperacillin-tazobactam 12% vs. meropenem 4% ($p<0.05$)
- Study terminated early
  - Unlikely to demonstrate non-inferiority



Harris PNA, et al. JAMA 2018; 320:984-994.

Which one of the following antibiotics represents the most appropriate initial treatment?

1. Cefepime
2. Trimethoprim-sulfamethoxazole
3. Meropenem
4. ~~Piperacillin-tazobactam~~

Clinical Infectious Diseases
IDSA GUIDELINES

Infectious Diseases Society of America 2023 Guidance on the Treatment of Antimicrobial Resistant Gram-Negative Infections

Question 1.5: Is There a Role for Cefepime in the Treatment of Infections Caused by ESBL-E?

Suggested Approach: Cefepime is not suggested for the treatment of infections caused by ESBL-E, even if susceptibility to the agent is demonstrated.

Tamma PD, et al. Clin Infect Dis. 2023 Jul 18:ciad428. doi: 10.1093/cid/ciad428. Online ahead of print.

Cefepime for ESBL-E Infections

- CTX-M enzymes generally hydrolyze cefepime
- Poorer outcomes with cefepime for the treatment of ESBL-E infections in observational studies

Wang R, Open Forum Infect Dis 2016; 3(3): ofw132. Lee NY, et al. Clin Infect Dis 2013; 56(4): 488-95. Chopra T, et al. Antimicrob Agents Chemother 2012; 56(7): 3936-42. Zanetti G, et al. Antimicrob Agents Chemother 2003; 47(11): 3442-7. Lee NY, et al. Antimicrob Agents Chemother 2015; 59(12): 7558-63.

Which one of the following antibiotics represents the most appropriate initial treatment?

1. ~~Cefepime~~
2. Trimethoprim-sulfamethoxazole
3. Meropenem
4. ~~Piperacillin-tazobactam~~

Clinical Infectious Diseases
IDSA GUIDELINES

Infectious Diseases Society of America 2023 Guidance on the Treatment of Antimicrobial Resistant Gram-Negative Infections

Question 1.3: What are preferred antibiotics for the treatment of infections outside of the urinary tract caused by ESBL-E?

Suggested Approach: Meropenem, imipenem-cilastatin, or ertapenem are preferred for the treatment of infections outside of the urinary tract caused by ESBL-E. After appropriate clinical response is achieved, transitioning to oral trimethoprim-sulfamethoxazole, ciprofloxacin, or levofloxacin should be considered, if susceptibility is demonstrated.

Tamma PD, et al. Clin Infect Dis. 2023 Jul 18:ciad428. doi: 10.1093/cid/ciad428. Online ahead of print.

Trimethoprim-Sulfamethoxazole (TMP-SMX) for ESBL-E Treatment

- TMP-SMX (and fluoroquinolones) not hydrolyzed by ESBL enzymes
- Reasonable treatment option for invasive ESBL-E infections (if susceptible), after clinical improvement observed

ESBL-E: Testable Points

- Hydrolyze traditional β-lactam antibiotics except carbapenems
- *E. coli*, *K. pneumoniae*, *K. oxytoca*, and *P. mirabilis* resistant to ceftriaxone = likely ESBL producer
- Carbapenems are treatment of choice
- TMP-SMX or fluoroquinolones reasonable after clinical improvement is observed

AmpC-E Infections

Clinical Case

- 62-year-old male with colon cancer
- Fevers, abdominal pain, and mental status changes one week after partial colectomy
- Multiple intra-abdominal abscesses
- Blood cultures are growing gram-negative rods

Which of the following bacterial species is most likely to produce AmpC β-lactamase enzymes?

1. *Escherichia coli*
2. *Enterobacter cloacae*
3. *Serratia marcescens*
4. *Proteus mirabilis*

Inducible Chromosomal *ampC* expression

- AmpC enzymes assist with bacterial cell wall recycling
  - Organisms producing AmpC enzymes even at low levels produce sufficient enzymes to hydrolyze ampicillin, ampicillin-sulbactam, cefazolin, cephamycins
- Inducible AmpC production: Capable of hydrolyzing certain antibiotics even though the bacteria initially seems susceptible to those agents
  - Most notorious = ceftriaxone (and other third-generation cephalosporins)
- *Enterobacter cloacae*, *Citrobacter freundii*, *Klebsiella aerogenes* have a reasonable likelihood of excessive AmpC production if exposed to ceftriaxone
  - Emergence of resistance while receiving ceftriaxone ~20% of the time
- *Serratia marcescens*, *Morganella morganii*, and *Providencia* spp. are significantly less likely to have excessive AmpC production if exposed to ceftriaxone
  - Emergence of resistance while receiving ceftriaxone <5% of the time

Clinical Infectious Diseases
IDSA GUIDELINES

IDSA Infectious Diseases Society of America | hivma hiv medicine association | OXFORD

Infectious Diseases Society of America 2023 Guidance on the Treatment of Antimicrobial Resistant Gram-Negative Infections

Question 2.3: What is the role of cefepime for the treatment of infections caused by Enterobacterales at moderate risk of clinically significant AmpC production due to an inducible ampC gene?

Suggested Approach: Cefepime is suggested for the treatment of infections caused by organisms at moderate risk of significant AmpC production (i.e., *E. cloacae* complex, *K. aerogenes*, and *C. freundii*).

Tamma PD, et al. Clin Infect Dis. 2023 Jul 18:ciad428. doi: 10.1093/cid/ciad428. Online ahead of print.

Cefepime

- Cefepime has the advantage of both being a weak inducer of *ampC* and of withstanding hydrolysis by AmpC β-lactamases
  - It is considered a preferred agent for the treatment of AmpC-E infections

Girlich D, et al. Antimicrob Agents Chemother 2000; 44: 3220-3. Sanders CC, et al. Antimicrob Agents Chemother 1997; 41: 2013-5.

E. coli Isolate	bla_{CMY-2} copy number	Piperacillin-tazobactam (μg/mL)	Aztreonam (μg/mL)	Ceftazidime (μg/mL)	Cefepime (μg/mL)	Imipenem (μg/mL)	Ertapenem (μg/mL)
Parent strain	1	4	2	32	0.12	0.12	0.02
Mutant 1	13	512	64	512	4	0.5	0.38
Mutant 2	3	64	32	128	0.5	0.12	0.12
Mutant 3	7	256	32	256	1	0.25	0.19

Kurpiel KM, et al. J Antimicrob Chemother 2012; 67:339-45.

AmpC-E: Testable Points

- Inducible AmpC enzymes most problematic for *E. cloacae*, *C. freundii*, & *K. aerogenes*
- Ceftriaxone not suggested for invasive infections caused by these 3 organisms
  - Cefepime generally treatment of choice
- When these 3 organisms are recovered in clinical cultures (outside of an uncomplicated cystitis) cefepime is the preferred treatment
  - Similar to ESBL-E, non-beta-lactam agents are not impacted

DTR *P. aeruginosa* Infections

PREVIEW QUESTION

Clinical Case

- 24-year-old male with acute myelogenous leukemia
  - Absolute neutrophil count = 0 cells/mL
- Acute onset fevers and respiratory distress
- Multifocal pneumonia
- *P. aeruginosa* recovered from bronchoalveolar lavage fluid

PREVIEW QUESTION

Antibiotic	MIC	Interpretation
Amikacin	> 8 µg/mL	R
Aztreonam	> 16 µg/mL	R
Cefepime	> 16 µg/mL	R
Ceftazidime	> 16 µg/mL	R
Ciprofloxacin	> 2 µg/mL	R
Colistin	2 µg/mL	I
Gentamicin	> 8 µg/mL	R
Meropenem	16 µg/mL	R
Piperacillin/tazobactam	> 64/4 µg/mL	R
Tobramycin	> 8 µg/mL	R

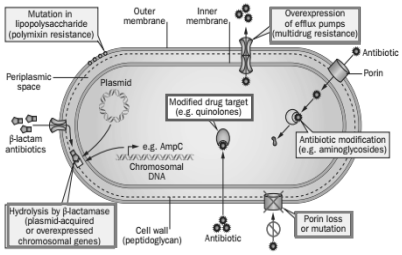
***Pseudomonas aeruginosa* with "difficult-to-treat resistance" = resistance to all traditional beta-lactam and fluoroquinolone agents**

PREVIEW QUESTION

Which one of the following antibiotics is least likely to be effective against DTR-*P. aeruginosa* infections?

1. Ceftolozane-tazobactam
2. Ceftazidime-avibactam
3. Meropenem-vaborbactam
4. Imipenem-cilastatin-relebactam

Common Mechanisms of Resistance



1. Reduction in outer membrane porins
2. Upregulation of efflux pumps
3. Increased production of Pseudomonal AmpCs
4. Mutations in penicillin binding proteins

Zowawi, et al. Nat Rev Urol 2015;12:570.

Why Have the Polymyxins Fallen out of Favor?

- Penetration into pulmonary epithelial lining fluid is suboptimal
- Colistin is administered IV as inactive prodrug colistin methanesulfonate; slowly and incompletely converted to colistin
- Difficult to achieve adequate colistin plasma concentrations in patients with normal renal function
- Several reports of clinical failure and resistance emergence during polymyxin monotherapy

Adverse Events Associated with Polymyxins

- **Nephrotoxicity**
  - ~40-60% with colistin
  - ~20-30% with polymyxin B
  - Usually reversible upon drug discontinuation
- **Neurotoxicity**
  - <5% of patients; mostly due to polymyxin B
  - Manifests as paresthesias, seizures, neuromuscular blockade
  - Usually reversible upon drug discontinuation

Activity of β-Lactams Against DTR *P. aeruginosa*

β-Lactam Agents	DTR-*P. aeruginosa*
Ceftolozane-tazobactam (2014)	
Ceftazidime-avibactam (2015)	
Meropenem-vaborbactam (2017)	
Cefiderocol (2019)	
Imipenem-cilastatin-relebactam (2020)	
Sulbactam-durlobactam (2023)	

Antibiotics Active Against DTR *P. aeruginosa*

- Susceptibility to ceftolozane-tazobactam, ceftazidime-avibactam, and imipenem-cilastatin-relebactam ranges from 50-90%
- Risk of emergence of resistance after a single treatment course is highest for ceftolozane-tazobactam or ceftazidime-avibactam treatment
  - Repeat antibiotic susceptibility testing for future *P. aeruginosa* infections
- Generally avoid imipenem-cilastatin-relebactam if receiving concomitant valproic acid

Rubio AM, et al. Antimicrob Agents Chemother. 2021;65:e00084-21. Tamma PD, et al. Clin Infect Dis. 2022;75:187-212. Tamma PD, et al. Clin Infect Dis 2021;73:e4599-e4606. Canon JP, et al. Journal of Antimicrobial Chemotherapy. 2014;69:2043-2055.

Cefiderocol

- Cephalosporin combined with a siderophore
- Siderophores are iron chelators that enable cefiderocol to bind iron and enter bacteria through iron-transport channels
- Resistance mostly because of mutations in iron transport proteins
- Second-line agent for DTR *P. aeruginosa* infections

O'Donnell JN, et al. Antimicrob Agents Chemother. 2022;66:e0025622.

DTR *P. aeruginosa*: Testable Points

- Polymyxins not suggested for DTR *P. aeruginosa*
  - Exception: colistin for uncomplicated cystitis
- Preferred: ceftolozane-tazobactam, ceftazidime-avibactam, imipenem-cilastatin-relebactam
- Emergence of resistance most concerning for ceftolozane-tazobactam and ceftazidime-avibactam
- Avoid imipenem-cilastatin-relebactam if receiving valproic acid
- Cefiderocol is unique: siderophore enabling entry into bacteria through iron transport channels

CRE Infections

Clinical Case

- 30-year-old female with a cardiac transplant at age 4 years for a hypoplastic left heart
  - Complicated clinical course requiring multiple, prolonged hospitalizations
- Acute onset fevers, rigors, and hypotension
- *Klebsiella pneumoniae* in blood cultures

Antibiotic	MIC	Interpretation
Amikacin	> 8 µg/mL	R
Aztreonam	> 16 µg/mL	R
Cefepime	> 16 µg/mL	R
Ceftazidime	> 16 µg/mL	R
Ciprofloxacin	> 2 µg/mL	R
Ertapenem	2 µg/mL	R
Gentamicin	> 8 µg/mL	R
Meropenem	8 µg/mL	R
Piperacillin/tazobactam	> 64 µg/mL	R
Tobramycin	> 8 µg/mL	R

bla_{KPC} gene present

Which of the following antibiotics is not expected to be effective at treating a KPC-producing infection?

1. Ceftolozane-tazobactam
2. Ceftazidime-avibactam
3. Meropenem-vaborbactam
4. Imipenem-cilastatin-relebactam

Defining Carbapenem-Resistant Enterobacterales (CRE)

- Resistant to at least one carbapenem
- ~50% of CRE have a carbapenemase gene
- Common carbapenemases:
  - *Klebsiella pneumoniae* carbapenemases **(KPCs)**
  - New Delhi metallo-β-lactamases **(NDMs)**
  - Verona integron-encoded metallo-β-lactamases **(VIMs)**
  - Imipenem-hydrolyzing metallo-β-lactamases **(IMPs)**
  - Oxacillinases **(OXA-48-like)**

Activity of β-Lactams Against CRE Isolates

β-Lactam Agents	KPCs	NDMs	OXA-48-like
Ceftazidime-avibactam (2015)			
Cefotolozane-tazobactam (2014)			
Meropenem-vaborbactam (2017)			
Cefiderocol (2019)			
Imipenem-cilastatin-relebactam (2020)			
Sulbactam-durlobactam (2023)			

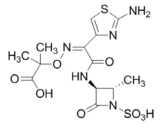
KPC-Producing Enterobacterales

- Class A β-lactamases
- Most common carbapenemases in the United States
- In many Enterobacterales species; not unique to *K. pneumoniae*
- **Treatment options**
  - Preferred: Ceftazidime-avibactam, meropenem-vaborbactam, imipenem-cilastatin-relebactam
  - Alternative: Cefiderocol

NDM-Producing Enterobacterales

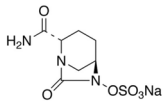
- Class B β-lactamases
- 10% of carbapenemase-producing Enterobacterales in the Untied States
  - Main risk factor: previous medical care in Indian subcontinent
- **Treatment options**
  - Preferred: Cefiderocol or ceftazidime-avibactam PLUS aztreonam

Aztreonam



NDMs

Avibactam



ESBLs, AmpCs, KPCs, OXA-48-like

OXA-48-like-Producing Enterobacterales

- Class D β-lactamases
- Rare in the United States (<5% of carbapenemase-producing Enterobacterales)
  - Main risk factor: previous medical care in Indian subcontinent, Middle East, or Europe
- **Treatment options**
  - Preferred: Ceftazidime-avibactam or cefiderocol

CRE: Testable Points

- CRE: carbapenemase or non-carbapenemase-producing
- KPC: most common carbapenemase
- NDM: medical care in South Asia
- Unlikely to be tested on VIM, IMP, OXA-48-like carbapenemases
- **Preferred treatment**
  - KPC-producers: ceftazidime-avibactam, meropenem-vaborbactam, imipenem-cilastatin-relebactam
  - NDM-producers: cefiderocol, ceftazidime-avibactam PLUS aztreonam

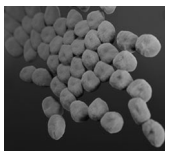
CRAB Infections

Clinical Case

- 39-year-old male recovering from a motor vehicle accident in a burn unit
  - Prolonged hospitalization
  - Requiring intubation
- Fevers, increased oxygen support, new pulmonary infiltrates
- *Acinetobacter baumannii* recovered in endotracheal aspirate

General Challenges with CRAB

- Distinguishing colonization from infection can be difficult
  - Commonly recovered from non-sterile sites (e.g., respiratory specimens, wounds)
- Patient population at risk has underlying reasons for poor outcomes (e.g., burn patients, mechanical ventilation, combat wounds)
  - Interpretation of comparative effectiveness studies difficult



https://arpsp.cdc.gov/profile/antibiotic-resistance/carbapenem-resistant-acinetobacter

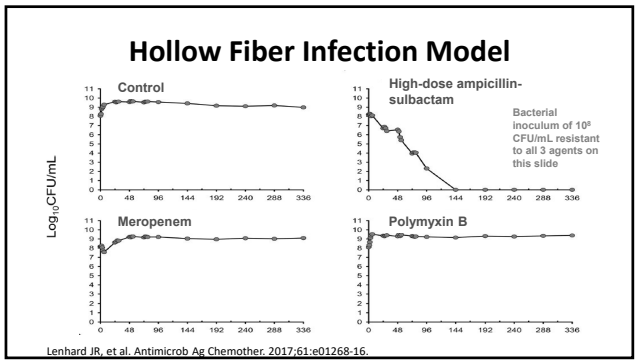
Benefits of Sulbactam

- Ability to function as a β-lactam and can saturate PBP1a/1b and PBP3 of *A. baumannii* isolates
- Unique activity against *A. baumannii* isolates demonstrated through in vitro studies, animal models, and clinical outcomes data

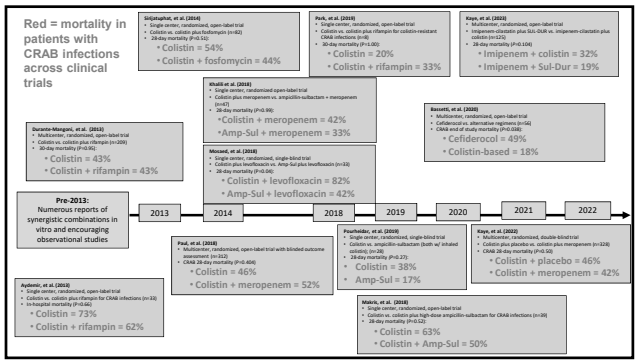
Lenhard JR, et al. Antimicrob Agents Chemother. 2017;61:e01268-01216. Beganovic M, et al. Antimicrob Agents Chemother. 2021;65:e01680-01620. Abdul-Mutakabbir JC, et al. Antibiotics (Basel). 2021;10. Rodriguez-Hernandez MJ, et al. J Antimicrob Chemother. 2001;47:479-482. Makris D, et al. Indian J Crit Care Med. 2018;22:67-77. Betrosian AP, et al. Scand J Infect Dis. 2007;39:38-43. Assimakopoulos SFet al. Infez Med. 2019;27:11-16. Liu J, et al. J Glob Antimicrob Resist. 2021;24:136-147. Jung SY, et al. Crit Care. 2017;21:319.

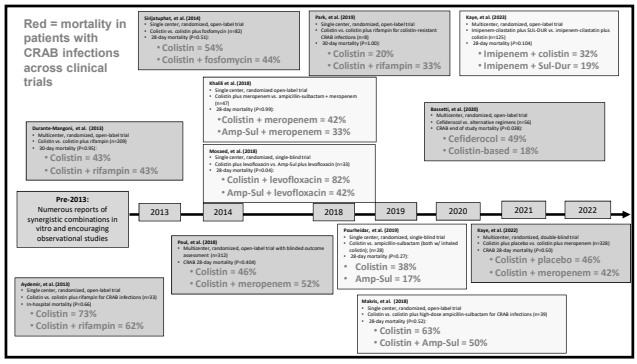
13 – Core Concepts: Antibacterial Drugs I Gram Negative Organisms

Speaker: Pranita Tamma, MD



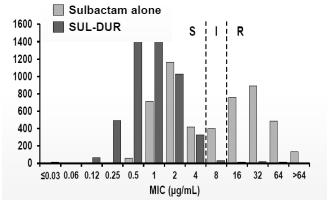
Lenhard JR, et al. Antimicrob Ag Chemother. 2017;61:e01268-16.





Sulbactam-Durlobactam (Sul-Dur)

- Durlobactam is β-lactamase inhibitor
- Inhibits class D β-lactamases very commonly produced by CRAB isolates (e.g., OXA-23)
- Does NOT inhibit class B β-lactamases (e.g., NDM)
- 98% of large global collection of *A. baumannii* isolates susceptible to sulbactam-durlobactam



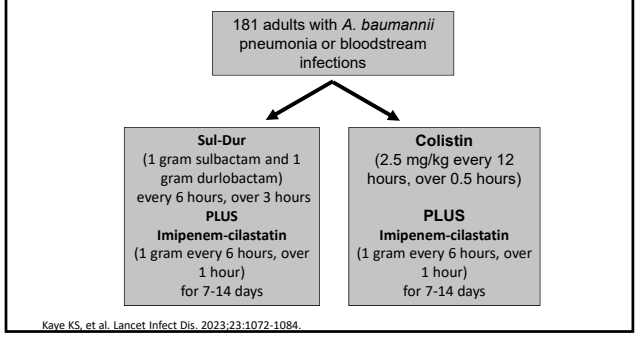
Karlowsky JA, et al. Antimicrob Ag Chemother. 2022:e007812.

THE LANCET

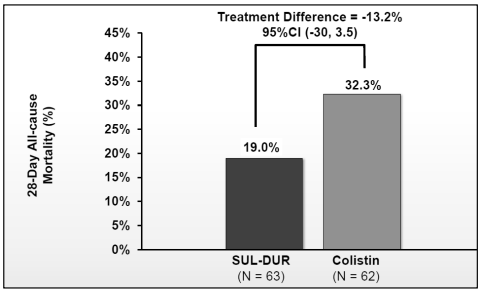
Efficacy and safety of sulbactam–durlobactam versus colistin for the treatment of patients with serious infections caused by *Acinetobacter baumannii–calcoaceticus* complex: a multicentre, randomised, active-controlled, phase 3, non-inferiority clinical trial (ATTACK)

Keith S Kaye, Andrew F Shorr, Richard G Wunderink, Bin Du, Gabrielle E Poirier, Khurram Rana, Alita Miller, Drew Lewis, John O'Donnell, Lan Chen, Harald Reinhart, Subasree Srinivasan, Robin Isaacs, David Altarac

Kaye KS, et al. Lancet Infect Dis. 2023;23:1072-1084.



Kaye KS, et al. Lancet Infect Dis. 2023;23:1072-1084.



Kaye KS, et al. Lancet Infect Dis. 2023;23:1072-1084.

CRE: Testable Points

- Identification of CRAB in a clinical specimen does not always mean antibiotic therapy is indicated
- Sulbactam-based regimens remain the cornerstone of treatment
  - First choice: **Sulbactam-Durlobactam** (with imipenem or meropenem)
  - Second choice: **High-dose Ampicillin-Sulbactam** (with an additional agent)
- Potential "additional agents" include **polymyxin B** or **minocycline** or **cefiderocol**

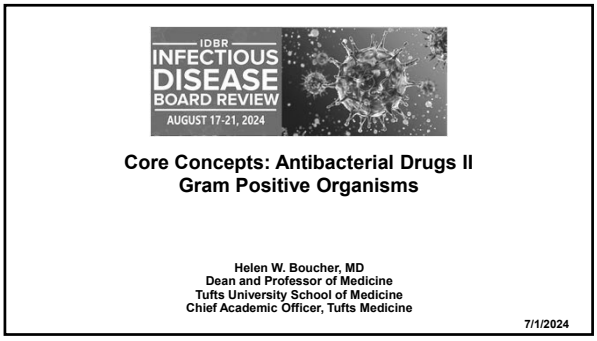
14

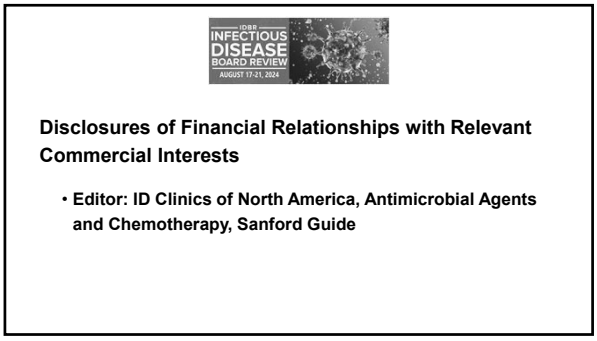
Core Concepts: Antibacterial Drugs II: Gram Positive Organisms

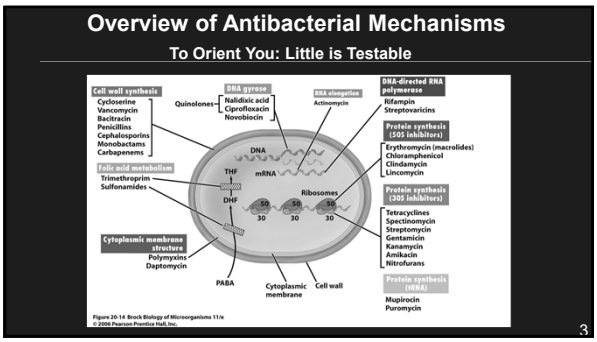
Dr. Helen Boucher

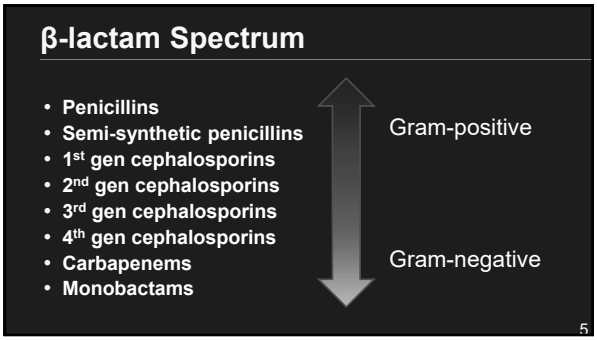
14 – Core Concepts: Antibacterial Drugs II Gram Positive Organisms

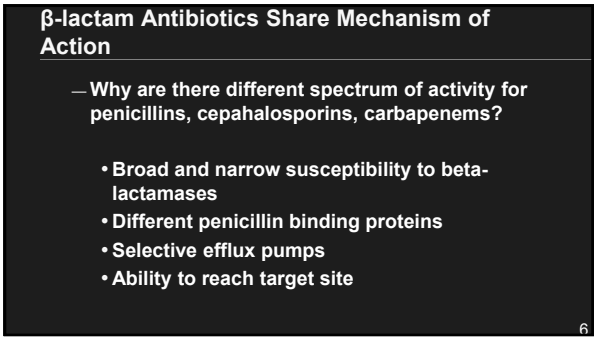
Speaker: Helen Boucher, MD











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

Question

- What is the only cephalosporin active against MRSA

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

8

Cephalosporins

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

9

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

- 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

11

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
  - Similar spectrum to ceftriaxone
- Bactericidal, time dependent killing

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

12

14 – Core Concepts: Antibacterial Drugs II Gram Positive Organisms

Speaker: Helen Boucher, MD

Vancomycin

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

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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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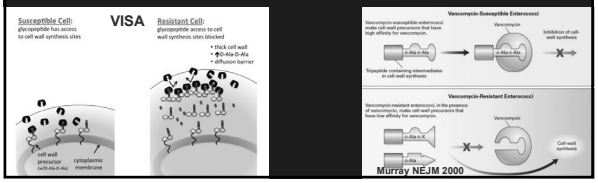
Vancomycin Resistance

- VISA thickened cell wall + xs vancomycin binding sites (D-Ala-D-Ala); result: vanco trapping with reduced cellular targets
- VRE – replacement of D-Ala-D-Ala with D-alanyl-D-lactate termini – result: decreased vancomycin binding affinity --- high level resistance: MIC increase x 1000

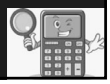


Vancomycin for MRSA Bloodstream Infection

- 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
- DRESS
- Immune thrombocytopenia
- Neutropenia

Drug Interactions

- Increased nephrotoxicity when given with other nephrotoxins
  - Aminoglycosides
  - NSAIDs
  - Contrast
  - Cyclosporine
  - Tacrolimus
  - Loop Diuretics
  - ACE inhibitors
  - Pip/tazo (pseudo interaction)

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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

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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	Mechanism of Action	Mechanism of Resistance	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 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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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

22

Question

- Which quinolone has activity against MRSA

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

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Antibiotics Active Intracellularly

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

24

14 – Core Concepts: Antibacterial Drugs II Gram Positive Organisms

Speaker: Helen Boucher, MD

Fluoroquinolone Mechanism of Action And Resistance

- 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
  - Susceptible to drug modifying enzymes

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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 *Stenotrophomonas* spp.	Some
Moxi	Good strep Good MSSA	Not effective Don't use for UTI	Best

Drs. Tamma and Gilbert will address Gram-negative activity

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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, ascitic fluid and prostate gland
- 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++

28

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

29

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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14 – Core Concepts: Antibacterial Drugs II Gram Positive Organisms

Speaker: Helen Boucher, MD

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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Newer Tetracyclines

	Omadacycline	Eravacycline
FDA approval	ABSSSI, CABP	cIAI, not cUTI (failed studies)
Dosing	200 mg loading dose over 60 min day 1, 100mg IV over 30 min or 300mg orally once daily No dose adjustment for renal/hepatic impairment	1mg/kg IV q 12h (over 60 minutes) Dose adjustment with hepatic impairment
Activity	Broad spectrum: Gram-pos including MRSA, VRE; Gram-neg including ESBL, CRE (not all); anaerobes	
Issues	Limited activity vs carbapenem-resistant *K. pneumoniae*	High MIC *Pseudomonas*, *Burkholderia* spp.
Safety	GI, rash, ?heart rate	GI, rash

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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 *S.aureus* reported
  - Mycobacteria
- Resistance is rare; target change
- Linezolid twice daily; Tedizolid once daily
- 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

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Linezolid Adverse Events

- Adverse events related to mitochondrial toxicity:
  - Cytopenias
    - Monitor CBC
  - Peripheral and optic neuropathy
  - Rare:
    - Lactic acidosis, serotonin syndrome (w SSRIs)
- ↑ mortality in study of intravenous 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

35

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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14 – Core Concepts: Antibacterial Drugs II Gram Positive Organisms

Speaker: Helen Boucher, MD

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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14 – Core Concepts: Antibacterial Drugs II Gram Positive Organisms

Speaker: Helen Boucher, MD

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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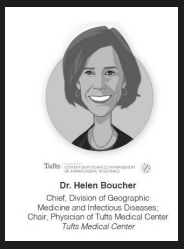
Questions, Comments?

- @hboucher3
- Helen.boucher@tufts.edu
- Helen.boucher@tuftsmedicine.org



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Appendix

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Penicillins

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	

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Cephalosporins

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 Clinical Use

- 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)

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14 – Core Concepts: Antibacterial Drugs II Gram Positive Organisms

Speaker: Helen Boucher, MD

Ceftaroline Safety and Monitoring

- 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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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

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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

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Dalbavancin

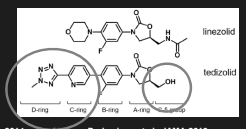
- Other uses
  - Limited data, varying dosing regimens
    - Endocarditis and osteomyelitis
    - Persons who inject drugs
- Case reports of failure with emergence of VISA, presumably associated with low-level drug exposure
  - One patient had VISA detected in urine while on dalbavancin for CLASBI
 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

52

Tedizolid - Oxazolidinone Drug Class Once Daily Dosing, Lower Dose

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

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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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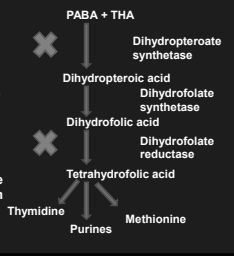
14 – Core Concepts: Antibacterial Drugs II Gram Positive Organisms

Speaker: Helen Boucher, MD

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

HIGH PLASMA PROTEIN BINDING

COMPETES FOR TUBULAR SECRETION

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Clindamycin

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

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

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Protein Synthesis Inhibitors - Summary

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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15

CMV, EBV, HHV6, and HHV8 in Immunocompetent and Immunocompromised Patients

Dr. Camille Kotton

15 – 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

7/1/2024

Disclosures of Financial Relationships with Relevant Commercial Interests		
Company	Role	Details
Evrys	Consultant	CMV treatment in transplant
Kamada Biotest	Consultant, research	Immunoglobulins and organ transplant infection prevention
Merck	Consultant, Adjudication committee member, Data monitoring committee, symposium speaker (CME)	Transplant infections CMV antiviral trial, adjudication Pneumococcal vaccine, adjudication
QIAGEN	Consultant, research	Novel diagnostics in transplant patients
Shire/Takeda	Consultant, Adjudication committee member	CMV management in transplant patients
Roche Diagnostics	Research	Review of risk factors for herpes viral infections after transplant

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)**

Differential Diagnosis of Pharyngitis

Table 1. **Differential Diagnosis of Pharyngitis.***

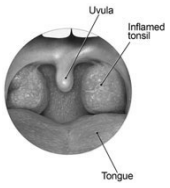
Pathogen	Affected Age Group	Season†	Associated Diagnosis and Distinguishing Feature‡
Respiratory viruses			
Rhinovirus	All	Fall and spring	Common cold
Coronavirus	Children	Winter	Common cold
Influenza virus	All	Winter and spring	Influenza
Adenovirus	Children, adolescents, and young adults	Summer (outbreaks) 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 (5 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%) Mononucleosis-like illness, 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 Bruno.[58]
† 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.

Features of 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 (>10%)	++++	+++	+	++
Elevated LFTs	++++	+++	0	+



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**

15 – CMV, EBV, HHV6 and HHV8 in Immunocompetent and Immunocompromised Patients

Speaker: Camille Kotton, MD

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 disease (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
  - High risk in EBV seronegative organ transplant recipients for infection, lymphoma
- Latently infected memory B lymphocytes serve as lifelong viral reservoirs
  - EBV is capable of transforming B lymphocytes, resulting in malignancy

Epstein-Barr virus Mononucleosis

- Transmission - saliva (due to prolonged shedding for months), sexual
- Long incubation period – 4 to 8 weeks
- 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 - **> 40% lymphocytosis** with atypical lymphocytes
- Diagnosis - **serology**
  - Non-specific heterophile Ab ("**monospot**") sensitivity 87%, specificity 91%
  - EBV specific Ab panel
- EBV viral load/PCR - *not necessary for routine mononucleosis*, may be useful in transplant or other immunocompromised patients
- Therapy - supportive, no antiviral therapy, steroids for upper-airway obstruction, hemolytic anemia, and thrombocytopenia (rash with ampicillin)
- Prevention - no vaccine (Moderna mRNA vaccine phase 1 Eclipse Trial, ending 2025)
- EBV reactivation mostly asymptomatic; can reflect extent of immunosuppression

Complications of Primary EBV Infection/Infectious Mononucleosis

General:

- Splenic rupture in 0.5-1%, male > female, mostly w/in 3 weeks (up to 7 weeks)

****avoid contact sports for 4 weeks minimum****

- Prolonged fatigue/malaise (>6 mo. in 10%)
- Hepatitis, rarely with fulminant hepatic failure
- Pneumonitis
- Peritonsillar abscess
- Airway obstruction from massive adenopathy

Heme syndromes:

- Neutropenia
- TTP-HUS
- DIC
- Acquired hypogammaglobulinemia
- X-linked lymphoproliferative disease (EBV as trigger)
- Hemophagocytic lymphohistiocytosis (HLH) (estimated 50% of all HLH cases from EBV)

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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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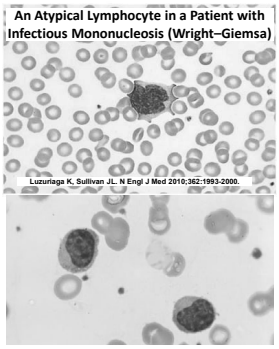
An Atypical Lymphocyte in a Patient with Infectious Mononucleosis (Wright–Giemsa)



From https://phil.cdc.gov/Details.aspx?pid=19469

Atypical lymphocytes

- 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:

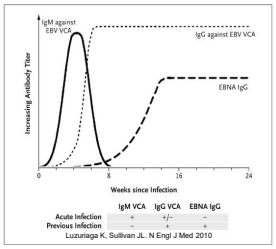
- Low nuclear / cytoplasmic ratio
- Indented or lobulated nuclei with nucleoli
- Cytoplasm often basophilic; can be "sky blue", with vacuoles and granules

15 – CMV, EBV, HHV6 and HHV8 in Immunocompetent and Immunocompromised Patients

Speaker: Camille Kotton, MD

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.** → "VCA is here to stay"
- **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



	IgM VCA	IgG VCA	EBNA IgG
Acute Infection	+	+/-	-
Previous Infection	-	+	+

Luzuriaga K, Sullivan JL. N Engl J Med 2010

https://www.cdc.gov/epstein-barr/laboratory-testing.html

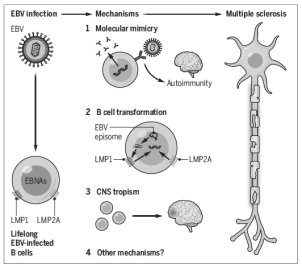
Longitudinal analysis reveals high prevalence of Epstein-Barr virus associated with multiple sclerosis

Kjetil Bjornevik[1]; Marianna Cortese[1]; Brian C. Healy[2,3,4]; Jens Kuhle[5]; Michael J. Mina[6,7,8]; Yumei Leng[9]; Stephen J. Elledge[9]; David W. Niebuhr[10]; Ann I. Scher[11]; Kassandra L. Munger[1]; Alberto Ascherio[1,12,13]*

Science 375, 296–301 (2022)

Multiple sclerosis (MS) is a chronic inflammatory demyelinating disease of the central nervous system of unknown etiology. We tested the hypothesis that MS is caused by Epstein-Barr virus (EBV) in a cohort comprising more than 10 million young adults on active duty in the US military, 955 of whom were diagnosed with MS during their period of service. Risk of MS increased 32-fold after infection with EBV but was not increased after infection with other viruses, including the similarly transmitted cytomegalovirus. Serum levels of neurofilament light chain, a biomarker of neuroaxonal degeneration, increased only after EBV seroconversion. These findings cannot be explained by any known risk factor for MS and suggest EBV as the leading cause of MS.

My interpretation:
- Interesting observation
- Nothing for us to do clinically, no antiviral treatments
- EBV vaccine could be helpful in the future (?)



Model for multiple sclerosis development
From Robinson & Steinman, Science, Jan 2022 Vol 375 Issue 6578

EBV after Organ/Stem Cell 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 EBV viral load periodically for the first two years after transplant
  - If EBV viremia, reduce immune suppression whenever possible
- Low EBV viremia (<~5,000 IU/ml) may reflect immunosuppressed state
- No evidence that any currently available 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
Preiksaitis et al, The IPTA Nashville Consensus Conference on Post-Transplant lymphoproliferative disorders after solid organ transplantation in children: III - Consensus guidelines for Epstein-Barr virus load and other biomarker monitoring, Pedia Transplant 2024

QUESTION

PREVIEW 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?

Response	VCA IgM	VCA IgG	EBNA IgG	EA IgG
A	+	+	+	+
B	+	+	-	+
C	-	+	+	+
D	-	-	+	-

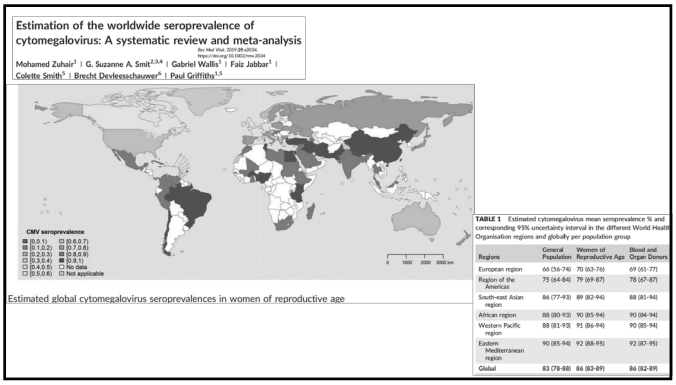
CMV

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*)
  - In low-income regions, 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+)
- Immunocompromised hosts
  - Seen with inflammatory bowel disease
  - Can see atypical syndromes – worth checking

15 – CMV, EBV, HHV6 and HHV8 in Immunocompetent and Immunocompromised Patients

Speaker: Camille Kotton, MD



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 (Moderna mRNA CMV)

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)

CMV: Congenital infection

- Leading cause of nonhereditary sensorineural hearing loss in USA
  - Can cause other long-term neurodevelopmental issues, including cerebral palsy, intellectual disability, seizures, vision impairment
- Congenital CMV 0.6% prevalence in high income countries
  - 40,000 children/year in USA
- Primary maternal CMV infection - 30-40% risk of congenital infection
  - Having children in daycare is major risk
- Reactivation maternal CMV infection - 0.9-1.5% risk of congenital infection
- Newborn screening under evaluation, sensitivity of dried blood spots for detecting congenital CMV infection is 73-78%

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.

CMV INFECTION AFTER ORGAN/STEM CELL TRANSPLANT: A SPECTRUM OF DISEASE

Direct Effects

Asymptomatic Viremia

CMV Viral Syndrome
- Flu-like syndrome: fever, malaise, myalgia
- Leukopenia, thrombocytopenia

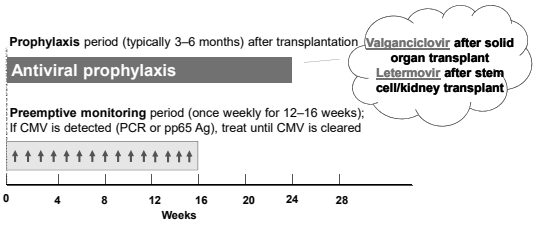
Tissue-Invasive Disease
- GI diseases: Colitis, Hepatitis
- Pneumonitis
- Myocarditis
- Myocarditis
- Nephritis
- Encephalitis, retinitis

Torres-Madriz G, Boucher HW. Clin Infect Dis. 2008;47(5):702-711; Kotton CN, CMV: Prevention, Diagnosis and Therapy, AJT 2013

15 – CMV, EBV, HHV6 and HHV8 in Immunocompetent and Immunocompromised Patients

Speaker: Camille Kotton, MD

PREVENTION: Prophylaxis vs. Preemptive Therapy

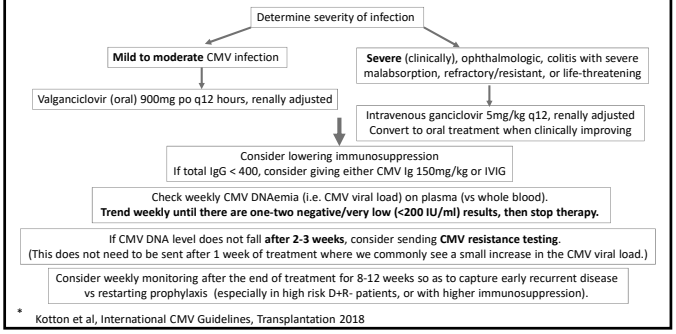


Humar A, Snydman D; AST Infectious Diseases Community of Practice. *Am J Transplant.* 2009;9 (Suppl 4):S78-S86.

CMV Diagnostics

- Serology
  - To diagnose acute infection in normal host, 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 – for immunocompromised
  - **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)

Treatment of CMV after Transplant



* Kotton et al, International CMV Guidelines, Transplantation 2018

Ensure Correct CMV Resistance Testing Ordered

Detects Resistance to:	UL97 Phosphotrans-ferase	UL54 Polymerase	UL27	UL56 Terminase
Maribavir, Letermovir, Ganciclovir, Foscarnet, Cidofovir	x			
Maribavir, Ganciclovir, Foscarnet, Cidofovir		x		
Maribavir			x	
Letermovir				x

What is the definition of resistant/refractory CMV?

Resistant CMV infection: The presence of a ***known viral genetic mutation(s)*** that decreases the susceptibility to one or more anti-CMV medications.

Refractory CMV infection: Persistent signs and symptoms of CMV disease and/or persistent CMV viremia that fails to improve [<1 $\log^{10}$ (<10x) decrease in CMV viral load] or increases after **at least 2 weeks** of appropriately dosed antiviral therapy.

Chemaly R *et al*, Definitions of Resistant and Refractory Cytomegalovirus Infection and Disease in Transplant Recipients for Use in Clinical Trials. CID 2018

Maribavir: Current State of Regulatory Approval

- Approved by Federal Drug & Food Administration (FDA) in December 2021 (≥ 12 years old) and European Medicines Agency in September 2022 (adults) for **treatment of resistant/refractory CMV disease after SOT/HSCT**
- **Not yet approved for treatment outside of resistant/refractory CMV disease**
  - "A Phase 3, Multicenter, Randomized, Double-blind, Double-dummy, Active-controlled Study to Assess the Efficacy and Safety of Maribavir Compared to Valganciclovir for the **Treatment of Asymtomatic Cytomegalovirus (CMV) Infection in Hematopoietic Stem Cell Transplant Recipients**", ClinicalTrials.gov: NCT02927067 → did not reach non-inferiority endpoint
- **Unlikely to move forward as prophylaxis** in the near future
  - Prior failure in stem cell and liver transplant (likely due to doses used)
- / JOAJMPN@R IIC M@CII IIINUM$ / 4 PIN@<N@

15 – CMV, EBV, HHV6 and HHV8 in Immunocompetent and Immunocompromised Patients

Speaker: Camille Kotton, MD

Clinically significant drug interactions with maribavir

Cytochrome-P450 (CYP)/P-glycoprotein	Concomitant medication	Clinical implication of interaction	Clinical management of interaction
CYP-3A4 substrate/ P-glycoprotein substrate	Cyclosporine	Increase cyclosporine concentration	Patients concomitantly receiving maribavir and CYP-3A4/ P-glycoprotein substrates (cyclosporine, everolimus, tacrolimus, sirolimus) should have plasma levels monitored starting at initiation through discontinuation of maribavir.
	Everolimus	Increase everolimus concentration	
	Tacrolimus	Increase tacrolimus C_{max} 38% and AUC 51%	
	Sirolimus	Increase sirolimus concentration	
	Digoxin	Increase digoxin concentrations	Digoxin plasma concentrations should be monitored starting at initiation through discontinuation of maribavir.
	Rosuvastatin	Increase rosuvastatin concentrations	Monitor for myopathy and rhabdomyolysis
CYP-3A4/ P-glycoprotein strong-moderate inhibitor	Diltiazem	Increase maribavir C_{max} 6% and AUC 9%	Can consider co-administering maribavir with strong CYP3A4 inhibitors without dose adjustment, based on lack of toxicities associated with doses up to 1200mg twice daily in studies and lack of 3-fold increase in AUC with strong-moderate CYP-3A4 inhibitors.
	Erythromycin	Increase maribavir C_{max} 26% and AUC 44%	
	Ketoconazole	Increase maribavir C_{max} 17% and AUC 54%	
	Ritonavir	Increase maribavir C_{max} 37% and AUC 63%	
CYP3A4/P P-glycoprotein strong-moderate inducer	Carbamazepine	Decrease maribavir C_{max} 23% and AUC 29%	Consider increasing maribavir doses to 800-1200 mg twice daily
	Efavirenz	Decrease maribavir C_{max} 25% and AUC 42%	Consider increasing maribavir doses to 1200-1600 mg twice daily
	Phenobarbital	Decrease maribavir C_{max} 27% and AUC 39%	Consider increasing maribavir doses to 800-1200 mg twice daily
	Phenytoin	Decrease maribavir C_{max} 31% and AUC 42%	Consider increasing maribavir doses to 1200mg twice daily
	Rifampin	Decrease maribavir C_{max} AUC 61%	Co-administration should be avoided and alternative antimicrobial or antituberculosis therapy should be considered if alternative CMV agents cannot be used.
CYP2C19 substrate	Voriconazole	No effect	Maribavir and voriconazole may be co-administered without dose adjustment. Unknown if interactions with posaconazole, itraconazole, and isavuconazole, exist, but unlikely based on voriconazole data.

*

Gandhi RG & Kotton CN, Evaluating the Safety of Maribavir for the Treatment of CMV, Therapeutics and Clinical Risk Management 2022:18 223–232

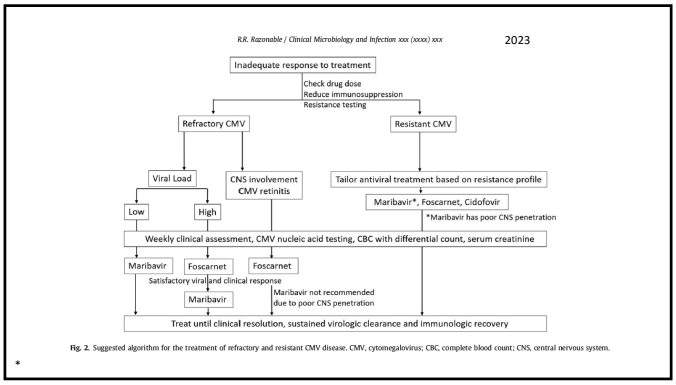


Fig. 2. Suggested algorithm for the treatment of refractory and resistant CMV disease. CMV, cytomegalovirus; CBC, complete blood count; CNS, central nervous system.

*

JAMA | Original Investigation

Letermovir vs Valganciclovir for Prophylaxis of Cytomegalovirus in High-Risk Kidney Transplant Recipients

A Randomized Clinical Trial June 2023

Ajit P. Limaye, MD; Klemens Budde, MD; Atul Humar, MD, MSc; Flavio Vincenti, MD; Dirk R. J. Kuypers, MD, PhD; Robert P. Carroll, BM, BCh, DM; Nicole Stauffer, BS; Yoshihiko Murata, MD, PhD; Julie M. Strizki, PhD; Valerie L. Teal, MS; Christopher L. Gilbert, BS; Barbara A. Haber, MD

- D+R- kidney transplants
- Compared letermovir 480mg, orally daily (with acyclovir) or valganciclovir 900mg, orally daily (adjusted for kidney function) for up to 200 days after transplant
- **Confirmed CMV disease: 10.4% on letermovir vs 11.8% on valganciclovir = SAME**
- **Leukopenia or neutropenia** by week 28 lower w/ letermovir vs valganciclovir (26% vs 64%; P < .001)
- Quantifiable CMV DNAemia detected in 2.1% on letermovir vs 8.8% on valganciclovir by week 28
  - Of participants evaluated for suspected CMV disease or CMV DNAemia, none (0/52) who received letermovir and 12.1% (8/66) who received valganciclovir had resistance-associated substitutions.
- Fewer participants in the letermovir group than the valganciclovir group discontinued prophylaxis due to adverse events (4.1% vs 13.5%) or drug-related adverse events (2.7% vs 8.8%)

MERCK

Media > News releases > News release

June 6, 2023

U.S. FDA Approves New Indication for Merck's PREVYMIS® (letermovir) for Prevention of Cytomegalovirus (CMV) Disease in High-Risk Adult Kidney Transplant Recipients

*previously approved for stem cell transplant prophylaxis

important drug interactions
Tacrolimus
Cyclosporine
Azoles

PREVYMIS® (letermovir) tablets, for oral use
PREVYMIS® (letermovir) injection, for intravenous use
Initial U.S. Approval: 2017

----------RECENT MAJOR CHANGES----------

Indications and Usage, CMV Prophylaxis in Kidney Transplant Recipients (1.2)	06/2023
Dosage and Administration, Recommended Dosage for Adult Patients (2.2)	06/2023

----------INDICATIONS AND USAGE----------

PREVYMIS is a CMV DNA terminase complex inhibitor indicated for:

- Prophylaxis of cytomegalovirus (CMV) infection and disease in adult CMV-seropositive recipients [R+] of an allogeneic hematopoietic stem cell transplant (HSCT). (1.1)
- Prophylaxis of CMV disease in adult kidney transplant recipients at high risk (Donor CMV seropositive/Recipient CMV seronegative [D+/R-]). (1.2)

---------- DOSAGE AND ADMINISTRATION ----------

- HSCT: 480 mg administered once daily orally or as an intravenous (IV) infusion over 1 hour through 100 days post-transplant. (2.1, 2.2)
- Kidney Transplant: 480 mg administered once daily orally or as an IV infusion over 1 hour through 200 days post-transplant. (2.1, 2.2)

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[3,5] | Camille N. Kotton[3]

"Cytomegalo-tumor"

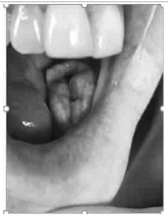


FIGURE 1 Fungating ulcerated lesion on oral mucosa of the left lower mandible at the site of prior SCC resection and marginal mandibulectomy

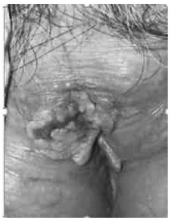


FIGURE 3 Six centimeter cluster of verrucous papules in a cluster encompassing the entire right labia minora, the right clitoral hood, and the margin of the right labia majora and sparing the perlurethral area

Transpl Infect Dis. 2020;00:e13535.
https://doi.org/10.1111/tid.13535

QUESTION

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

15 – CMV, EBV, HHV6 and HHV8 in Immunocompetent and Immunocompromised Patients

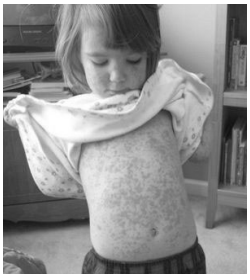
Speaker: Camille Kotton, MD

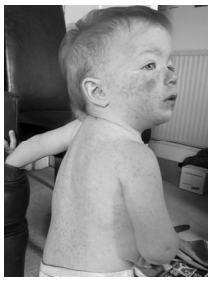
HHV-6

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

Exanthem subitum (roseola, sixth disease)





Slide courtesy of John W. Gnann Jr., MD, Medical University of South Carolina

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

**because it was the sixth common childhood rash that scientists named:*
measles, scarlet fever, rubella, Dukes' disease (now same as scarlet fever), and erythema infectiosum (parvovirus B19)

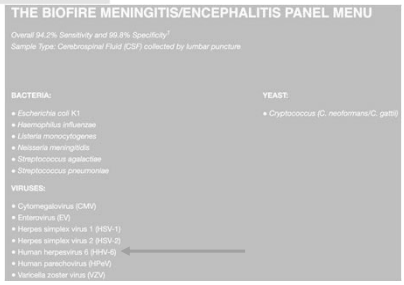
HHV-6: Immunocompromised Hosts

- Associated syndromes
  - Reactivation disease in transplant patients
  - **Encephalitis – mostly allogeneic HCT recipients (1-3%), often in first 60 days**
    - 1% of those with HHV-6 viremia
    - Acute memory loss, altered mental status, and seizures; fever is rare
  - 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 – Mild CSF lymphocytic pleocytosis, temporal abnormalities shown on EEG, and MRI hyperintense lesions in the limbic system
- Therapy
  - Ganciclovir or foscarnet x ≥ 3 weeks; decide based on toxicities; cidofovir last choice
  - Treat if encephalitis; not all need treatment, not if just low level HHV-6+ in blood/CSF
  - Reduce immunosuppression if possible; do not use steroids

The BioFire® FilmArray® Meningitis/Encephalitis (ME) Panel

Distinguishing bacterial from viral meningitis based on clinical presentation alone is challenging. Getting fast, pathogen-specific answers can help save lives and guide appropriate therapy.

Make sure that the pathogen you detect fits the clinical scenario



https://www.biofiredx.com/products/the-filmarray-panels/filmarrayme/

15 – CMV, EBV, HHV6 and HHV8 in Immunocompetent and Immunocompromised Patients

Speaker: Camille Kotton, MD

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

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.

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

Antiviral Prophylaxis & Treatment Agents

*acyclovir/valacyclovir/famciclovir and letermovir *for prophylaxis only*

**foscarnet, cidofovir, maribavir not usually used for prophylaxis

Antiviral agent	CMV	EBV	HHV-6	HHV-8	HSV	Varicella	BK	Adeno-virus
Commercially available								
acyclovir/valacyclovir/famciclovir*	high dose +/-				x	x		
ganciclovir IV/valganciclovir PO	x		x	+/-	x	x		
foscarnet**	x		x	+/-	x	x		
cidofovir**	x		x	+/-	x	x	poor	+/- IC50
letermovir (prophylaxis only)	x							
maribavir (treatment only)	x	*in vitro*						
Novel/investigational antiviral agents (SOT)								
brincidofovir (not available)	*x*	*x*			*x*	*x*	*x*	*x*
pritelivir (phase III)					*x*			

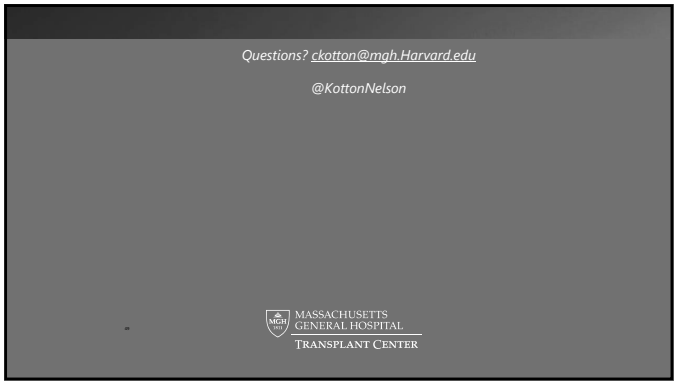
Modified from Kotton CN, Updates on antiviral drugs for cytomegalovirus prevention and treatment, Curr Opin Organ Transplant 2019, 24:469–475

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

15 – CMV, EBV, HHV6 and HHV8 in Immunocompetent and Immunocompromised Patients

Speaker: Camille Kotton, MD



BR2

Board Review Session 2

Drs. Alexander (Moderator), Boucher, Kotton, Platts-Mills, Saullo, Tamma, Trautner, and Whitley

Board Review: Day 2

Moderator: Barbara D. Alexander, MD, MHS
Faculty: Drs. Boucher, Kotton, Platts-Mills, Saullo, Tamma, Trautner, and Whitley

7/1/2024

BOARD REVIEW DAY 2 2024

#14 **A patient with HIV infection, CD4 = 20 cells/uL, viral load 500,000 copies/mL, and chronic cytopenias (WBC = 800 cells/uL) has never been willing to start antiretroviral therapy.**

He is admitted with fever and pulmonary nodules: on lung biopsy, invasive aspergillosis is seen on pathology and grows from biopsy culture (Aspergillus fumigatus).

Voriconazole is started.

1 of 3

BOARD REVIEW DAY 2 2024

#14 **Which of the following would be the best choice as a backbone of antiretroviral therapy for this patient on voriconazole if a goal is to minimize drug-drug interactions?**

A) Efavirenz

B) Darunavir-ritonavir

C) Elvitegravir-cobicistat

D) Dolutegravir

2 of 3

BOARD REVIEW DAY 2 2024

#15 **A 39-year-old male working in a pork processing plant developed a painful, violaceous lesion on his right hand.**

He remembers injuring himself at the site when a bone shard penetrated his glove 3 days prior.

He denies fevers but developed erythema extending from the initial site of injury.

1 of 4

BOARD REVIEW DAY 2 2024

#15 **He was diagnosed with cellulitis and was started on vancomycin, but the well demarcated board of erythema continued to enlarge, now involving the entire dorsal surface of the hand.**

A biopsy of the initial lesion is growing a Gram-positive rod.

2 of 4

BOARD REVIEW DAY 2 2024

#15 **The most likely pathogen is:**

A) *Bacillus cereus*

B) *Cutibacterium acnes*

C) *Listeria monocytogenes*

D) *Erysipelothrix rhusiopathiae*

3 of 4

BOARD REVIEW DAY 2 2024

#16 **A CMV seronegative renal transplant recipient received his allograft from a CMV seropositive donor.**

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

1 of 2

BOARD REVIEW DAY 2 2024

#17 **A 23-year-old bartender from Washington, DC came to the emergency department with a three-week history of abdominal pain, fever, and diarrhea.**

His symptoms began three weeks ago while he was spending two weeks visiting family in La Paz, Bolivia.

Symptoms resolved after a week without therapy, so he traveled back to the US a week ago but started up again two days ago with lower abdominal pain, non-bloody diarrhea, headache, and low-grade fever.

1 of 6

BOARD REVIEW DAY 2 2024

#17 **In the ER he was afebrile but tachycardic (pulse 94) and hypotensive (70/50).**

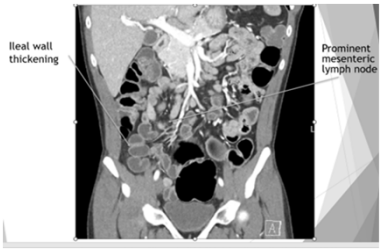
His abdomen was tender with some guarding but no rebound. His blood pressure responded to two liters of saline, but he was admitted to the floor and started on cefepime and metronidazole for possible abdominal sepsis.

WBC 8,600 with 24% bands. Liver function showed ALT 114, AST 60, otherwise normal. A rapid HIV test was negative.

2 of 6

BOARD REVIEW DAY 2 2024

#17 **An abdominal CT showed the following:**



3 of 6

BOARD REVIEW DAY 2 2024

#17 **He had never been incarcerated, had no history of substance use disorder, was taking no medications here or in Bolivia, was born and raised in the USA, and had no sick contacts in Bolivia or the USA.**

4 of 6

BOARD REVIEW DAY 2 2024

#17 **This case is best explained by which diagnosis?**

A) Yersinia pseudotuberculosis

B) Tuberculous peritonitis

C) Crohn's disease

D) Amoebiasis

E) Typhoid fever

5 of 6

BOARD REVIEW DAY 2 INFECTIOUS DISEASE BOARD REVIEW 2024

#18 **A 63-year-old male with end-stage renal disease underwent a deceased-donor kidney transplant with thymoglobulin induction and maintenance immunosuppression inclusive of prednisone, tacrolimus, and mycophenolate.**

He received 6 months of valganciclovir prophylaxis due to high risk for cytomegalovirus (CMV) infection (i.e., donor CMV seropositive/recipient CMV seronegative).

1 of 5

BOARD REVIEW DAY 2 INFECTIOUS DISEASE BOARD REVIEW 2024

#18 **One and a half months after completing valganciclovir, serial quantitative plasma CMV PCR testing demonstrated progressively rising CMV DNAemia and valganciclovir treatment was initiated.**

During this period, he also developed worsening allograft function with the creatinine rising from 1.6 mg/dL to 3 mg/dL. A renal biopsy demonstrated antibody-mediated rejection without evidence of CMV nephritis and high dose steroids, plasmapheresis and intravenous immunoglobulin were initiated.

2 of 5

BOARD REVIEW DAY 2 INFECTIOUS DISEASE BOARD REVIEW 2024

#18 **Following institution of antibody-mediated rejection therapy, his quantitative plasma CMV PCR values, which initially had become undetectable on valganciclovir treatment, proceeded to rise by 2-log despite several additional weeks of appropriately dosed valganciclovir treatment.**

Genotypic resistance testing demonstrated the UL97 mutation M460V.

The patient was otherwise clinically stable and without evidence of CMV end-organ disease.

3 of 5

BOARD REVIEW DAY 2 INFECTIOUS DISEASE BOARD REVIEW 2024

#18 **With this information, a transition to which antiviral therapy below would be most appropriate?**

A) Intravenous ganciclovir

B) Oral letermovir

C) Oral maribavir

D) Intravenous letermovir

E) Intravenous acyclovir

4 of 5

BOARD REVIEW DAY 2 INFECTIOUS DISEASE BOARD REVIEW 2024

#19 **A 24-year-old healthy G0P1A0 female, 28 weeks pregnant, presents with a 2-day history of fever, dysuria, and supra-pubic pain.**

She had a screening urine culture at 18 weeks which was negative.

Physical exam reveals a patient in no acute distress with a temperature of 38° C.

Vital signs are otherwise normal.

1 of 4

BOARD REVIEW DAY 2 INFECTIOUS DISEASE BOARD REVIEW 2024

#19 **There is no CVA tenderness.**

The uterus is palpable above the umbilicus.

There is mild suprapubic pain.

A dipstick performed in clinic shows 2+ leukocyte esterase and 2+ nitrites.

2 of 4

BOARD REVIEW DAY 2 INFECTIOUS DISEASE BOARD REVIEW 2024

#19 **What is the most appropriate empiric treatment in this patient?**

A) Amoxicillin-clavulanic acid

B) Trimethoprim sulfamethoxazole

C) No antibiotics needed

D) Levofloxacin

E) Amoxicillin

3 of 4

BOARD REVIEW DAY 2 INFECTIOUS DISEASE BOARD REVIEW 2024

#20 **A 55-year-old male undergoes emergency surgery for a ruptured appendix with severe bacterial peritonitis and septic shock.**

He has no antibiotic allergies or intolerances.

1 of 3

BOARD REVIEW DAY 2 INFECTIOUS DISEASE BOARD REVIEW 2024

#20 **Which one of the following antibiotics would be appropriate in this clinical setting but would require concomitant administration of IV metronidazole to ensure optimal treatment?**

A) Piperacillin-tazobactam

B) Ampicillin-sulbactam

C) Ceftolozane-tazobactam

D) Imipenem-cilastatin-relebactam

E) Omadacycline

2 of 3

BOARD REVIEW DAY 2 INFECTIOUS DISEASE BOARD REVIEW 2024

#21 **A 66-year-old man with a past medical history of end stage renal disease received a deceased donor kidney transplant 4 years ago.**

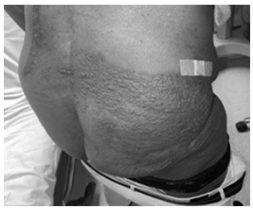
He presented with vesicular rash on right flank/groin (see pictures).

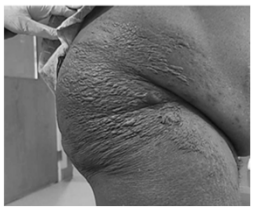
A skin scraping is positive by PCR for varicella zoster virus.

1 of 4

BOARD REVIEW DAY 2 INFECTIOUS DISEASE BOARD REVIEW 2024

#21 **He had a dose of zoster vaccine live (Zostavax) prior to kidney transplant.**





2 of 4

BOARD REVIEW DAY 2 INFECTIOUS DISEASE BOARD REVIEW 2024

#21 **What would have been the optimal approach for preventing this episode of shingles in this patient?**

A) He should not have needed any further prophylaxis because he had live zoster vaccine (Zostavax)

B) He should have been taking lifelong acyclovir after kidney transplant

C) He could have gotten recombinant zoster vaccine (Shingrix)

D) He should have had his antibody titer tested to be certain he responded to Zostavax

3 of 4

BOARD REVIEW DAY 2 INFECTIOUS DISEASE BOARD REVIEW 2024

#22 **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.

The 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.

1 of 4

BOARD REVIEW DAY 2 INFECTIOUS DISEASE BOARD REVIEW 2024

#22 **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.

2 of 4

BOARD REVIEW DAY 2 INFECTIOUS DISEASE BOARD REVIEW 2024

#22 **What is the most appropriate antimicrobial therapy for this patient?**

A) Piperacillin-tazobactam

B) Ampicillin-sulbactam

C) Meropenem plus fluconazole

D) Cefepime plus vancomycin plus metronidazole

E) Cefepime plus clindamycin

3 of 4

BOARD REVIEW DAY 2 INFECTIOUS DISEASE BOARD REVIEW 2024

#23 **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.

1 of 3

BOARD REVIEW DAY 2 INFECTIOUS DISEASE BOARD REVIEW 2024

#23 **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

2 of 3

BOARD REVIEW DAY 2 INFECTIOUS DISEASE BOARD REVIEW 2024

#24 **A 72-year-old male with underlying acute myeloid leukemia (AML) underwent allogeneic hematopoietic cell transplantation (HCT) and presented to care on day + 190 with complaints of fever, cough, and new skin lesions.**

His pre-transplant serologies for cytomegalovirus and Toxoplasma were positive and negative, respectively and his post-transplant course was complicated by skin / gastrointestinal graft-versus-host disease necessitating high dose steroids and tacrolimus.

1 of 7

BOARD REVIEW DAY 2 2024

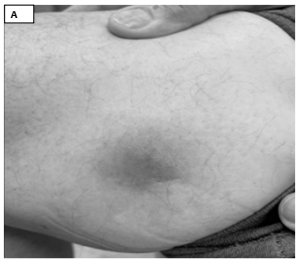
#24 **Antimicrobial prophylaxis consisted of posaconazole (recent trough 2.0 mcg/mL), atovaquone (for Pneumocystis jirovecii prevention due to sulfa allergy), letermovir and acyclovir.**

On exam, he had a tender medial thigh lesion (Figure A) and similar smaller tender nodular lesions on his right flank and back. He denied direct trauma but admitted to spending significant amounts of time outdoors driving his tractor and working on his farm in the post-transplant period.

2 of 7

BOARD REVIEW DAY 2 2024

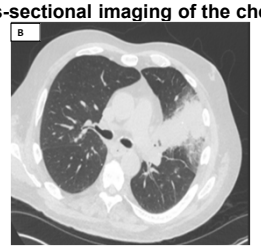
#24



3 of 7

BOARD REVIEW DAY 2 2024

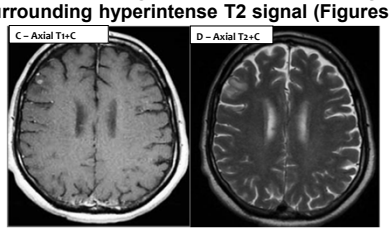
#24 **Blood cultures and a punch biopsy of the thigh skin lesion ensued. Cross-sectional imaging of the chest is shown in Figure B.**



4 of 7

BOARD REVIEW DAY 2 2024

#24 **Biopsy results prompted brain MRI imaging which showed a 4mm right frontal lobe enhancing lesion with surrounding hyperintense T2 signal (Figures C and D).**



5 of 7

BOARD REVIEW DAY 2 2024

#24 **Blood cultures also turned positive on hospital day 5, further confirming the diagnosis.**

What is the most likely diagnosis?

A) Cytomegalovirus

B) Cryptococcosis

C) Aspergillosis

D) Toxoplasmosis

E) Nocardiosis

6 of 7

BOARD REVIEW DAY 2 2024

#25 **A 72-year-old man with a history of diabetes and obesity presents to his primary care physician with a complaint of foul-smelling, cloudy urine.**

He does not have dysuria or voiding difficulties, but he reports recent loss of 10 pounds without dieting.

He has not seen a urologist or had any urinary instrumentation.

No recent fevers noted, and he is afebrile at this visit.

1 of 6

BOARD REVIEW DAY 2 INFECTIOUS DISEASE BOARD REVIEW 2024

#25 **Urinalysis shows 100 WBC/HPF and many bacteria; culture grows E. coli sensitive to trimethoprim-sulfamethoxazole.**

He is treated with a 7-day course of trimethoprim-sulfamethoxazole.

He returns to his primary care physician a week after completing the course of antibiotics and reports his urine is still cloudy and foul-smelling.

2 of 6

BOARD REVIEW DAY 2 INFECTIOUS DISEASE BOARD REVIEW 2024

#25 **Now he notices that his urine has bubbles towards the end of emptying his bladder.**

He has no other urinary symptoms.

CBC shows anemia and mild leukocytosis.

Repeat urine culture grows Proteus, sensitive to trimethoprim-sulfamethoxazole, ceftriaxone, fosfomycin and ertapenem.

3 of 6

BOARD REVIEW DAY 2 INFECTIOUS DISEASE BOARD REVIEW 2024

#25 **Stool is positive for occult blood.**

His vital signs are normal on physical examination, but he is slightly pale.

He does not have suprapubic tenderness.

4 of 6

BOARD REVIEW DAY 2 INFECTIOUS DISEASE BOARD REVIEW 2024

#25 **Which of the following is the most appropriate management?**

A) 14-day course of oral trimethoprim-sulfamethoxazole

B) IV ertapenem

C) Ultrasound of prostate

D) Abdominal/pelvic CT scan with rectal contrast

E) Oral Fosfomycin

5 of 6

BOARD REVIEW DAY 2 INFECTIOUS DISEASE BOARD REVIEW 2024

#26 **A 61-year-old man is admitted to the hospital for fever and abdominal discomfort.**

On physical examination, he has a temperature of 39°C, heart rate of 120/min, blood pressure of 100/60, and tenderness to deep palpation with rebound in the left lower quadrant.

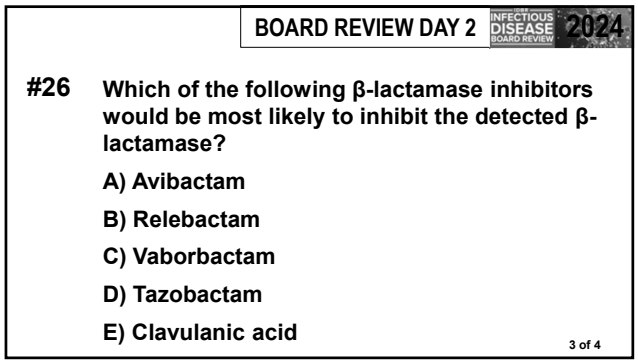
1 of 4

BOARD REVIEW DAY 2 INFECTIOUS DISEASE BOARD REVIEW 2024

#26 **After 9 hours of incubation, blood cultures are positive for a Gram-negative bacillus; a rapid multiplex PCR panel performed on the positive blood culture bottle detects Escherichia coli and $bla_{OXA-48-like}$.**

A β-lactam/β-lactamase inhibitor is considered for therapy.

2 of 4



16

Infections in the Neutropenic Cancer Patient and Hematopoietic Stem Cell Recipients

Dr. Jennifer Saullo

16 – Infections in the Neutropenic Cancer Patient and Hematopoietic Stem Cell Recipients

Speaker: Jennifer Saullo, MD

Infections In Neutropenic Cancer Patients and Hematopoietic Cell Transplant Recipient

Jennifer Saullo, MD, PharmD, FIDSA
Associate Professor of Medicine
Duke University Medical Center

7/1/2024

Disclosures of Financial Relationships with Relevant Commercial Interests

- **None**

Objectives

- Review testable complications in relevant immunocompromised hosts
- Broadly categorized, this includes
  - Risks of underlying diseases and applied chemo-, immunomodulatory and cellular therapies
  - Recognition of breakthrough infections
  - Recognition of specific clinical "syndromes"

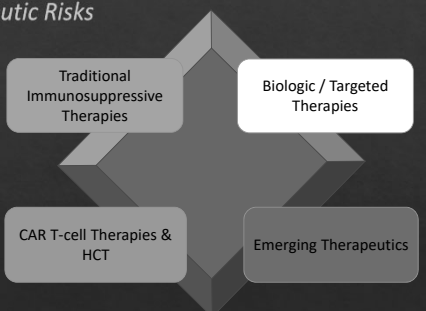
Fundamental Concepts

Risk of Underlying Disease

- Important immune deficits associated with underlying disease
- Examples include
  - Acute myelogenous leukemia (AML) and myelodysplastic syndromes (MDS) – *qualitative and quantitative neutropenia*
  - Lymphomas – *functional asplenia*
  - Chronic lymphocytic leukemia (CLL) – *hypogammaglobulinemia, complement deficiencies, neutrophil/monocyte defects*
  - Multiple myeloma – *hypogammaglobulinemia*
  - Aplastic anemia – *severe, prolonged neutropenia*

Fundamental Concepts

Therapeutic Risks



CAR: Chimeric Antigen Receptor; HCT: hematopoietic cell transplant

Fundamental Concepts

Therapeutic Risks

- Drugs that impact neutrophils
  - Cytotoxic chemotherapy (e.g. anthracycline, cyclophosphamide)
    - Infectious risks greatest when prolonged (> 7 days) and profound (< 500 cells/mm^3) neutropenia
    - Severe bacterial and fungal infections

16 – Infections in the Neutropenic Cancer Patient and Hematopoietic Stem Cell Recipients

Speaker: Jennifer Saullo, MD

Fundamental Concepts
Therapeutic Risks

- Drugs that impact T cells
  - Purine analogs (fludaribine, cladribine, clofarabine) and temozolomide
    - Infections associated with
      - Herpesviruses (e.g. CMV, HSV, VZV)
      - Intracellular and other less common bacteria (e.g. Mycobacteria, *Nocardia*)
      - Fungi (e.g. PJP, *Aspergillus*)

CMV: Cytomegalovirus, HSV: herpes simplex virus; VZV: varicella zoster virus; PJP: *Pneumocystis jirovecii* pneumonia

Biologic / Targeted Therapies
Monoclonal Antibodies

Case #1: 68 year old man, originally from Taiwan, underlying follicular lymphoma with plans to initiate single-agent **rituximab** therapy.

Which of the baseline serologies would be **most important** when assessing infectious risks and relevant need for prophylaxis with rituximab therapy?

A. Cytomegalovirus
B. Toxoplasmosis
C. Hepatitis A
D. Hepatitis B ⬅
E. Hepatitis C

Biologic / Targeted Therapies
Monoclonal Antibodies

- RITUXIMAB – an anti-CD20 (B-cell) monoclonal antibody
  - *Others: ofatumumab, obinutuzumab*
- Results in prolonged B-cell depletion, hypogammaglobulinemia and neutropenia
- Appreciably impairs **response to vaccinations**
- Other notable infectious risks
  - Hepatitis B viral (HBV) reactivation - greatest risk in HBsAg+ (high) and HBcAb+ (moderate)
    - Baseline HBV testing recommended before immunosuppressive, cytotoxic, or immunomodulatory therapy
    - HBV viral prophylaxis (e.g., entecavir, tenofovir) recommended
    - Typically continued x 12 months post cessation of anti-CD20 Mab therapy
  - Other viruses (herpesvirus, PML)
  - PJP infection

Hwang JP et al. J Clin Oncol. 2020;38(31):3698.
Terrault NA et al. Hepatology. 2018;67(4):1560.

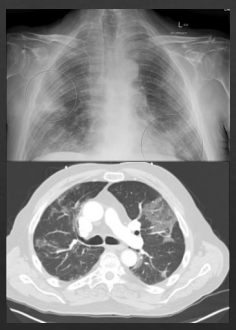
Biologic / Targeted Therapies
Monoclonal Antibodies

Case #2: 63 year old man with T-cell prolymphocytic leukemia on single-agent **alemtuzumab** therapy. Receiving acyclovir prophylaxis (for HSV/VZV) alongside pre-emptive screening with serial CMV PCR testing (all negative to-date).

Presents with a several week history of slowly progressing shortness of breath and new low-grade non-neutropenic fevers. CXR followed by cross-sectional chest imaging are shown (R).

This presentation is likely due to the **lack of** which of the following recommended prophylactic therapies?

A. Letermovir
B. Valganciclovir
C. Entecavir
D. Levofloxacin
E. Sulfamethoxazole-Trimethoprim ⬅



Biologic / Targeted Therapies
Monoclonal Antibodies

- Recognize **ALEMTUZUMAB**
  - Monoclonal Ab targeting CD52 (Anti-CD52 Mab) present on B and T lymphocytes, macrophages, and NK cells
  - Results in prolonged B- and T-cell depletion
- Infectious risks
  - Viral infections - especially herpesvirus (e.g. CMV, VZV, HSV)
  - Mycobacterial and fungal infections (e.g. PJP, *Aspergillus*)
- Infection prevention - viral and PJP prophylaxis typically given a minimum of 2 months after alemtuzumab and until CD4 ≥ 200 cells/mcL

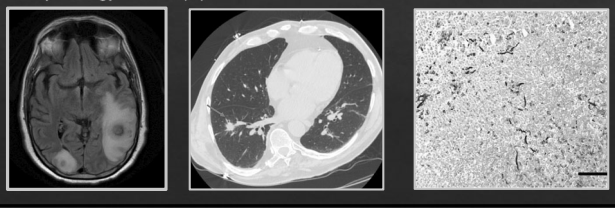
Biologic / Targeted Therapies
Bruton's Tyrosine Kinase (BTK) Inhibitors

Patient: 62 year old man, underlying CLL on **single-agent ibrutinib** x 4 months

Presentation: fevers, confusion, dysarthric with significant word finding difficulties

Imaging: brain MRI + chest CT

Histopathology: brain biopsy



16 – Infections in the Neutropenic Cancer Patient and Hematopoietic Stem Cell Recipients

Speaker: Jennifer Saullo, MD

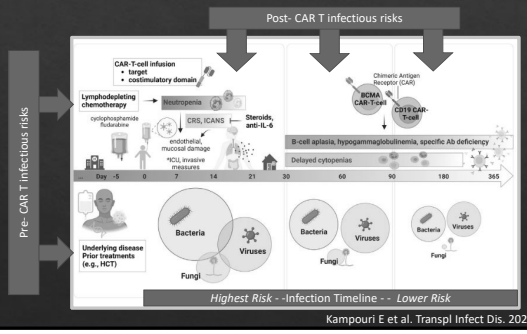
Biologic / Targeted Therapies

Bruton's Tyrosine Kinase (BTK) Inhibitors

- BTK inhibitors include - **Ibrutinib,** Acalabrutinib, Zanbrutinib
- Most commonly applied in CLL, lymphoma
- Block downstream activation of B-cell receptor pathway, cell growth, macrophage function
- Infectious risks include
  - Bacterial infections (most common)
  - Opportunistic fungal infections, inclusive of CNS involvement (e.g. *Aspergillus, Cryptococcus,* PJP)
- Infection prevention
  - Consider fungal (mold, PJP) and HSV/VZV prophylaxis if additional risk factors (inclusive of concomitant therapies)

Shah M et al. Transpl Infect Dis. 2024:e14283.

Chimeric Antigen Receptor T-cell Therapy



Cytokine Release Syndrome (CRS)

- Most common acute toxicity
- Systemic inflammatory syndrome
- Grading based on fever +/- hypotension +/- hypoxia
- Difficult to differentiate from infection + increases infection risk

Kampouri E et al. Transpl Infect Dis. 2023;Suppl 1:e14157.

Neutropenic Fever and "Syndromes"

Case #3

70 year old male with AML, recent initiation of azacitidine and venetoclax with neutropenic fever (102F) and fatigue

VS – 120/80, HR 100, RR 14, Sa02 96% on ambient air

Exam – no significant OP lesions, lungs cta, abd soft, nt/nd, no peri-rectal lesions/pain, no skin rash or lesions, no pain/redness/tenderness over central access site

Cultures – blood/urine pending

CXR – non-focal

Current Prophylaxis – levofloxacin and acyclovir

Prior infection history – none

Which of the following is the most appropriate change in therapy?

A. Levofloxacin → IV cefepime
B. Levofloxacin → IV cefepime + vancomycin
C. Levofloxacin → IV cefepime + metronidazole
D. Acyclovir → IV ganciclovir
E. Addition of antifungal therapy

Case #3 – Neutropenic Fever

- Empiric antibiotic therapy factors in prior therapies, infections/colonization, local epidemiology and clinical presentation
- Standard recommendations → monotherapy with an IV anti-pseudomonal β-lactam agent (e.g., cefepime, a carbapenem or piperacillin-tazobactam)
  - Caution with anti-pseudomonal beta-lactams lacking significant gram-positive coverage (e.g. ceftazidime)
- Addition/modification based on other factors
  - IV vancomycin → catheter-related infection, skins/soft tissue infection, pneumonia, hemodynamic instability
  - Alternate therapies → prior infection and/or colonization with MDR pathogens (e.g. methicillin-resistant *S. aureus*, vancomycin-resistance enterococcus, extended-spectrum and AmpC β-lactamase and/or carbapenemase-producing organisms)
  - Anaerobic coverage → select scenarios (e.g. intrabdominal infection such as neutropenic enterocolitis, peri-rectal abscess, necrotizing gingivitis/mucositis)

Freifeld AG et al. Clin Infect Dis. 2011;52(4):427.
Taplitz RA et al. J Clin Oncol. 2018;36(14):1443.

Case #4

PREVIEW QUESTION

35 year old woman with AML, day 15 of induction therapy.

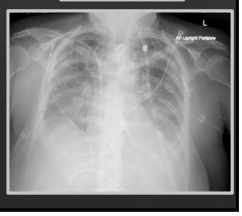
Presentation - fever, chills, diffuse erythematous rash.

Exam – 100/62, HR 120, grade 2 oral mucositis, diffuse, blanching, erythematous rash.

Cultures - Blood cultures with **GPC in chains.**

CXR - bilateral diffuse infiltrates.

Prophylaxis - 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*

16 – Infections in the Neutropenic Cancer Patient and Hematopoietic Stem Cell Recipients

Speaker: Jennifer Saullo, MD

Viridans Group Streptococci (VGS)

- VGS include *S. mitis, S. oralis*
- Normal flora of the oral cavity, upper respiratory and GI/GU tract
- Clinical presentation
  - Can include fevers, chills, flushing, stomatitis, pharyngitis
  - VGSS - toxic shock-like syndrome
    - Early vs late (2–3 days after presentation)
    - Hypotension, progression to respiratory failure and ARDS
    - Maculopapular rash starting on trunk and spreading centrifugally +/- desquamation of palms and soles
- Treatment: beta-lactams (increasing PCN resistance), vancomycin
- Case "clues": neutropenia, oral mucositis, high-dose cytarabine, fluoroquinolone prophylaxis

Shelburne et al. Clin Infect Dis. 2014;59(2):223.
Toonkel AR, Sepkowitz KA. Clin Infect Dis 2002;34(11):1524.

Testable Scenarios: Breakthrough BSIs

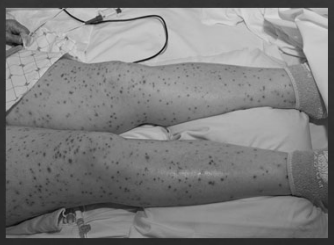
- Typical patient - neutropenic, progressive sepsis
- Recognize clinical presentation and holes in antimicrobial coverage
  - ARDS, rash, quinolones, mucositis → viridans Streptococci
  - Sepsis with β-lactams → *Stenotrophomonas*, Extended-spectrum (ESBL) and AmpC β-lactamase-Producing Enterobacterales
  - Sepsis with carbapenems → Carbapenem-resistant Enterobacterales/*Acinetobacter baumannii*
  - Lung and skin lesions → *P. aeruginosa*, fungi, *Nocardia*
  - Mucositis (upper, lower tract) → *Fusobacterium* spp., *Clostridium spp.*, *Stomatococcus mucilaginosis*

Case #5

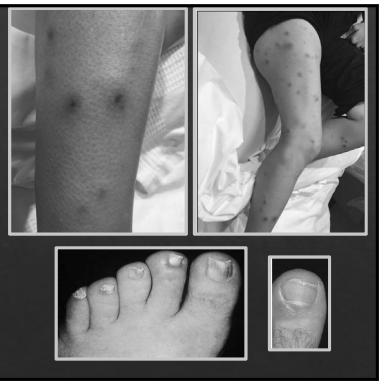
59 year old woman with AML with neutropenia for 25 days and now febrile for 6 days. She is receiving meropenem, vancomycin and acyclovir. Now with new skin lesions that are small, tender papules without central ulceration.

This is most consistent with infection with which of the following organisms?

A. *Rhizopus* spp.
B. Varicella zoster virus
C. *Cryptococcus neoformans*
D. Vancomycin resistant Enterococci
E. *Candida tropicalis*

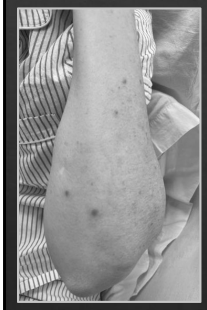


-35 year old woman with relapsed AML with dense neutropenia for over 30 days.
-Ongoing fevers with rapidly progressing, painful papular and nodular lesions, varying stages, some with central necrosis.
-Receiving meropenem, vancomycin, micafungin and acyclovir.
-Micro lab update that blood cultures are growing a "mold".

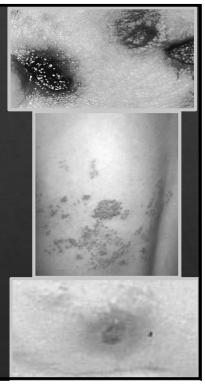


FUSARIOSIS

Skin Lesions



- Candidiasis
  - Small, tender papules
- Herpes
  - Vesicular
- *Aspergillus*
  - Ulcerative, necrotic
- Other filamentous fungi (*Fusarium* spp, *Scedosporium* spp)
- *P. aeruginosa*
  - Ecthyma gangrenosum



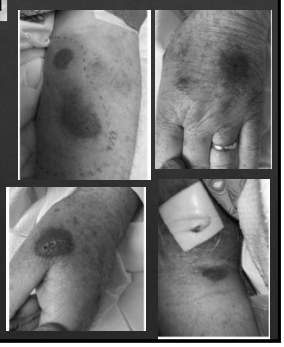
Case #6

PREVIEW QUESTION

70 year-old male with newly diagnosed AML developed erythematous, tender and edematous plaques over sites of trauma (blood draws, peripheral IV). He has been febrile to 38.7°C for the past several days.

The most likely etiology is:

A. *Candida albicans*
B. Sweet's syndrome
C. *Aspergillus niger*
D. Varicella Zoster virus
E. *Pseudomonas aeruginosa*



16 – Infections in the Neutropenic Cancer Patient and Hematopoietic Stem Cell Recipients

Speaker: Jennifer Saullo, MD

Sweet's Syndrome

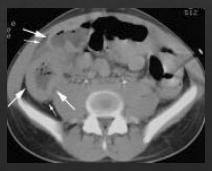
- Acute febrile neutrophilic dermatosis
- Variants: classic (idiopathic), malignancy-associated (hematologic, most common - AML), drug-induced
- Tender erythematous plaques and nodules (typical); also bullous, cellulitic, subcutaneous and necrotizing lesions
- Can demonstrate pathergy (lesions at site of trauma/injury)
- Classic stem: neutropenia resolving with GCSF assist, fever, skin lesions, cultures negative
- Treatment with steroids

Case #7

70 year old woman with AML receiving induction chemotherapy and neutropenic for 15 days. Develops fever, diarrhea and abdominal pain. Exam with decreased bowel sounds and tenderness with deep palpation in her RLQ. CT shows inflammation in cecum. Receiving levofloxacin and fluconazole prophylaxis. Four days prior to her admission for chemotherapy she ate out at a Chinese restaurant and had fried rice.

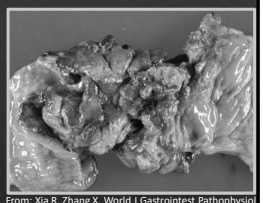
Which is the most likely etiology?

A. Norovirus
B. *Clostridioides (Clostridium) difficile*
C. Mixed anaerobic and aerobic bacteria
D. *Candida albicans*
E. *Bacillus cereus*



Neutropenic Enterocolitis

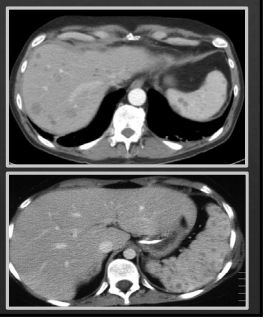
- AKA typhilitis, ileocecal syndrome
- Necrotizing inflammation with transmural infection of damaged bowel wall
- Related to cytotoxic chemotherapy, dense neutropenia
- Mixed infection with gram-negative, gram-positive, anaerobic bacteria and fungi
- Can be accompanied by bacteremia
  - Hint: mixed, anaerobic (*C. septicum, C. tertium, Bacteroides* spp.)
- Medical and (less often) surgical management



From: Xia R, Zhang X. World J Gastrointest Pathophysiol 2019;10(3):36.

Hepatosplenic Candidiasis

- Form of chronic disseminated candidiasis
- Clinical clues
  - Hematologic malignancy, preceding prolonged neutropenia, broad spectrum antibiotics
  - Fever, abdominal/flank pain, hepatosplenomegaly, nausea, vomiting
  - Occurring with neutrophil recovery/engraftment
  - Labs: abnormal hepatic panel (↑alk phos)
- *C. albicans* most common, blood cultures often negative
- Imaging: ultrasound, CT, MRI
- Differential: other fungi, bacteria, underlying malignancy
- Treatment: echinocandin or lipid formulation of amphotericin B, step-down course with oral azole (+/- steroids)



Pappas PG. Clin Infect Dis. 2016;62(4):e1.

Infections in Neutropenic Cancer Patients

Summary of Key Points

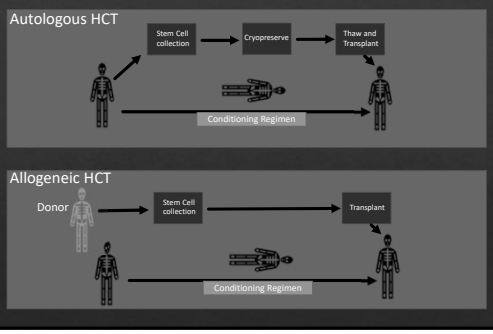
- Recognize typical infections associated with neutropenia and/or immunomodulatory therapies
- Predict breakthrough pathogens based on applied therapies
- Know specific syndromes
  - VGS sepsis
  - Differential of skin lesions
  - Invasive fungal infections in neutropenic patients
    - Sinopulmonary
    - Bloodstream
    - Hepatosplenic candidiasis
  - Neutropenic enterocolitis

Infections in Hematopoietic Cell Transplant Recipients

16 – Infections in the Neutropenic Cancer Patient and Hematopoietic Stem Cell Recipients

Speaker: Jennifer Saullo, MD

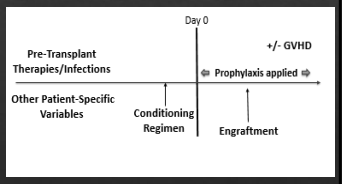
Fundamental Concepts



Fundamental Concepts

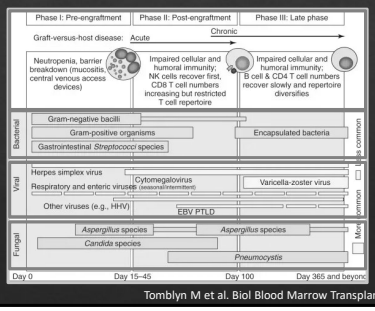
Transplant Variables and Infection Risk

- Transplant type
  - Autologous vs Allogeneic
- Underlying disease
- Donor/recipient Age
- HLA matching
  - MRD, MUD, MMRD and UCD
- Conditioning regimen
  - Myeloablative, nor-myeloablative and reduced intensity
- Source of stem cells
  - Bone marrow, peripheral blood, cord blood
- Graft manipulation
- Graft versus host disease



Fundamental Concepts

Transplant Timeline



Tomblyn M et al. Biol Blood Marrow Transplant. 2009;15(10):1143.

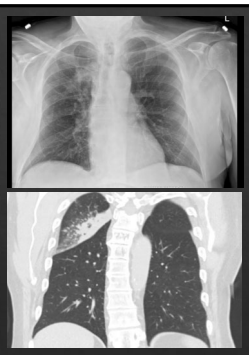
Case #1

42 year old male, d+20 following a matched unrelated donor (MUD), non-myeloablative (NMA) HCT develops fevers, cough and a new pulmonary infiltrate.

Pre-transplant serologies: CMV D+/R-, Toxo D-/R-; recipient otherwise HSV/VZV+

Exam: T 38.3, BP 120/70, HR 115, SaO2 98% on 1L, rhonchi on R

Labs: Cr 1.5, ANC 1200/µL, platelets 43. Current prophylaxis includes acyclovir and posaconazole.



Case #1

What is the most likely cause of his current process?

A. *Candida albicans*
B. *Pseudomonas aeruginosa*
C. Cytomegalovirus
D. Parainfluenza virus
E. Hemorrhage

Pulmonary Complications

Hematopoetic Cell Transplant

- Key elements of the question stem
  - Timing post transplant
  - Donor/recipient serologies
  - Applied prophylaxis
- Differential
  - **Infection**
  - Non-infectious "mimics"

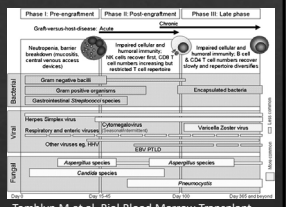
16 – Infections in the Neutropenic Cancer Patient and Hematopoietic Stem Cell Recipients

Speaker: Jennifer Saullo, MD

Pulmonary Complications

Infections

- Bacterial pathogens
  - *E. coli, P. aeruginosa, S. pneumonia, S. aureus, K. pneumoniae*
  - Aspiration events, particularly with mucositis
- Fungal infections
  - *Aspergillus* most common (early & late post-transplant)
  - PJP – uncommon early, typically late + consider lapses in prophylaxis, suboptimal regimens

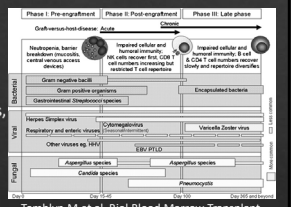


Tomblyn M et al. Biol Blood Marrow Transplant. 2009;15(10):1143.

Pulmonary Complications

Infection

- Viral pathogens
  - Community acquired respiratory viruses
    - Influenza, Parainfluenza, RSV, Human metapneumovirus, Adenovirus, Rhinovirus, SARS-CoV-2
    - Increased risk for lower respiratory tract involvement
  - Herpesvirus
    - CMV >> HSV/VZV
    - CMV typically occurs post-engraftment, onset delayed with primary prophylaxis
- Other (Toxoplasmosis, Strongyloidiasis)

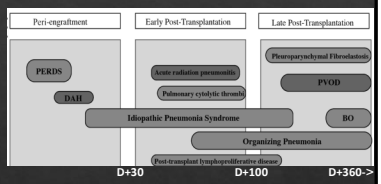


Tomblyn M et al. Biol Blood Marrow Transplant. 2009;15(10):1143.

Pulmonary complications

Non-Infectious

- Early non-infectious considerations
  - Pulmonary edema
  - Engraftment syndrome / PERDS
    - Fever, rash, diffuse pulmonary opacities
  - Diffuse alveolar hemorrhage
    - Heterogenous etiology – infection, GVHD, alveolar injury
    - Progressively hemorrhagic return on bronchoalveolar lavage
  - Idiopathic pulmonary syndrome
    - Dry cough, hypoxia, diffuse infiltrates



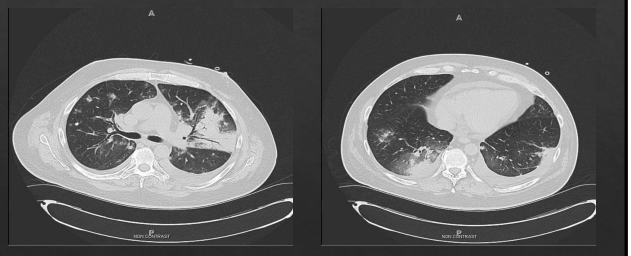
Adapted from: Astashchanka A et al. J Clin Med. 2021;10(15):3227.

Case #2

A 46 year old male **18 months s/p HLA mismatched HCT.** History of GVHD skin, GI tract, and lung. Treated with steroids 3 months ago. One month ago had Parainfluenza 3 with chest CT demonstrating tree-in-bud opacities in LLL. Received levofloxacin for 10 days.

He now has increasing shortness of breath and cough.

Case #2



Case #2

Blood cultures are negative. Sputum cultures grow oropharyngeal flora. Serum galactomannan is negative. What is the most likely cause of his current process?

A. *Cryptococcus neoformans*
B. *Escherichia coli*
C. *Staphylococcus aureus*
D. *Aspergillus fumigatus*
E. *Fusarium* spp.

16 – Infections in the Neutropenic Cancer Patient and Hematopoietic Stem Cell Recipients

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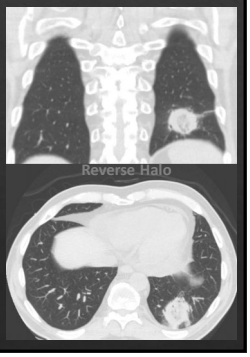
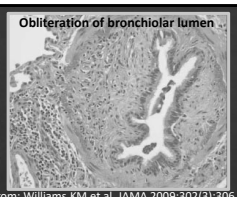
Pulmonary Complications
Late/Post Engraftment +

- Infectious
  - Bacterial (encapsulated, *Nocardia*), Mycobacteria
  - Fungal - *Aspergillus*, PJP, other molds
  - Respiratory viruses, CMV
- Non-infectious
  - Organizing pneumonia
  - Bronchiolitis obliterans syndrome

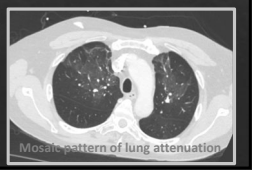


Pulmonary Complications
Bronchiolitis Obliterans

- Chronic GVHD of the lungs
- Chronic inflammatory and fibroproliferative process
  - Focused on terminal and respiratory bronchioles
  - Narrowing of the bronchiolar lumen → airflow obstruction (PFT detection)
- Clinical presentation with cough, increasing shortness of breath and dyspnea on exertion

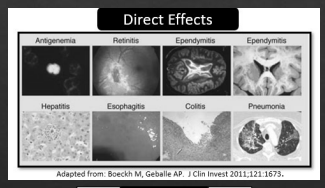


From: Williams KM et al. JAMA 2009;302(3):306.



CMV Infection in HCT
The "Troll of Transplant"

Direct Effects



Adapted from: Boeckh M, Geballe AP. J Clin Invest 2011;121:1673.

Indirect Effects

- Bacteremia
- Invasive Fungal Infections
- GVHD
- Non-Relapse Mortality

CMV Risks

- CMV Seropositivity (R+ >>> D+/R- >> D-/R-)
- GVHD and associated therapies (e.g. steroids, particularly prednisone > 1mg/kg/day)
- T-cell depletion (e.g. alemtuzumab, ATG)
- Cord blood transplant
- Haploidentical, mismatched/unrelated donors
- Older Age
- Lymphopenia

Hakki M et al. Transplant Cell Ther. 2021;27(9):707.

CMV Infection in HCT
Prevention

Pre-Emptive

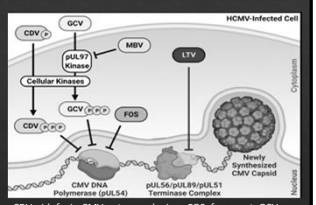
- Weekly CMV DNA PCR monitoring through at least day +100
- CMV DNAemia > threshold = initiation of antiviral
  - Typical therapy – (val)ganciclovir >> foscarnet

Primary Prophylaxis

- Initiated by day +28 through at least day +100 in highest risk (R+)
- Letermovir (FDA-approved)
  - Lacks side effects - cytopenias and nephrotoxicity
  - Lacks activity against HSV/VZV
  - Relevant DDI (azoles, calcineurin inhibitors)

CMV Infection in HCT
Treatment of Infection/Disease

- Induction therapy and maintenance therapy typically with (val)ganciclovir
- Resistance to (val)ganciclovir is rare (*compared to SOT*)
  - Most failures due to profound immunocompromise – e.g. steroids, other T cell depletion
  - Clues for resistance - long exposure to suboptimal doses, poor cellular immunity
  - Resistant and refractory disease
    - Foscarnet; Maribavir now approved
    - Letermovir is for CMV prevention NOT treatment



CDV, cidofovir; CMV, cytomegalovirus; FOS, foscarnet; GCV, ganciclovir; LTV, letermovir; MBV, maribavir.

Figure from: Saullo JL, Miller RA. Annu Rev Med. 2023;74:89.

Pneumocystis jirovecii in HCT

- Allogeneic >> Autologous
  - Shift with routine prophylaxis – now a late complication
  - Risks – steroids, T-cell depletion
- Prophylaxis applied at least 6 months post-transplant
  - Primary – sulfamethoxazole-trimethoprim (SMX-TMP)
  - Non SMX-TMP alternatives *(less effective, potential for breakthrough)*
    - Atovaquone
    - Dapsone
    - Aerosolized pentamidine
- Tropism for lungs, rare disseminated infection
- Radiograph findings – "any and none", most commonly diffuse radiographic infiltrates

16 – Infections in the Neutropenic Cancer Patient and Hematopoietic Stem Cell Recipients

Speaker: Jennifer Saullo, MD

Toxoplasmosis in HCT

- Seroprevalence higher in in NE US (30%), foreign born (25-50%)
- Risk in allogeneic HCT >>> autologous HCT
- 90% of cases within the first 6 months post-HCT
  - Most occur between post-transplant months 2 thru 4
  - Over 2/3 represent reactivation in seropositive recipients
- Presentation with fever, pneumonia, encephalitis *(recognize the lack of prophylaxis in the question stem)*
- Uncommon but deadly - high mortality, diagnosis often delayed

Gajurel K et al. Curr Opin Infect Dis. 2015;28(4):283.

Case #3

35 year old female, d+80 after allogeneic HCT presenting with **5 days of anorexia, nausea, epigastric pain, and diarrhea.** CMV D-/R+, HSV+, VZV+.

Exam: **faint maculopapular rash** on upper body. Afebrile.

Antimicrobials: acyclovir, letermovir, TMP-SMX and fluconazole.

Labs: ANC 1200, ALC 250. Hepatic panel within normal limits.

What is the most appropriate initial work-up and management?

A. Perform serum VZV PCR
B. Empiric corticosteroid treatment
C. Send *Clostridioides difficile* stool testing and start oral vancomycin
D. CMV PCR, stool *C. difficile*, bacterial culture
E. Choice D *and* upper, lower endoscopy

Graft Versus Host Disease

- Immune cells from the donor graft recognize host cells as "foreign"
- 3 forms exist: acute, chronic and GVHD overlap (NIH consensus criteria)
- Acute – typically early post transplant
  - Rash +/- fever
  - GI manifestations (nausea, vomiting, anorexia, diarrhea), acute hepatitis
- Chronic – typically later post transplant
  - Can affect virtually any organ
    - Skin - lichen planus, scleroderma-like
    - Liver - hepatitis, cholestatic picture
    - GI tract - nausea, vomiting, chronic diarrhea, weight loss
    - Lungs - bronchiolitis obliterans syndrome
    - Eyes - dry, painful eyes

GVHD in HCT

GI manifestations (infection mimic)

Hepatitis	Diarrhea
GVHD	GVHD
Herpesviruses (CMV, VZV, HSV)	CMV
Other viral hepatitis	*C. difficile*
Hepatitis B (less common A/C/E)	Norovirus (chronic diarrhea)
Adenovirus	Adenovirus

Case #4

40 year old male, d+60 following allogeneic HCT from a MUD presents with bloody urine for 6 days. Has skin GVHD and initiated on high-dose prednisone (1mg/kg/day) with ongoing taper. Exam demonstrates a faint diffuse erythematous rash. Cr 1.2, hepatic panel within normal limits. CMV quantitative plasma PCR is negative.

The most likely etiology is:

A. Cyclophosphamide
B. Cytomegalovirus
C. Epstein-Barr virus
D. BK virus
E. HHV-6

Hemorrhagic Cystitis in HCT

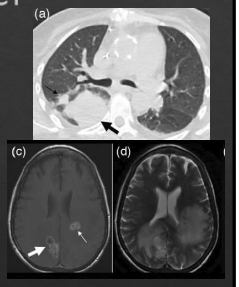
- Early occurrence
  - Following conditioning regimen
  - Therapy-related (e.g. cyclophosphamide, busulfan)
- Later occurrence
  - Post-engraftment
  - Viral infection (e.g. BK virus, adenovirus)

16 – Infections in the Neutropenic Cancer Patient and Hematopoietic Stem Cell Recipients

Speaker: Jennifer Saullo, MD

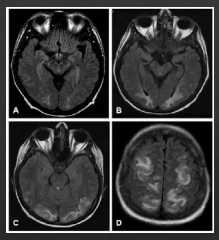
Neurologic Syndromes in HCT

- Infection
  - Viral pathogens
    - Herpes viruses – HSV, VZV, CMV, **HHV-6***, EBV
    - West Nile virus
    - JCV – PML
  - Pulmonary – CNS lesions
    - Invasive fungal infections
    - *Nocardia*
    - Toxoplasmosis
- Non-Infectious
  - Antibiotics – carbapenems, cefepime
  - Posterior reversible encephalopathy syndrome (PRES)



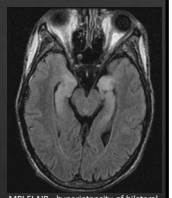
Neurologic Syndromes in HCT

- Infection
  - Viral pathogens
    - Herpes viruses: HSV, CMV, **HHV-6***
    - West Nile virus
    - JCV – PML
  - Pulmonary – CNS lesions
    - Invasive fungal infections
    - *Nocardia*
    - Toxoplasmosis
- Antibiotics - carbapenems, cefepime
- Posterior reversible encephalopathy syndrome (PRES*) – calcineurin inhibitors



Human Herpes Virus-6 (HHV-6) in HCT

- HHV-6 seroprevalence > 95% after age 2
  - Viremia common post-allogeneic HCT (~ 40-60%)
  - Clinical associations - rash, fever, myelosuppression, hepatitis, pneumonitis
- **Meningoencephalitis**** (testable manifestation; HHV-6B)
  - Nonspecific presentation (confusion, memory loss, seizures; EEG / MRI: temporal region)
  - Generally early post-transplant (~ D+60)
  - Risks include mismatched/unrelated donors, umbilical cord blood; T-cell depletion
- Diagnosis: PCR of CSF
- Chromosomal integration
- Treatment: ganciclovir, foscarnet >> cidofovir (acyclovir resistant)



MRI FLAIR - hyperintensity of bilateral mesial temporal areas including uncl/hippocampi; From: Yassin A et al. Ann Med Surg. 2020;60:81.

Other Viral Infections in HCT

HSV/VZV

Herpes Simplex Virus (HSV)

- Risk generally greatest early post-transplant
- Clinical presentation
  - Mucositis /esophagitis most common
  - Visceral, neurologic and ocular less common
- Resistance emergence (acyclovir/valacyclovir)
  - Uncommon (3.5-10%)
  - Mechanism: altered thymidine kinase *(UL23 mutation)*>>> altered DNA polymerase *(UL30 mutation)*

Varicella Zoster Virus (VZV)

- Risk generally late post-transplant
- Clinical presentation
  - Cutaneous most common
  - Visceral (pneumonitis, hepatitis), neurologic and ocular less common
    - Can occur without skin lesions *(consider in case of severe abdominal pain, transaminitis & without rash)*
- Resistance rare

Pearls

- Fundamentals – Risks (temporality, prophylaxis)
  - Early – mucositis, neutropenia
  - Late – GVHD (steroids, asplenia, T cell dysfunction and other delays in IRC)
- Syndromes
  - Early pulmonary syndromes
    - Bacterial, fungal pneumonia
    - Non-infectious: Alveolar hemorrhage, IPS, engraftment
  - Late pulmonary syndromes
    - CMV, respiratory viruses, fungal infections
    - Non-infectious: BO, organizing pneumonia
- Hemorrhagic cystitis
  - BK >> adenovirus
  - Non-infectious: conditioning
- Diarrhea – colitis – hepatitis
  - Herpesviruses
  - Non-infectious: GVHD
- Neurologic syndromes
  - Herpesviruses (+HHV-6), west nile, angioinvasive molds, toxoplasmosis
  - PML
  - Non-infectious: PRES, antibiotics

Thank You

Questions/Comments:

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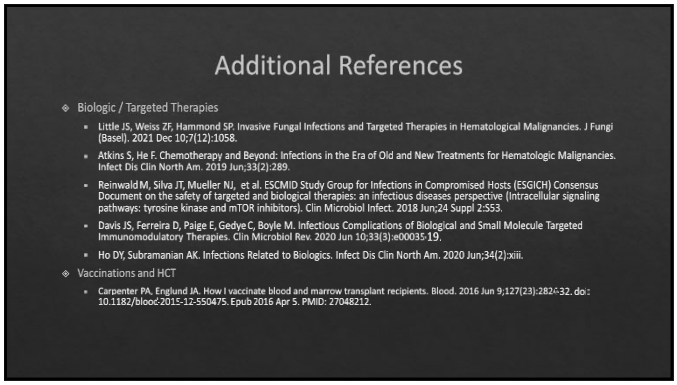
16 – Infections in the Neutropenic Cancer Patient and Hematopoietic Stem Cell Recipients

Speaker: Jennifer Saullo, MD



17

Infections in Solid Organ Transplantation

Dr. Barbara Alexander

17 – Infections in Solid Organ Transplant Recipients

Speaker: Barbara Alexander, MD

Infections in Solid Organ Transplant Recipients

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7/1/2024

Disclosures of Financial Relationships with Relevant Commercial Interests:

- **Consultant:** Scynexis, GSK, Astellas, Merck, HealthTrackRx, Basilea
- **Research Grant to My Institution:** Karius
- **Clinical Trials (Site PI/Study PI):** Scynexis, F2G
- **Royalties (Chapter Author):** UpToDate

Infections in Solid Organ Transplant (SOT) Recipients

- SOT is a life-saving intervention
  - 987,787 SOTs performed in U.S. since 1988
  - 46,629 SOTs performed in 2023
  - 38% increase over past 10 years
- SOT recipients
  - have compromised immunity / increased infection risk
  - are targets for common, emerging & opportunistic pathogens encountered pre- and post-transplant
  - often have atypical infection presentation owing to their compromised immunity / decreased inflammatory response
  - are on complex medical regimens; drug interactions common

Data from Organ Procurement and Transplantation Network database as of June 27, 2023

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 another 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**
- **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**

17 – Infections in Solid Organ Transplant Recipients

Speaker: Barbara Alexander, MD

FREQUENCY, TYPE & INFECTION SOURCE IN THE 1ST POST TRANSPLANT YEAR

Transplant Type	Infection Episodes per Patient	Bacteremia	CMV Disease * (%)	Fungal Infections (%)	Most Common Source
Lung	3.19	8-25	39	8.6	Pulmonary
Liver	1.86	10-23	29	4.7	Abdomen & Biliary tract
Heart	1.36	8-11	25	3.4	Pulmonary
Kidney	0.98	5-10	8	1.3	Urinary tract

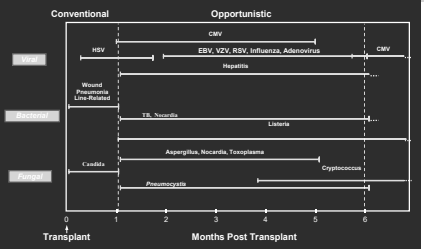
*CMV, Cytomegalovirus; CMV disease rates in the absence of routine antiviral prophylaxis

Table Modified from: Principles and Practices of Infectious Diseases, 8th Edition. Chapter 372: 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.

Pappas P et al. CID. 2009;48:1100-1111

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

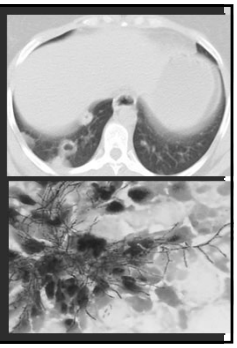
80% OF LATE BACTERIAL INFECTIONS ARE COMMUNITY ACQUIRED

- *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
- 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+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 weekly monitoring with detection assay

NOTE: Typically Valganciclovir or IV Ganciclovir used for prophylaxis
Letermovir now approved for use after Renal Transplant

CMV PROPHYLAXIS AFTER SOT

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, then weekly until negative
- Treat for 2-3 weeks…
  - Resolution of symptoms AND clearance of CMV DNAemia
  - DO NOT STOP TIL VIREMIA CLEARs (high risk for relapse)

CMV DISEASE AFTER SOT
GANCICLOVIR RESISTANCE

- **Suspect resistance if prolonged (> 6 weeks) (val)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 maribavir or 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

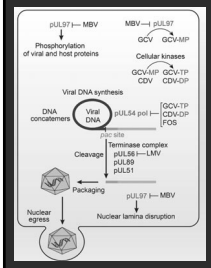
Key mutations have been associated with resistance

- UL97 CMV Phosphotransferase gene mutations (most common)
  - Imply ganciclovir resistance

- 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 2018;102(6):900-931. Torre-Cisneros et al Transplantation Reviews 2016.

CMV RESISTANCE: NEW DRUG



Maribavir (MBV)
- Multi-modal CMV activity
  - Inhibits CMV DNA replication
  - Interferes with nuclear egress of viral capsid 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
  - Superior to SOC (Valgan/Gan, Foscarnet, or Cidofovir) in HSCT & SOT pts with refractory/resistant CMV infection
    - Cleared CMV viremia & resolved symptoms at 8 weeks
  - FDA approved Nov 2021 for "CMV (with or without genetic mutations that cause resistance) that does not respond to available antiviral treatment…"
  - ⚠ No activity against other herpes viruses (HSV/VZV)

Piret J, Boivin G. Antiviral Research 2019;163:91-105.
Avery RK, et al. Clin Infect Dis. 2021 Dec: Online ahead of print.

CASE 1

PREVIEW QUESTION

- 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

PREVIEW QUESTION

The most appropriate treatment for this condition is:

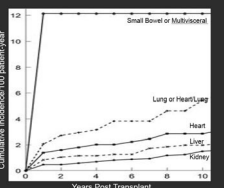
A. Cidofovir
B. Ganciclovir
C. Acyclovir
D. Cyclophosphamide
E. Rituximab

EPSTEIN BARR VIRUS: POST TRANSPLANT LYMPHOPROLIFERATIVE DISORDER (PTLD)

- Virus establishes latency in B-lymphocytes which serve as lifelong reservoirs
- 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 > Kidne)y

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
- WHO Pathology Classification based is gold standard for diagnosis
- Molecular (PCR) tests available
  - WHO Standard for Assay Calibration available
  - Whole Blood vs Plasma controversial
  - Misses EBV-negative and some localized cases
  - 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 (antivirals only work in lytic phase)
- 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

Allen et al. Clin Transplant. 2019;33(9):e13652.

CASE 2

PREVIEW QUESTION

- 52 yo female S/P cadaveric renal transplant receiving tacrolimus, prednisone and mycophenylate.
- Week 30 post transplant serum creatinine rose from 1.5 to 2.3 mg/dl.
- Tacrolimus levels were in therapeutic range.
- Urinalysis revealed one plus protein and no cells or casts.

QUESTION #2

PREVIEW QUESTION

Which would be most helpful in understanding if BK virus was causing her renal failure?

A. Presence of decoy cells in urine cytology
B. Urine BK viral load
C. Urine culture for BK virus
D. Plasma BK viral load
E. Demonstration of BK inclusions in renal tubular epithelium on renal biopsy

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*

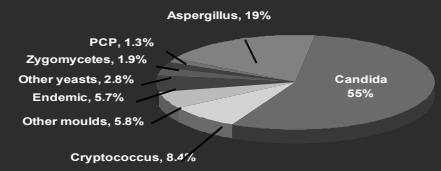
- Reduce immunosuppression
- Case series with variable success using:
  - Low-dose cidofovir
  - Leflunomide
- New drugs & randomized controlled trials needed
- Preemptive monitoring key to prevention

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.

17 – Infections in Solid Organ Transplant Recipients

Speaker: Barbara Alexander, MD

INVASIVE FUNGAL INFECTIONS IN SOLID ORGAN TRANSPLANT RECIPIENTS



Type of fungal infection varies depending on organ transplanted

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.
Aslam S, Rolstein C. AST ID COP. *Am J Transpl.* 2019;33:e13623.
Husain S, Camargo J. AST ID COP. *Am J Transpl.* 2019;33:213544

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

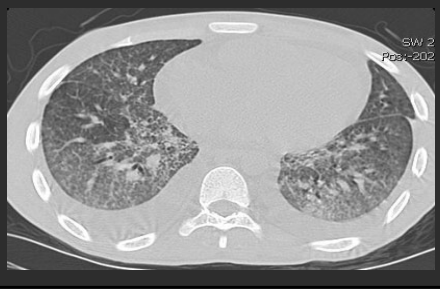
CASE 3

- 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.

17 – Infections in Solid Organ Transplant Recipients

Speaker: Barbara Alexander, MD

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

- After SOT, acute toxoplasmosis can develop from reactivation, acquisition via blood transfusion or ingestion of contaminated food or water, or from the donated organ
- 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 on bactrim & valganciclovir prophylaxis

presented 21 days post transplant with confusion, tremors, lethargy, anorexia

- Rapid progressive neurologic decline → agitation & delirium →intubation
- Brain MRI: non-revealing
- Blood & urine cultures: negative
- CSF: lymphocytic pleocytosis (25 WBCs/mm^3) & elevated protein
  - Gram stain, bacterial, fungal cultures negative for organisms
- 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

17 – 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 2015;50:1112-1119 Mathner 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. possible bat bites, new pet hamsters, tap water nasal irrigations, recent travel to a region endemic for certain pathogens)

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:

- COVID
- Hepatitis A, Hepatitis B, Flu, TDaP, Pneumococcal
- Live Varicella, MMR vaccines (≥4 wks pre-tx)
- HIB, Meningococcal if planned splenectomy (e.g. Multivisceral Tx)

Recommended post SOT:

(Delay 1 month post-tx; 3–6 months to maximize response)

- COVID
- 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**
  - **STIs**
  - **MDR-TB**
  - **BLOOD SUPPLY (need for TRANSFUSIONS), etc.…**
- **AVOID LIVE VACCINES: Yellow Fever, Oral typhoid, etc.**
- **DRUG INTERACTIONS →Transplant meds + travel related prophylactic agents**

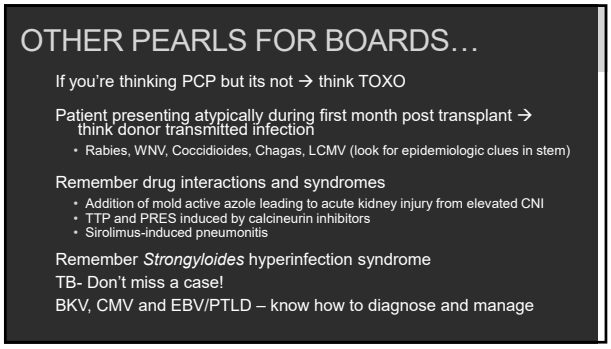
KEY DRUG TOXICITIES / SYNDROMES

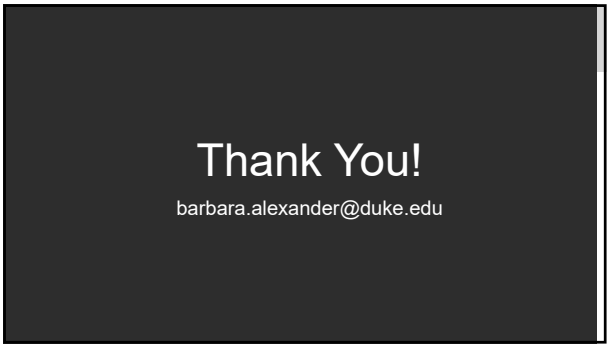
- Calcineurin inhibitors and TTP and PRES (RPLS)
- Sirolimus-induced pneumonitis
  - Progressive interstitial pneumonitis (22% in one study)
  - Risk factors: late switch to sirolimus & impaired renal function
  - Symptoms: dyspnea, dry cough, fever, and fatigue
    - Radiographic & bronchoalveolar lavage 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.

17 – Infections in Solid Organ Transplant Recipients

Speaker: Barbara Alexander, MD





18

GI Infections: Part I

Dr. James Platts-Mills

18 – GI Infections: Part I

Speaker: James Platts-Mills, MD

GI Infections Part 1

James A. Platts-Mills, MD
Associate Professor of Medicine
Division of Infectious Diseases and International Health
University of Virginia

7/29/2024

- **Disclosures of Financial Relationships with Relevant Commercial Interests**

  - None

Q1. The morning after families had arrived at a camp for a week-long retreat, approximately one-third of participants had developed nausea (65%), vomiting (44%), abdominal cramps (85%) and diarrhea (94%) during the night. The night prior, they shared a meal which consisted of a casserole containing macaroni, frozen mixed vegetables, ground beef, turkey, and gravy. The mean onset of symptoms was 11 hours after the meal. All affected persons were substantially improved within 24 hours after onset and there were no apparent secondary cases.

Which one of the following is most likely responsible for this outbreak?

A) *Staph aureus*
B) *Clostridium perfringens*
C) Enterotoxigenic *E. coli*
D) *Listeria monocytogenes*
E) Norovirus

Time from food exposure to symptoms and differential for foodborne illness

- Symptoms (mostly vomiting) that begin within six hours suggest ingestion of a preformed toxin of *Staphylococcus aureus* or *Bacillus cereus* (emetic syndrome)
- Symptoms that begin from 6 to 24 hours suggest infection with *Clostridium perfringens* or *Bacillus cereus* (diarrheal syndrome)
- Symptoms that begin after more than 24 hours can be consistent with a much broader differential (*Salmonella*, *Campylobacter*, *E. coli*, norovirus, etc)

Q2. A nursing home experiences an outbreak of diarrhea with fever among long-term residents. Over the course of several weeks, additional residents develop illness one to three days after contact with illness cases.

Which one of the following organisms is the most likely cause?

A) *Salmonella enterica* (non Typhi)
B) *Vibrio cholerae*
C) *Shigella sonnei*
D) Enterotoxigenic *E. coli* (ETEC)
E) Toxin-producing strain of *Staph aureus*

Infectious doses for common enteric pathogens

10^{5-8}	10^{1-3}
*Salmonella**	*Shigella*
E. coli (ETEC, EPEC, EAEC, EIEC, EHEC)	*Giardia lamblia*
V. cholerae	*E. histolytica*
Campylobacter jejuni	*Cryptosporidium*
	Viruses
Only from food, water, other non-human sources	... also can be spread person to person

Q3. A previously healthy 30-year-old traveler went to India for a one week work trip and developed diarrhea and fever on the fifth day of travel. After 36 hours of watery diarrhea, they experience increasing abdominal pain and frequent small-volume bowel movements containing blood and mucous.

Which of the following would be the most appropriate empiric therapy for this patient?

A) Ciprofloxacin
B) Azithromycin
C) Nitazoxanide
D) No antibiotic therapy recommended
E) Rifaximin

Q4. A 45-year-old male with no past medical history develops watery diarrhea 4 days into a two-week trip to South Asia. He has had to limit his activities, but is able to eat and drink and has access to a bathroom in his hotel room.

Which of the following would be the most appropriate empiric therapy for this patient?

A) Ciprofloxacin
B) Azithromycin
C) Nitazoxanide
D) No antibiotic therapy recommended
E) Rifaximin

2017 IDSA guidelines: Empiric therapy for traveler's diarrhea

"We suggest not treating most cases of travelers' diarrhea with antibiotics. Antibiotic treatment is reasonable for travelers with **severe diarrhea**, which is characterized by fever and blood, pus, or mucus in the stool, or for travelers with diarrhea that **substantially interferes with the purpose of travel**. Antibiotic treatment can reduce the duration of travelers' diarrhea from several days to one or two days. However, drawbacks to antibiotics include cost, potential side effects, and promotion of bacterial resistance, which is an increasing concern. The **benefit of antibiotics may not outweigh the drawbacks** in many individuals with travelers' diarrhea."

If treating, favor azithromycin>ciprofloxacin 2/2 resistance, adverse effect profile

Guideline definition of severe diarrhea: diarrhea that is incapacitating or completely prevents planned activities; all dysentery (passage of grossly bloody stools) is considered severe.

Q5. A 35-year-old female presents for a post-travel evaluation six weeks after return from a trip to Costa Rica. During travel, she had fever and diarrhea and self-administered azithromycin 500mg PO x 3 days. Since returning, she has had intermittent abdominal pain, bloating, and loose stools. A multiplex PCR panel including common bacteria, viruses, and intestinal protozoa is negative.

Which of the following would be the most appropriate next step in management for this patient?

A) Serologic testing for Celiac disease
B) Referral for endoscopy
C) Initiate treatment with nitazoxanide
D) Reassurance and expectant management
E) Modified acid-fast stain of a stool sample

2017 IDSA guidelines – role of diagnostics

(Culture-independent) diagnostic testing is recommended for diarrhea accompanied by: 1) fever; 2) bloody or mucoid stools; 3) severe abdominal pain/cramping/tenderness; 4) sepsis; 5) immunocompromised state (include testing for *Cryptosporidium*, *Cyclospora/Isospora*, microsporidia, MAC, CMV)

Also if concern for an outbreak, or populations with public health implications (e.g. food workers, healthcare workers)

Consider *Yersinia* if abdominal pain/concern for mesenteric adenitis; consider *Vibrio* if rice water stools/exposure to salty/brackish water/consumption of shellfish/travel to cholera-endemic regions; **Consider intestinal parasites in the setting of persistent diarrhea after travel**

A typical GI pathogen panel

BACTERIA:
- *Campylobacter (jejuni, coli, and upsaliensis)*
- *Clostridium difficile* (toxin A/B)
- *Plesiomonas shigelloides*
- *Salmonella*
- *Yersinia enterocolitica*
- *Vibrio (parahaemolyticus, vulnificus, and cholerae)*
- *Vibrio cholera*

DIARRHEAGENIC E. COLI/SHIGELLA:
- *Enteroaggregative E. coli* (EAEC)
- *Enteropathogenic E. coli* (EPEC)
- *Enterotoxigenic E. coli* (ETEC) *lt/st*
- *Shiga-like toxin-producing E. coli* (STEC) *stx1/stx2*
- *E. coli* O157
- *Shigella/Enteroinvasive E. coli* (EIEC)

PARASITES:
- *Cryptosporidium*
- *Cyclospora cayetanensis*
- *Entamoeba histolytica*
- *Giardia lamblia*

VIRUSES:
- Adenovirus F40/41
- Astrovirus
- Norovirus GI/GII
- Rotavirus A
- Sapovirus (I, II, IV, and V)

18 – GI Infections: Part I

Speaker: James Platts-Mills, MD

A typical GI pathogen panel (Additional stool-based diagnostic needed)

BACTERIA:
- *Campylobacter (jejuni, coli, and upsaliensis)*
- *Clostridium difficile* (toxin A/B)
- *Plesiomonas shigelloides*
- *Salmonella*
- *Yersinia enterocolitica*
- *Vibrio (parahaemolyticus, vulnificus, and cholerae)*
- *Vibrio cholera*

DIARRHEAGENIC E. COLI/SHIGELLA:
- *Enteroaggregative E. coli* (EAEC)
- *Enteropathogenic E. coli* (EPEC)
- *Enterotoxigenic E. coli* (ETEC) *lt/st*
- *Shiga-like toxin-producing E. coli* (STEC) *stx1/stx2*
- *E. coli* O157
- *Shigella/Enteroinvasive E. coli* (EIEC)

PARASITES:
- *Cryptosporidium*
- *Cyclospora cayetanensis*
- *Entamoeba histolytica*
- *Giardia lamblia*
- Microsporidia (*E. bieneusi, E. intestinalis, etc)*
- *Cystoisospora* belli

VIRUSES:
- Adenovirus F40/41
- Astrovirus
- Norovirus GI/GII
- Rotavirus A
- Sapovirus (I, II, IV, and V)

Post-infectious Irritable Bowel Syndrome

- ~10-30% of patients will develop IBS after acute gastroenteritis, which can be persistent, in particular after bacterial diarrhea (*Campylobacter*, *Shigella*, *Salmonella*).
- Pathophysiology includes dysbiosis, SIBO, altered gut motility, enteropathy. Can persists for months to years, but generally follows a progressively improving course.
- Treatment options include rifaximin, low FODMAP diet, loperamide, anti-depressants

Q6. A 24-year-old male presents to the emergency room with several days of watery diarrhea, nausea, and vomiting. He returned three days prior from a weeklong trip to India. Vital signs are T 37.5C, BP 80/52, HR 118, O2 98%. Physical examination is notable for dry mucous membranes. Labs are notable for HCT 50, Na 144, K 3.0, HCO3 12, BUN 41, Cr 1.2.

What is the most likely cause of his illness?

A) *Campylobacter jejuni*
B) Rotavirus
C) *Vibrio cholerae*
D) *Shigella sonnei*
E) Adenovirus Type F

Q7. A 42-year-old male presents to the emergency room with fever, abdominal pain, and constipation. He returned from a business trip to India two weeks prior and was in his usual state of health until the onset of fever and fatigue 4 days prior to presentation. His fevers worsened and were accompanied by abdominal pain, poor appetite, and constipation. Blood cultures revealed a Gram negative rod.

What is the most likely cause of his illness?

A) *Campylobacter jejuni*
B) Plasmodium falciparum
C) *Salmonella Typhi*
D) *Shigella flexneri*
E) Enteroinvasive *E. coli*

Geography/pathogen associations

Location	Pathogen
India/Bangladesh/Pakistan	*Salmonella* Typhi
Africa > Asia	Nontyphoidal *Salmonella*
South/Southeast Asia and Africa	*Vibrio cholerae*

To be continued…

19

Skin and Soft Tissue Infections

Dr. Helen Boucher

19 – Skin and Soft Tissue Infections

Speaker: Helen Boucher, MD

Skin and Soft Tissue Infection

Helen W. Boucher, MD
Dean and Professor of Medicine
Tufts University School of Medicine
Chief Academic Officer, Tufts Medicine

7/1/2024

Disclosures of Financial Relationships with Relevant Commercial Interests

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

Question #1

A 25 year old female suffers a cat bite on the forearm.

She presents one hour later for care.

If no antibacterial is administered, the percentage of such patients that get infected is:

A. 0-10 %
B. 10-30 %
C. 30-70 %
D. 70-100 %

3

Management of Animal Bites

- Wound care: irrigation, debridement
- Image for fracture or as baseline for osteo or to detect foreign body ?
- Wound closure: NO
- Anticipatory (prophylactic) antibiotics
- Vaccines (tetanus and rabies)

4

Cat Bites

- 30-50% cat bites become infected with bacteria
- Wound types: puncture
- Microbiology: 63% polymicrobial
- Infection type:
  - Nonpurulent wound with cellulitis, lymphangitis, or both (42%)
  - Purulent wound without abscess (39%)
  - Abscesses (19%)

	Frequency (%)
Aerobic organisms	
Pasteurella	75
Streptococcus	46
Staphylococcus	35
Neisseria ±	35
Moraxella	35
Corynebacterium	28
Enterococcus	12
Bacillus	11
Anaerobic organisms	
Fusobacterium	33
Porphyromonas	30
Bacteroides	28

Abrahamian FM1, Goldstein EJ. Microbiology of animal bite wound infections. Clin Microbiol Rev. 2011 Apr;24(2):231-46. doi: 10.1128/CMR.00041-10; *NEJM 1999; 340: 85-92*

5

Pasteurella multocida

- In saliva of > 90% of cats and over 50% of wounds get infected
- Different species, *Pasturella canis*, in saliva of 50% of dogs and only 2-10% get infected
- Small aerobic gram-negative bacillus
- Hard to remember antibiotic susceptibility profile, but amoxicillin sensitive; alternatives can be tricky

6

19 – Skin and Soft Tissue Infections

Speaker: Helen Boucher, MD

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***

7

Question #2

PREVIEW QUESTION

A 50 year old female with alcohol substance abuse disorder 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**

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Question #2 (Cont.)

PREVIEW QUESTION

Which one of the following is the most likely etiologic bacteria?

A. ***Pasteurella canis***
B. ***Capnocytophaga canimorsus***
C. ***Fusobacterium sp.***
D. ***Bartonella henselae***

9

Dog Bites and Splenectomy

- **Only 2-10 % of dog bites get infected**
- **Potential pathogens from**
  - **Dog's mouth:**
    - ***Pasteurella canis, Capnocytophaga canimorsus***
  - **Human skin: *S. aureus, S. pyogenes***
- ***Capnocytophaga is an important* cause of overwhelming sepsis in splenectomized patients**
- ***Capnocytophaga spp.***
  - ***Susceptible to: amox/clav, pip/tazo, penicillin G, and clindamycin***
  - ***Resistant to: TMP/SMX and maybe vancomycin***

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Question #3

PREVIEW QUESTION

A 45 year old USA male experiencing homelessness 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***

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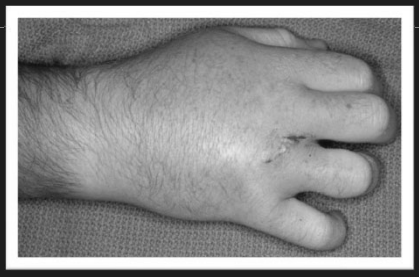
Rat bite fever

- **USA: *Streptobacillus moniliformis***
- **Asia: *Spirillium minus***
- **Bites or contaminated food/water**
- ***S. moniliformis*:**
  - **Fever, extremity rash**
    - **Macular/papular, pustular, petechial, purpuric**
  - **Symmetrical polyarthralgia**
- **Treatment: penicillin or doxycycline**

12



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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***

***Talan, D. CID 2003; 37: 1481**

14

Eikenella corrodens

- **Anaerobic small gram-negative bacillus**
- **Susceptible to:**
  - **Penicillins, fluoroquinolones, doxycycline, and extended spectrum cephalosporins (ceftriaxone, ceftazidime)**
- **Resistant to:**
  - **Cephalexin/cefazolin, clindamycin, erythromycin, diclox/oxacillin, metronidazole, and TMP/SMX**

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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***

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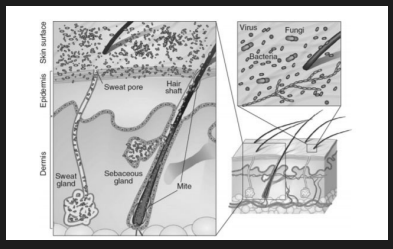
Aeromonas spp.

- ***Aeromonas spp.* - aerobic gram-negative bacilli**
  - ***Aeromonas hydrophila* (most common)**
  - ***Aeromonas veronii***
  - ***Aeromonas shubertii***
- **Causes gastroenteritis (most common), wound infection (following trauma/exposure to leeches) or bacteremia after exposure to an Aeromonas species in fresh, brackish, or marine water**
- **Variable antimicrobial susceptibility; need culture and susceptibility testing of infected wound, stool, and blood**
  - **Resistance to beta-lactams and fluoroquinolones in selected areas of the world**
  - **Uniformly resistant to ampicillin, penicillin, and cefazolin**

17

The Skin: Local Invasion by Structure



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

18

19 – Skin and Soft Tissue Infections

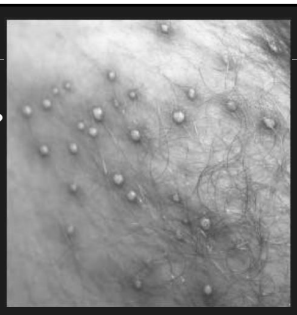
Speaker: Helen Boucher, MD

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

19

What is this?



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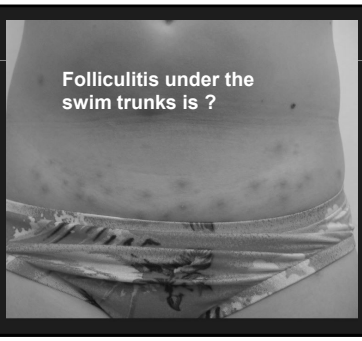
Superficial Folliculitis

- 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

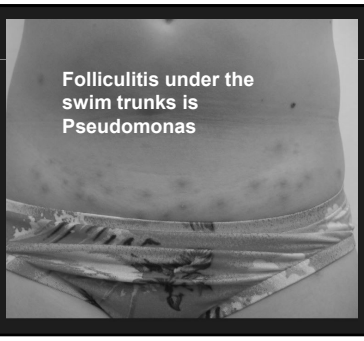
21

Folliculitis under the swim trunks is ?



22

Folliculitis under the swim trunks is Pseudomonas



23

"Honey Crust"

Microbial Etiology?

24

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.

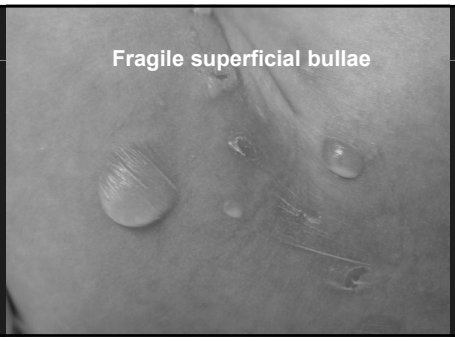
Microbial etiology

- Streptococci: Groups A, B, C, G

Name?

- Streptococcal impetigo

25



26

Fragile Bullae in Epidermis

Diagnosis?

- Bullous impetigo

Etiology?

- *S. aureus*

27

Impetigo ("to attack")

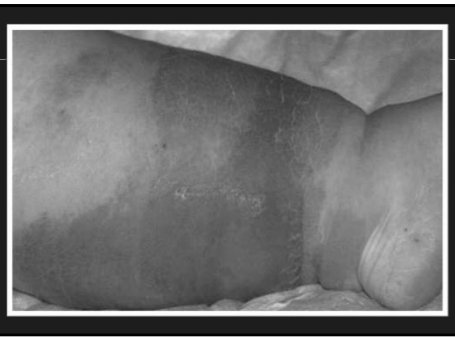
- Bullous impetigo: *S. aureus*
- Non-bullous impetigo: *S. pyogenes,* group A
- So, empiric therapy aimed at *S. aureus* as could be MRSA
- Topical: topical antibiotic ointment (TAO), mupirocin, retapamulin
- Oral rarely needed
  - e.g., clindamycin, doxycycline

28

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

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

29



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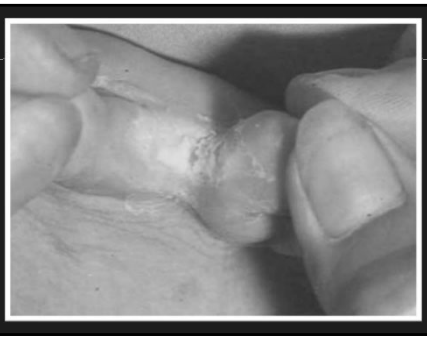


31

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

NO PURULENCE

Diagnosis?

32

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

NO PURULENCE

Diagnosis:

Erysipelas: Non-purulent cellulitis

33

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

NO PURULENCE

Diagnosis:

- Erysipelas: Non-purulent cellulitis

Etiology?

34

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

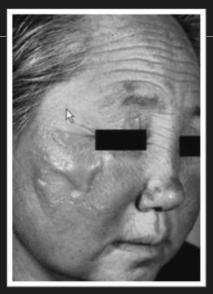
Diagnosis?

- Erysipelas: Non-purulent cellulitis

Etiology?

- Hemolytic Streptococci: Group A
  - Now less common than groups C and G
- If on the face, could be *S. aureus*

35



36

Erysipelas ("Red Skin")

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

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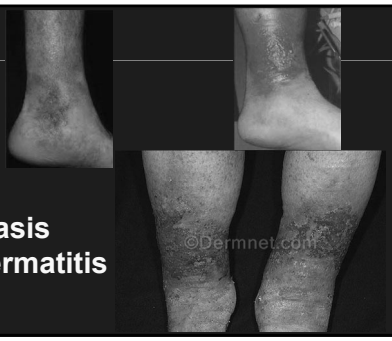
Erysipelas and Cultures

- Most often, 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

38



Stasis Dermatitis

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Stasis Dermatitis

- Looks like erysipelas; more frequent in obese individuals
- 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

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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

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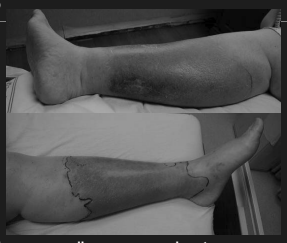
Cellulitis



- 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*

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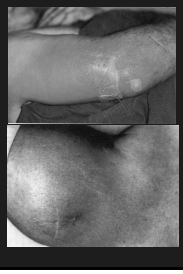
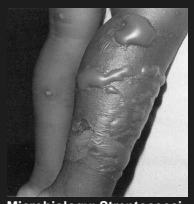
Severe Cellulitis





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

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Recurrent Cellulitis

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

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Risk Factors for Recurrent Erysipelas

- 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

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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

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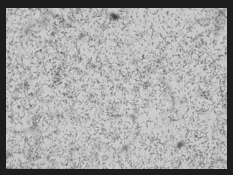
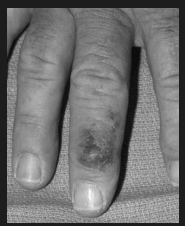
Erysipelothrix rhusiopathiae Infection



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



Resolving cellulitis caused by *Erysipelothrix rhusiopathiae*

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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; creatinine 3.2mg/dl

(Continued)

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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*?**

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Toxic Shock Syn. (TSS): Staph vs Strep

Feature	Staphylococcal	Streptococcal
Predisposition	Tampon, surgery; colonization	Cuts, Burns, Varicella, erysipelas
Focal Pain	No	Yes
Tissue necrosis/inflammation	Rare	Common
N/V, renal failure/DIC	Yes	Yes
Erythroderma	Very common	Less Common
Bacteremia	Very rare (5%)	60%
Mortality	<6%	30-70%

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Sore throat and skin rash

- **20 year-old male 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**

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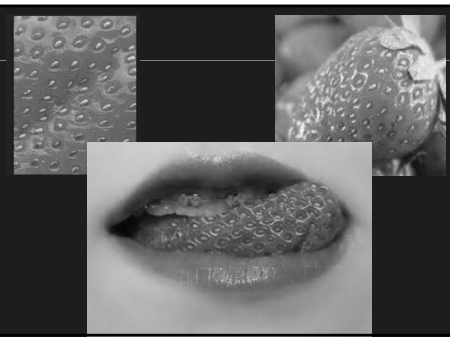

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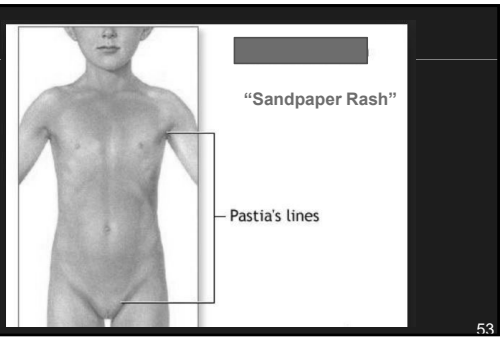

53

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 taking 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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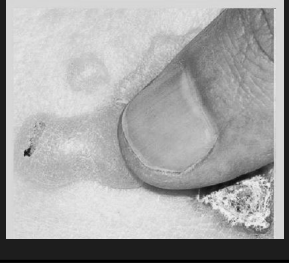
Question #7

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?

56

Nikolsky sign



Exfoliative Toxins cause Epidermal split
- Stratum granulosum

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The Skin and Toxins of *S. aureus* and *S. pyogenes*

Organism	Toxin	Clinical Diagnosis
S.aureus colonization	TSST	TSS & Erythroderma
S. aureus colonization	Exfoliative toxin	Impetigo; scalded skin syndrome
Strep. pyogenes invasion	TSST	TSS; Erythroderma (not always)
Strep. pyogenes	Pyrogenic exotoxin	Pharyngitis; Scarlet Fever (sandpaper rash)

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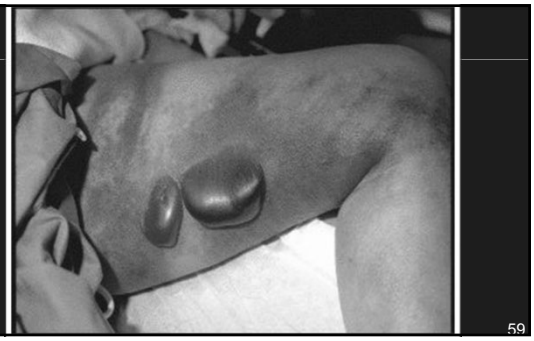

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Erysipelas with loss of pain, hemorrhagic bullae, rapid progression..

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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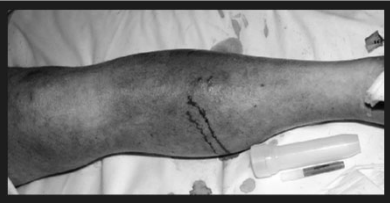
19 – Skin and Soft Tissue Infections

Speaker: Helen Boucher, MD

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 needed to achieve source control
- Appropriate antimicrobial therapy

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

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Question #8

A 50-year-old male african american fisherman with known 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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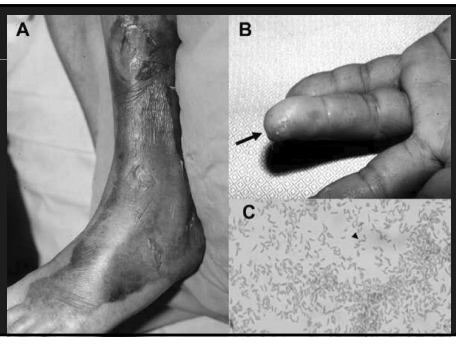

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Vibrio vulnificus

- Leading cause of shellfish (e.g., oysters)-associated deaths in USA
- Portal of entry: skin abrasions or GI tract
- Liver disease, hemochromatosis, and exposure to estuaries are major risk factors
- Infected wounds manifest as bullae in 75%; primary bacteremia also occurs.
- Treatment (look up): doxycycline plus ceftriaxone (alternative is a fluoroquinolone)

66

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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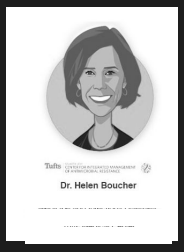
Questions, Comments?

- @hboucher3
- Helen.boucher@tufts.edu
- Helen.boucher@tuftsmedicine.org



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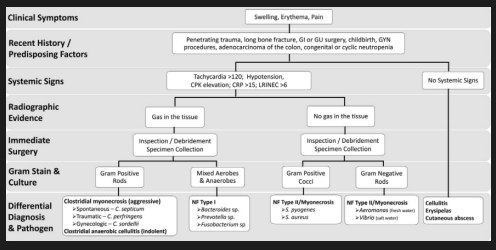
Algorithm for Diagnosis of Necrotizing Infections



Stevens, et al., Infect Dis Clin N Am 35 (2021) 135–155

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GI Infections: Part II

Dr. James Platts-Mills

20 – GI Infections: Part II

Speaker: James Platts-Mills, MD

GI Infections Part 2

James A. Platts-Mills, MD
Associate Professor of Medicine
Division of Infectious Diseases and International Health
University of Virginia

7/1/2024

- **Disclosures of Financial Relationships with Relevant Commercial Interests**

  - None

Q8. A 43-year-old woman presents with several days of watery diarrhea and one day of gross blood in her stools. Two other members of her family have similar symptoms. None of the family members have had a fever and she is afebrile on exam. Laboratory studies are notable for a hematocrit of 28%, platelets of 80,000 per ml and creatinine 2.4 mg/dl.

In addition to stool-based diagnostics, which of the following would be the most appropriate next step in management for this patient?

A) Start IV Ceftriaxone
B) Withhold antibiotic therapy
C) Start PO Azithromycin
D) Start IV Meropenem
E) Start PO Vancomcyin

Antibiotics for suspected and confirmed STEC

Best evidence: meta-analysis of 17 studies with 1896 patients – pooled OR for HUS with antibiotic use was 1.33 (.89-1.99) in all studies, and in those with a "low-risk of bias" + appropriate definition of HUS, OR 2.24 (1.45-3.46)(Freedman et al, CID 2016)

Relevant IDSA guideline recommendations:
1) Empiric treatment of bloody diarrhea in immunocompetent patients should be limited to a) infants < 3 months of age with suspicion of bacterial etiology; b) fever + abdominal pain + blood + scant stools/tenesmus with suspicion for *Shigella*; c) recent international travel + high fever or sepsis;

2) Antimicrobial therapy for people with infections attributed to STEC O157 and other STEC that produce Shiga toxin 2 (or if the toxin genotype is unknown) **should be avoided** (strong, moderate); infections attributed to other STEC that do not produce Shiga toxin 2 (generally non-O157 STEC) is **debatable** due to insufficient evidence of benefit.

Q9. A 21-year-old male was admitted to the hospital with fever and abdominal pain. The abdominal pain, which developed over the course of 48 hours, was initially generalized and then localized to the right lower quadrant. He was febrile and had abdominal guarding. His white blood cell count was elevated. Abdominal ultrasound revealed a normal appendix and multiple enlarged mesenteric lymph nodes.

Which of the following exposures was most likely to be the cause of his illness?

A) Consumption of undercooked chicken
B) Recent purchase of a pet lizard
C) Consumption of shellfish
D) Consumption of undercooked pork
E) Consumption of unwashed raspberries

Some source/pathogen associations you should know!

Source	Pathogen
Water	*Cryptosporidium/Giardia*
Custard	*Staph aureus* toxin
Hamburger	Shiga toxin-producing *E. coli* (STEC)
Leftover meat that is improperly stored after cooking and not sufficiently reheated	*Clostridium perfringens* toxin
Undercooked chicken/Handling eggs	*Campylobacter/Salmonella*
Produce (esp. raspberries)	*Cyclospora*
Seafood	*Vibrio*
Shellfish	*Vibrio*/norovirus
Undercooked pork/pork intestines	*Yersinia*
Turtles/Lizards/Frogs	*Salmonella*
Unpasteurized milk/soft cheese/deli meats	*Listeria*

20 – GI Infections: Part II

Speaker: James Platts-Mills, MD

Q10. An 81-year-old female was admitted to the hospital with vomiting, diarrhea, fever, and headache. She initially developed vomiting, diarrhea, and fever one week prior to presentation. The gastrointestinal symptoms resolved over the course of three days, but the fever continued and was accompanied by a progressive headache and dizziness. Her neurologic exam was notable for ataxia. A stool GI PCR panel was negative. An MRI revealed hyperintense lesions in the cerebellum on T2-weighted imaging. CSF analysis revealed a mild pleocytosis, mildly elevated protein, normal glucose, and a negative Gram stain. CSF and blood cultures are pending.

What type of organism is most likely to be isolated from CSF and/or blood cultures?

A) A Gram positive coccus
B) A Gram negative coccobacillus
C) A Gram positive bacillus
D) A Gram negative bacillus
E) A Gram negative coccus

Q11. A 75 year-old-male with a history of atherosclerosis presents with persistent fever. Two weeks prior to presentation, he developed watery diarrhea and fever. The diarrhea resolved but the fever persisted and was accompanied by chills, night sweats, and a headache. He denied bone or joint pain. No murmur was present on exam. Multiple sets of blood cultures yielded *Salmonella* typhimurium. Antibiotic therapy was initiated, and repeat blood cultures after 48 hours remained positive.

What is the next best diagnostic test?

A) Stool GI PCR panel
B) Lumbar puncture
C) CTA Chest
D) MRI Brain
E) Bone marrow biopsy

Major GI Syndromes

Diarrhea + systemic symptoms (fever, chills, headache, sepsis): Invasive *Salmonella*, *Listeria, Campylobacter*, *Yersinia*

"Food poisoning": vomiting>diarrhea, starts < 24 hours from exposure, short duration, causes are *Staph aureus* toxin, *B. cereus* toxin, *Clostridium perfringens*

Acute watery diarrhea/vomiting: > 24 hours after exposure, ~72 hours duration but variable, favors viral etiology but differential remains broad esp. *Salmonella, Campylobacter*

Colitis: Often a progression from watery diarrhea, but volume decreases, frequency increases, abdominal pain and cramping, tenesmus, mucus/pus/blood in otherwise scant stools, causes are *Campylobacter*, *Shigella, E. histolytica*

Dysentery/Bloody diarrhea: *Campylobacter*/*Shigella* (Fever common), Shiga toxin-producing *E. coli* (including EHEC)(Fever *uncommon*), *E. histolytica* (fever uncommon for luminal disease)

Persistent diarrhea (>14 days): *Cryptosporidium*, *Giardia,* broader differential in immunocompromised patients (including norovirus), but generally pre-test probability of infection is lower (and consider post-infectious IBS)

Q12. An outbreak of illness was reported among approximately 50 persons eating at an area restaurant. The illness consisted of nausea (97%), vomiting (97%), abdominal cramps (86%), chills (78%), muscle aches (67%), fever (64%), headache (61%) and watery diarrhea (58%). The median incubation period was 31.3 hours, one person was hospitalized and 10 sought medical care. The illness lasted approximately 48-72 hours.

What is the most likely cause of the outbreak?

A) Norovirus
B) Shiga toxin-producing E. coli 0157:H7 (STEC)
C) Campylobacter
D) Enterotoxigenic E. coli (ETEC)
E) Pre-formed Staphylococcus aureus enterotoxin

GI Pathogens on the ABIM list

Bacteria	**Protozoa (covered elsewhere)**
Listeria	*Cryptosporidium hominis/parvum*
Aeromonas	*Cyclospora cayetanensis*
Salmonella	*Cystoisospora belli*
Shigella	*Entamoeba histolytica*
Campylobacter	*Giardia*
Vibrio	*Dientamoeba fragilis*
Yersinia	*Balantidium coli*
Viruses	**Fungi/Chromists**
Rotavirus	*Blastocystis hominis*
Norovirus	Microsporidia (e.g. *E. bieneusi*, *E. intestinalis*)
Sapovirus	
Adenovirus	

Pathogen-specific therapy

Shigella (moderate/severe) – ciprofloxacin/azithromycin; ceftriaxone if hospitalized

C. jejuni (high fever, dysentery, bacteremia, immunocompromised) – azithromycin/ciprofloxacin; consider meropenem if severe/immunocompromised

Non-typhoidal Salmonella (severe, >50yrs, valve disease, severe atherosclerosis, AIDS) – ciprofloxacin/ceftriaxone

Salmonella Typhi/Paratyphi – ceftriaxone (severe) or ciprofloxacin/azithromycin (non-severe); if travel to Pakistan/Iraq: meropenem

Yersinia enterocolitica – TMP-SMX/ciprofloxacin or ceftriaxone+gentamicin (severe)

STEC – AVOID antibiotics

Vibrio cholerae – doxycycline; **Non-cholera *Vibrio* diarrhea** – doxycline/azithromycin/ciprofloxacin

Listeria – ampicillin/penicillin (in combination with gentamicin for invasive infection)

Giardia – tinidazole/metronidazole

Cryptosporidium (HIV/AIDS) – nitazoxanide

Intestinal amoebiasis – metronidazole (systemic) + diloxanide furoate OR paromomycin (intraluminal)

Cyclospora/Isospora – TMP-SMX

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Cyclospora/Isospora – TMP-SMX

Thank you!

21

Infections in Upper and Lower Urinary Tract Infections

Dr. Barbara Trautner

21 – Infections of Upper and Lower Urinary Tract Infections

Speaker: Barbara Trautner, MD

Infections of Upper and Lower Urinary Tract Infections

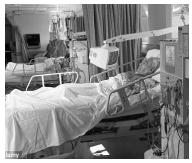
Barbara W. Trautner, MD, PhD
Baylor College of Medicine

7/1/2024

- **Disclosures of Financial Relationships with Relevant Commercial Interests**
  - **Advisor for Phiogen (past)**
  - **Stockholder in Abbott Laboratories, Bristol Myers Squibb, AbbVie, and Pfizer (past)**
  - **Research funding from Genentech and Peptilogics**
  - **Research funding from STRIVE (Shionogi arm)**

Topics to cover

- Acute cystitis in women
- Recurrent cystitis in women
- Asymptomatic bacteriuria
- Catheter-associated UTI
- Pyelonephritis
- Urosepsis and worse



UTI differs in different populations

UTI is not the same entity in these different populations

The Great Divide

My patient populations

- Men
- Older adults in long-term care
- Persons who require urinary catheters for bladder drainage
- Persons with neurogenic bladders

UTI treatment evidence base

- Pre-menopausal women
- Female college students and university staff

Question #1

A 24-year-old woman is evaluated for cystitis symptoms of 3 days' duration. She reports no fever, chills, flank pain, or vaginal discharge. She had similar symptoms three months ago and was treated with trimethoprim-sulfamethoxazole, with relief of symptoms.

On physical examination, vital signs and other findings are unremarkable.

On microscopic urinalysis, leukocytes are too numerous to count, erythrocyte count is 10/hpf, 4+ bacteria are present, and rare squamous epithelial cells are seen. Urine pregnancy test is negative.

Which of the following is the most appropriate management?

A. Nitrofurantoin
B. TMP/SMX
C. Fosfomycin
D. Ciprofloxacin
E. Ibuprofen

hpf, high-powered field; TMP/SMX, trimethoprim/sulfamethoxazole

21 – Infections of Upper and Lower Urinary Tract Infections

Speaker: Barbara Trautner, MD

Current Infectious Diseases Society of America (IDSA) UTI Guidelines*

*update in progress

These guidelines cover:
- Uncomplicated cystitis
- Uncomplicated pyelonephritis
- Premenopausal women
- Primarily outpatients

IDSA GUIDELINES

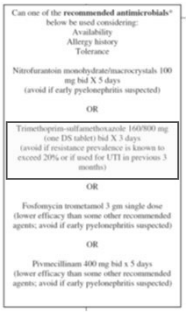
International Clinical Practice Guidelines for the Treatment of Acute Uncomplicated Cystitis and Pyelonephritis in Women: A 2010 Update by the Infectious Diseases Society of America and the European Society for Microbiology and Infectious Diseases

IDSA Cystitis Guidelines (2010)

First-line agents
- Nitrofurantoin
- Trimethoprim-sulfamethoxazole
- Fosfomycin

Alternative choices
- Fluoroquinolones
- Beta-lactams

bid, twice daily; DS, double strength



How long do you treat acute cystitis?

First line choices (5, 3, 1)
- Nitrofurantoin X 5
- Trimethoprim/sulfamethoxazole X 3
- Fosfomycin X1

IDSA Guidelines on Uncomplicated Cystitis, 2010

Nitrofurantoin: Clinical Use

- Interferes with several aspects of bacterial metabolism
- *E. coli* resistance uncommon
- Great for *E. coli* cystitis and prophylaxis
- Inadequate levels in tissue and blood
- Dyes urine yellow
- Intrinsic resistance in *Pseudomonas, Proteus, Serratia*
- Resistance frequent in *Klebsiella* and *Enterobacter*
- Renal excretion but OK to use if GFR >30 mL/min

GFR, glomerular filtration rate

Cunha et al, Eur J Clin Microbiol Infect Dis 2017; 36(7)
Singh, CMAJ 2015; 187(9)
AGS Beers Criteria 2019

Nitrofurantoin Adverse Events

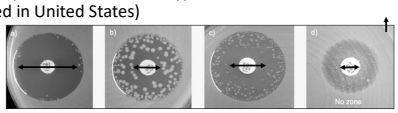
- Pulmonary toxicity--RARE
  - Acute: reversible hypersensitivity reaction
  - Subacute or chronic: diffuse pneumonitis
    - Dose dependent?
    - Favors use of lowest possible dose/less frequent dosing for chronic prophylaxis
- Hepatitis—RARE
- Nausea—common
  - Worse with micro- (QID) than macro-crystalline (BID) formulation

QID, four times daily

Santos, JAGS 2016, PMID: 27100576

Fosfomycin: Clinical use for UTI

- High levels in urine for over 24 hours
- Single 3 gm dose for cystitis
- Developing niche for ESBL- and KPC- Enterobacterales
  - 3gm every 48-72 hours
- IV fosfomycin associated with hypokalemia and elevated LFTs (not approved in United States)



Photos from eucast.org; arrows (↔) reflect CLSI recommendations

CLSI, Clinical and Laboratory Standards Institute; ESBL, extended-spectrum beta-lactamase; IV, intravenous; KPC, Klebsiella pneumoniae carbapenemase; LFT, liver function tests

21 – Infections of Upper and Lower Urinary Tract Infections

Speaker: Barbara Trautner, MD

Potential Harms of Quinolones: FDA warnings

- Dysglycemia
- Tendon rupture/damage
- Interstitial nephritis
- Neuropathy
- Diarrhea—with or without *C. diff*
- Aortic aneurysms?
- Arrhythmias

FDA WARNING

Safety Announcement

[05-12-2016] The U.S. Food and Drug Administration is advising that the serious side effects associated with fluoroquinolone antibacterial drugs generally outweigh the benefits for patients with acute sinusitis, acute bronchitis, and uncomplicated urinary tract infections who have other treatment options. For patients with these conditions, fluoroquinolones should be reserved for those who do not have alternative treatment options.

C. diff, *Clostridioides difficile*

New Oral Drugs in the Pipeline for Cystitis

FDA approved for uUTI

- Pivmecillinam
  - April 24, 2024
  - In use in Europe and Canada
  - Endorsed in 2010 IDSA guidelines
  - Pro-drug of mecillinam
  - Binds to PBP-2 in Gram-negative cell wall
  - 185 mg tid for 3-7 days
  - Use for
    - Enterobacterales, including ESBL+
    - Staph saprophyticus

Not FDA approved

- Gepotidacin
- Sulopenem
- Tebipenem

Not for *Pseudomonas*

Question #2

PREVIEW QUESTION

A 38-year-old woman comes in for recurrent UTI. This is her 3rd episode of symptomatic, culture-proven cystitis in the past 12 months. The recurrent UTIs are very inconvenient to her. She notes that her UTI symptoms usually begin within 2 days of sexual intercourse.

You offer an antibiotic prescription to allow her to self-treat when she feels the cystitis symptoms developing, but she travels internationally and would rather completely avoid developing a UTI.

Which of the following is the most appropriate strategy to prevent recurrent UTI in this woman?

A. Nitrofurantoin daily for 24 months
B. Nitrofurantoin one dose after intercourse for 6 months
C. Ciprofloxacin daily for 6 months
D. Trimethoprim-sulfamethoxazole twice daily for 6 months
E. Cranberry tablets

Prevention and Management of Recurrent UTI

- Self-treatment coupled with urine collection for culture is an appropriate strategy
- Use the most focused antibiotic and as sparingly as possible
- If the woman's episodes are related to sexual intercourse, one dose of antibiotics after intercourse is an effective strategy
- Guidelines suggest treating daily for 3-12 months
- No clarity on which antibiotic to use, other than to avoid fluoroquinolones given side effects and resistance

Recurrent Uncomplicated Urinary Tract Infections in Women: AUA/CUA/SUFU Guideline (2022)
https://www.auanet.org/guidelines-and-quality/guidelines/recurrent-uti

Non-antibiotic Strategies to Prevent Recurrent UTI

Likely helpful (FDA approved)

- Increasing fluid intake
- Vaginal estrogen in post-menopausal women
- Methenamine (?)

Uncertain benefit (not FDA approved)

- Other behavioral changes
- Cranberry products (?)
- D-mannose
- Probiotics
- Other supplement (liquid or other)

Fluid intake: Hooton TM, et al. *JAMA Intern Med*. 2018
Methenamine trials: Harding C, et al. *Health Technol Assess*. 2022
Botros C, et al. *Int Urogynecol J*. 2022
Systematic review of cranberry products: Williams G, et al. *Cochrane Database Syst Rev*. 2023

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Audience Response Question #3

A 69-year-old woman comes in for an annual checkup. No change in her baseline health status. When she coughs or sneezes, she notes slight leakage of urine. Her medical history is significant for three vaginal births, and she has hypertension and type 2 diabetes mellitus.

Her BMI is 30. Her vital signs and other physical examination findings are normal.

On dipstick urinalysis, urine is yellow and with a bad smell, specific gravity is 1.010, pH is 7.0, and moderate leukocyte esterase and nitrites are present; the urinalysis is negative for blood or glucose but 2+ for bacteria.

Which of the following is the most appropriate management?

A. Nitrofurantoin
B. Ciprofloxacin
C. Cystoscopy
D. Urine culture and sensitivities
E. No further infectious workup

BMI, body mass index

21 – Infections of Upper and Lower Urinary Tract Infections

Speaker: Barbara Trautner, MD

Prevalence of Asymptomatic Bacteriuria

Population	Prevalence, %
Children	
Boys	<1
Girls	1–2
Healthy women	
Premenopausal	1.0–5.0
Pregnant	1.9–9.5
Postmenopausal (age 50–70 y)	2.8–8.6
Persons with diabetes	
Women	10.8–16
Men	0.7–11
Elderly persons in the community (age ≥70 y)	
Women	10.8–16
Men	3.6–19
Elderly persons in a long-term care facility	
Women	25–50
Men	15–60
Persons with spinal cord injury	
Intermittent catheter use	23–69
Sphincterotomy/condom catheter	57
Persons with kidney transplant	
First month posttransplant	23–24
1 mo–1 y post-transplant	10–17
>1 y post transplant	2–9
Persons with indwelling catheter use	
Short-term	3%–5%/day catheter
Long-term	100

mo, month; y, year

Nicolle et al, IDSA Guidelines for Asymptomatic Bacteriuria, Clin Inf Dis 2019

Choosing Wisely®
An initiative of the ABIM Foundation

IDSA
Infectious Diseases Society of America

Five Things Physicians and Patients Should Question

Don't treat asymptomatic bacteruria with antibiotics.

Inappropriate use of antibiotics to treat asymptomatic bacteruria (ASB), or a significant number of bacteria in the urine that occurs without symptoms such as burning or frequent urination, is a major contributor to antibiotic overuse in patients. With the exception of pregnant patients, patients undergoing prostate surgery or other invasive urological surgery, and kidney or kidney pancreas organ transplant patients within the first year of receiving the transplant, use of antibiotics to treat ASB is not clinically beneficial and does not improve morbidity or mortality. The presence of a urinary catheter increases the risk of bacteruria, however, antibiotic use does not decrease the incidence of symptomatic catheter-associated urinary tract infection (CAUTI), and unless there are symptoms referable to the urinary tract or symptoms with no identifiable cause, catheter-associated asymptomatic bacteruria (CA-ASB) does not require screening and antibiotic therapy. The overtreatment of ASB with antibiotics is not only costly, but can lead to C. difficile infection and the emergence of resistant pathogens, raising issues of patient safety and quality.

IDSA Guidelines on ASB 2019

Screening and Treatment Indicated

- ✓Pregnant women
- ✓Prior to urologic surgery with mucosal trauma
  - Pre-operative urine culture recommended
  - Treat with 1-2 doses of antibiotics shortly prior to surgery

Screening and Treatment Discouraged

- X Infants and children
- X Non-pregnant women
- X Functionally-impaired older adults
- X Diabetic adults
- X Patients >1 month from kidney transplant
- X Neutropenic patients
- X Patients with solid organ transplant
- X Persons with spinal cord injury
- X Patients with indwelling catheters
- X Prior to non-urologic surgery

Guidelines on Screening for ASB in Pregnant Women

Agency	Year	Recommended?	Strength?	When?	How?	Desired Outcomes
IDSA (United States)	2019	Yes	Strong	12-16 weeks	Culture	Decreased pyelonephritis, decreased low birth weight Possible decrease in preterm labor
CTFPHC (Canadian)	2018	Yes	Weak	1st trimester	Culture	Decreased pyelonephritis, decreased low birth weight
USPSTF (United States)	2019	Yes	Grade B	12-16 weeks or first prenatal visit	Culture	Decreased pyelonephritis, decreased low birth weight

CTFPHC, Canadian Task Force on Preventive Health Care; USPSTF, United States Preventive Services Task Force

Myth-Busting (True Facts!)

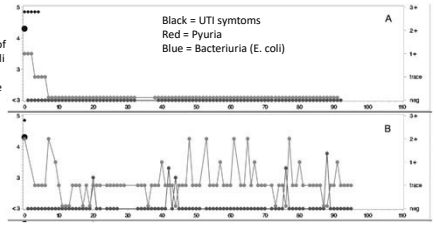
- Bacteriuria ≠ UTI
  - Bacteriuria in the urine can be bladder colonization **or** symptomatic urinary tract infection
- Pyuria ≠ UTI
  - The presence of WBC in the urine doesn't help much with diagnosis of UTI
  - Absence of pyuria suggests to look for a non-UTI diagnosis
- Foul smelling urine ≠ UTI
- Sediment or cloudy urine in catheter tubing ≠ UTI
  - All catheterized bladders develop high level bacteriuria
  - Flushing the catheter to make sure it is patent is a good idea
- Healthy bladders are not sterile in many people
- Take home points:
  - Order urine tests only in patients with urinary symptoms
  - The best thing you can do with asymptomatic bacteriuria is leave it alone
  - Pyuria is not a reliable marker for UTI
  - Changes in the urine are not reliable markers for UTI

WBC, white blood cell

21 – Infections of Upper and Lower Urinary Tract Infections

Speaker: Barbara Trautner, MD

Pyuria not very predictive (even in non-catheterized women)

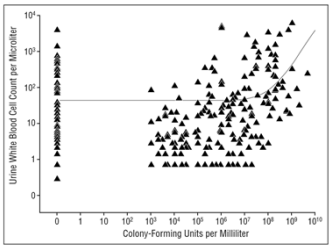


104 women followed for 3 months each with daily urine testing

Overall the PPV (positive predictive value) of pyuria for *E. coli* bacteriuria was 4%

Hooton et al., Clin Infect Dis. 2021 Apr 26;72(8):1332-1338

Relationship between pyuria and bacteriuria/candiduria in catheterized patients



1,497 newly catheterized patients followed daily with urine testing and symptom diaries

235 developed bacteriuria with at least 1,000 CFU/mL

No significant differences in fever or urinary symptoms between patients who did/did not develop bacteriuria

No correlation between pyuria and bacteriuria (flat line) until colony counts are over 10^8

Tambyah and Maki, Arch Intern Med. 2000 Mar 13;160(5):678-82 and 673-7

CFU, colony-forming unit

Audience Response Question #4

A 75-year-old man is seen in the pre-operative clinic. He is scheduled to undergo cystoscopy and possible biopsy for persistent hematuria. He is also scheduled for elective left total knee replacement, shortly after the urinary procedure. Other than the hematuria, he denies urinary-specific symptoms. He underwent kidney transplantation 3 years earlier, related to complications of diabetes.

On physical examination, vital signs are normal. His left knee has an effusion but is not red or excessively painful. No change in his baseline creatinine clearance.

On urinalysis, leukocyte count is 10/hpf, erythrocyte count is 100/hpf, 4+ bacteria are present, and no squamous epithelial cells are seen. Urine culture grew >10,000-<100,000 colony-forming units of *Klebsiella pneumoniae*.

Kidney ultrasonography is unremarkable.

Which of the following is the primary indication for antimicrobial therapy in this patient?

A. Cystoscopy and biopsy
B. Diabetes mellitus
C. Kidney transplant
D. Knee prosthesis placement

Audience Response Question #5

A 46-year-old man is admitted to the hospital for urgent repair of aortic dissection. An indwelling urinary catheter is inserted prior to surgery. Endovascular aortic aneurysm repair is successful, and he is transferred to the surgical intensive care unit. He has underlying diabetes and systolic heart failure.

In addition to removing the urinary catheter as soon as possible, which of the following will decrease this patient's risk of catheter-associated urinary tract infection?

A. Daily cleansing of the meatal area of the catheter with antiseptics
B. Routine catheter change every 3 days
C. Screening for and treatment of bacteriuria
D. Keeping the collecting bag below the level of the bladder
E. Use of antiseptic- or antibiotic-coated urinary catheters

Audience Response Question #6

A 37-year-old woman with a history of recurrent UTIs developed typical symptoms of urgency, frequency, and dysuria five days ago. On the advice of her close friend, she decided to treat this UTI with a nutritional supplement instead of antibiotics. Symptoms did not resolve, and she developed worsening low back pain. This morning she vomited once. In the office, her temperature is 100.5F, BP 135/70, HR 110, RR 16. She is not currently vomiting and can sip water.

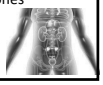
You do not have any prior urine cultures to guide your therapy. Assuming you can manage her as an outpatient, what treatment would you offer?

A. Oral trimethoprim-sulfamethoxazole for 5 days
B. Oral ciprofloxacin for 14 days
C. One dose of ceftriaxone IM plus oral ciprofloxacin for 7 days
D. Cephalexin for 7 days
E. Nitrofurantoin for 10-14 days

BP, blood pressure; HR, heart rate; IM, intramuscular; RR, respiratory rate

Management of Pyelonephritis

- Many clinical trials included pyelonephritis with complicated UTI
- Complicated UTI increasingly means urinary tract infection that has spread beyond the bladder (to kidneys, bloodstream)
- Empiric oral therapy
  - Trimethoprim-sulfamethoxazole 7-14 days
  - Fluroquinolones 5-7 days
  - Consider a one-time dose of IM ceftriaxone or gentamicin while awaiting cultures
  - Oral beta-lactams (cephalosporins, amoxicillin-clavulanate) 10-14 days
- Empiric intravenous therapy
  - IV cephalosporins, piperacillin-tazobactam, carbapenems, fluoroquinolones
- To avoid: nitrofurantoin and fosfomycin



Johnson and Russo, NEJM 2018. 378;1

Audience Response Question #7

68-year-old diabetic man with CHF, vascular disease, BPH presented with 2 days of vomiting, abdominal pain, and confusion.

Vital signs: T 99.9 BP 47/39, HR 110, RR 22

Physical exam: patient was obtunded but appeared to have tenderness in the epigastric area

Labs: WBC 23.7 (94% segs), platelets 96K; Creatinine 3.1 (from 1.7 baseline)

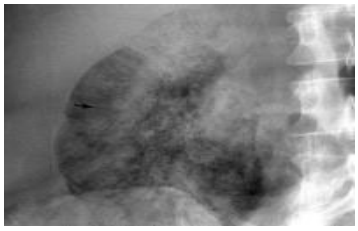
UA: WBC 250, RBC too numerous to count, no bacteria

Troponin 7.2, EKG with ST elevations; HgB A1c 10.5

He was admitted to the CCU and initiated on therapy for an ST elevation myocardial infarction. His blood pressure was labile, and he required pressor support. He required intubation. On hospital day 2, his blood cultures grew 4/4 bottles of *Klebsiella pneumoniae*.

The next slide shows an abdominal radiography (KUB) that had been performed at admission.

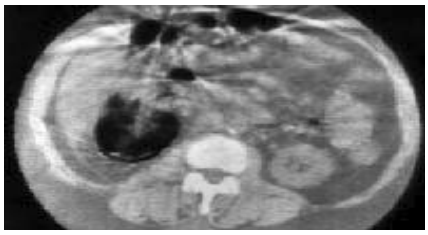
Audience Response Question #7: X-Ray of Abdomen



What would you order next?

A. Abdominal ultrasound
B. Abdominal CT
C. Nasogastric tube
D. Stool for *C. diff* testing

Abdominal CT with Emphysematous Pyelonephritis



CT showing gas within the renal parenchyma

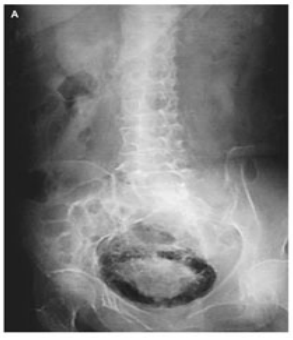
Clinical course of case #7

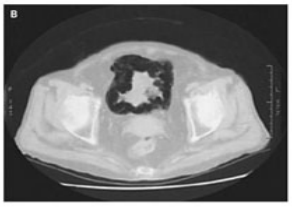
- Percutaneous drainage of the right kidney
- Renal drainage grew *Klebsiella*
- After weeks in the ICU was stable enough for nephrectomy
- 9 months later had then coronary artery bypass surgery

Diagnosis and management of emphysematous pyelonephritis

- 95% of cases in patients with diabetes (poorly controlled)
- Negative prognostic factors: shock, impaired consciousness, thrombocytopenia, renal failure
- Organisms: *E. coli, Klebsiella, Proteus*
- Diagnosis often delayed
- Differential: renal abscess, papillary necrosis
- Radiological diagnosis
- **Managed initially by drainage**—percutaneous nephrostomy or ureteral stent
- Nephrectomy for non-responders, severe cases

Kamei, J Infection and Chemotherapy 2021

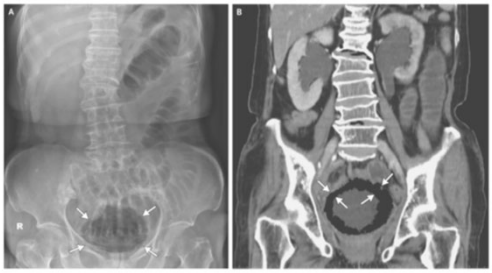




Emphysematous cystitis

Asada, NEJM 2003;349: 258

Emphysematous Cystitis



Tzou, NEJM 2016: 375; 18

Diagnosis and Management of Emphysematous Cystitis

- Female predilection
- Most cases in diabetics
- Commonly caused by *E. coli, Klebsiella* (*Candida* reported)
- Organisms produce gas in the bladder wall and lumen
- Can present with lower abdominal pain
- Diagnosed radiologically
- Relieve bladder obstruction if present
- Typically responds well to **medical management**

Audience Response Question #8

57-year-old man with spinal cord injury (T12) and a chronic indwelling urinary catheter. Two years prior he had a fever, and his blood grew *S. aureus* and *Pseudomonas*. Urine grew lactose negative GNR and gram-positive organisms.

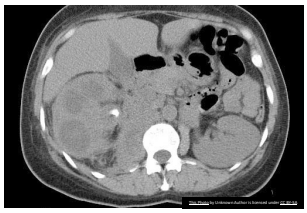
One year prior, he again had a fever, and his blood grew *Serratia, E. coli,* and *Pseudomonas*. Urine grew *Serratia* and *Pseudomonas*.

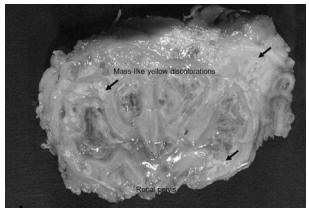
Both times he was treated with appropriate antibiotics, with resolution of fever and stabilization.

He has had many urine cultures, all of which grew multiple urinary pathogens.

Prior to entry in a research protocol, he had a screening abdominal ultrasound, which showed a hypoechoic mass in right kidney. In addition to CT scan, what will be the definitive therapy:

A. Renal biopsy
B. 3-6 months of antibiotics based on current urine culture
C. Percutaneous drainage
D. Nephrectomy

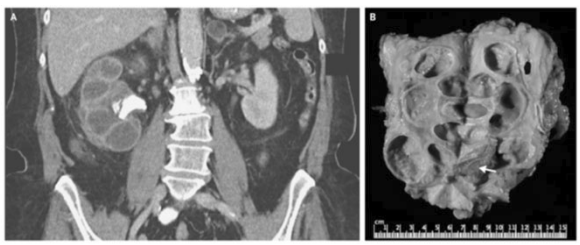




Xanthogranulomatous pyelonephritis

https://www.auanet.org/education/auauniversity/education-products-and-resources/pathology-for-urologists/kidney/inflammatory/necrotic-renal-lesions/xanthogranulomatous-pyelonephritis

Xanthogranulomatous Pyelonephritis



Bear paw sign

Marinacci, New England Journal of Medicine 2018; 378:10

Xanthogranulomatous Pyelonephritis

- Chronic polymicrobial infection of renal parenchyma
- Often starts with stone/obstruction
- Frequently insidious and mistaken for tumor
- Renal tissue is destroyed and replaced by granulomatous tissue
- Yellow from the foam cells (macrophages) full of lipids
- **Requires nephrectomy** plus antibiotics

- Our patient underwent right nephrectomy, with finding of a variegated tan-white mass, large amount of inflammatory reaction, purulence in right renal fossa

21 – Infections of Upper and Lower Urinary Tract Infections

Speaker: Barbara Trautner, MD

To Re-Cap

- Acute and recurrent cystitis in women-nitrofurantoin
- Asymptomatic bacteriuria
  - Pregnant women-screen and treat
  - Urologic surgery—screen and treat
  - Everyone else—don't test the urine
- Catheter-associated UTI—ensure drainage
- Pyelonephritis—treat with tissue-active agent
- Urosepsis and worse
  - Emphysematous pyelonephritis-drainage
  - Emphysematous cystitis-medical management
  - Xanthogranulomatous pyelonephritis-removal

Is everything clear now?

- trautner@bcm.edu
- @bwtrautner

22

HSV and VZV in Immunocompetent and Immunocompromised Hosts

Dr. Richard Whitley

22 – HSV and VZV in Immuno-competent and Immunocompromised Hosts

Speaker: Richard Whitley, MD

Herpes Viruses: HSV and VZV in Immunocompetent and Immunosuppressed Patients

Richard J. Whitley, MD
Co-Director, Division of Pediatric Infectious Diseases
Loeb Eminent Scholar Chair in Pediatrics
Professor of Pediatrics, Microbiology, Medicine, and Neurosurgery
The University of Alabama at Birmingham

7/1/2024

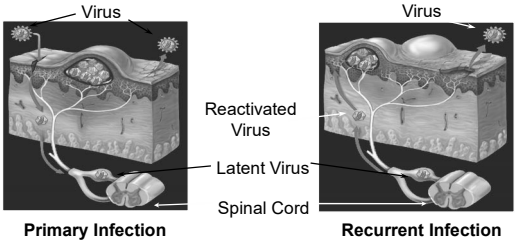
- **Disclosures of Financial Relationships with Relevant Commercial Interests**

Steering Committee: NIAID COVID-19 Recover Study, NIAID Recover VITAL Study
Scientific Advisory Board: Treovir, LLC
Scientific Advisory Board: Altesa Biosciences
Member, Board of Directors at Evrys Bio
Member, Board of Directors at Virios Therapeutics
Past Chairperson: Merck Letermovir DMC, GSK IDMC for Zoster and NIAID COVID-19 Vaccine DSMB

Herpes Viruses: The Family

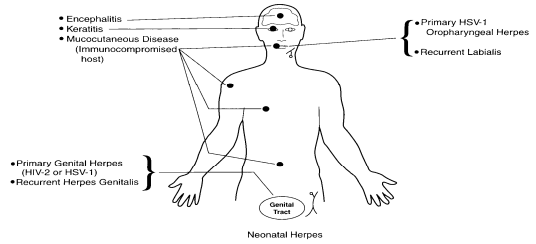
- Herpes simplex virus, type 1 (HSV-1)
- Herpes simplex virus, type 2 (HSV-2)
- Varicella zoster virus (VZV)
- Cytomegalovirus (CMV)
- Epstein Barr virus (EBV)
- Human herpesvirus 6 (HHV 6 A and B)
- Human herpesvirus 7 (HHV 7)
- Human herpesvirus 8 (HHV 8)

Viral Latency and Reactivation

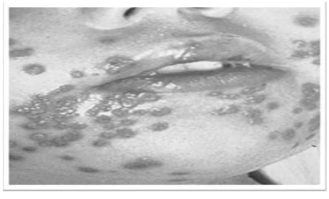


Netter FH. ©2001 by Icon Learning Systems.

Clinical Manifestations of Herpes Simplex Virus Infections



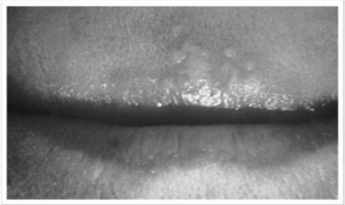
Primary Herpes Simplex Virus Infection: Cutaneous Lesions



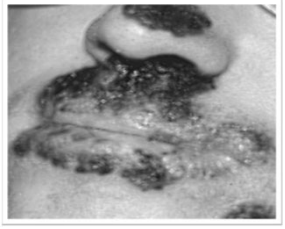
22 – HSV and VZV in Immuno-competent and Immunocompromised Hosts

Speaker: Richard Whitley, MD

Herpes Simplex Labialis

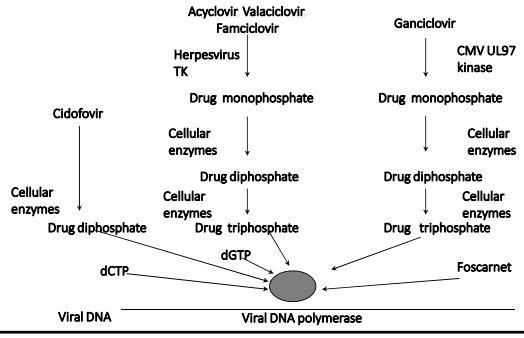


Immunocompromised Host



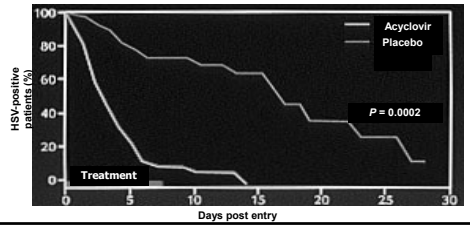
Most Widely Used Systemic Anti-HSV and VZV Drugs

- 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



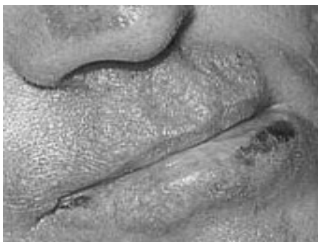
Acyclovir Prophylaxis for HSV Infection in BMT Patients

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	

22 – HSV and VZV in Immuno-competent and Immunocompromised Hosts

Speaker: Richard Whitley, MD



Question #1

PREVIEW QUESTION

A 30 year old heart transplant has received acyclovir for the past 60 days for 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

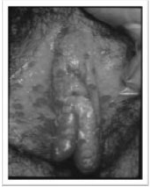
Total estimated number of people (in millions) infected with HSV-2 in 2012 by WHO region, gender and age range.
Source: WHO, as published in PLOS ONE (21 Jan 2015)

Acyclovir Therapy of Genital Herpes

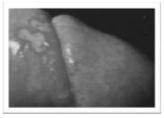
Summary of clinical benefit for treatment of:

- Primary
- Recurrent
- Suppressive

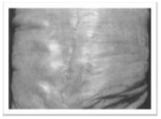
Spectrum of HSV Clinical Presentation



First infection

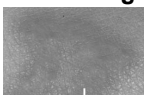


Classical recurrence

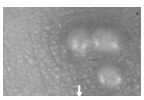


Atypical recurrence

Progression of Lesions



Early Redness/Swelling



Thin-Walled Fluid-Filled Vesicles and Pustules

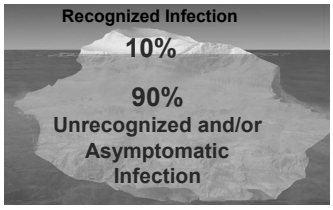
Early Healing of Vesicles, Erosions, or Ulcers

22 – HSV and VZV in Immuno-competent and Immunocompromised Hosts

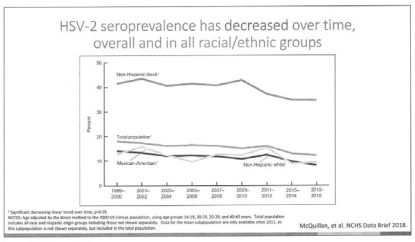
Speaker: Richard Whitley, MD

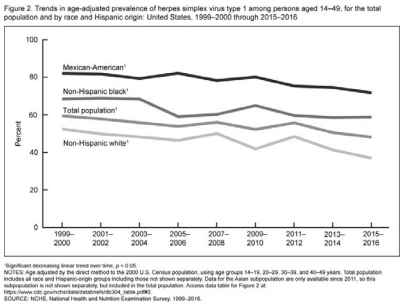
Clinical Spectrum of HSV-2

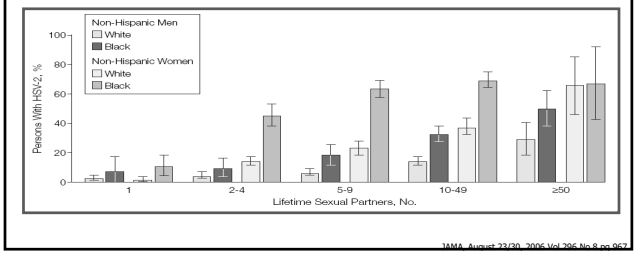
HSV-2 Seroprevalence

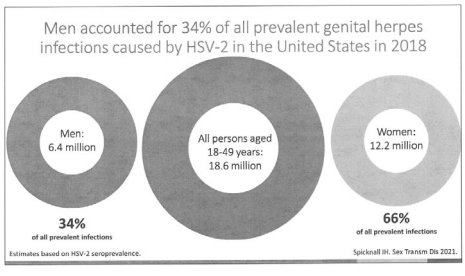


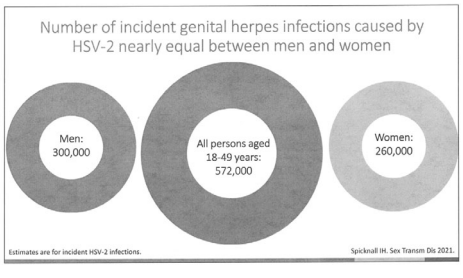
Mertz GJ. *Infect Dis Clin North Am*. 1993;7:825-839.



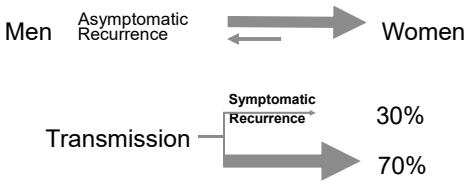






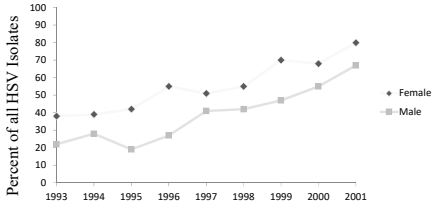


Genital Herpes: Transmission



Corey L. *Sex Transm Dis.* 1994;21(S38-S44.
Mertz GJ, et al. *Ann Intern Med.* 1992;116:197-202

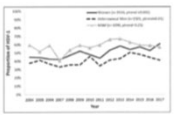
HSV-1 Genital Isolates Among U.S. College Students



Sex Transm Dis 2003;30:797-800

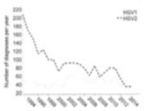
Changing epidemiology of first episode genital herpes

Melbourne Sexual Health Center



In 2017, 54% of first episode genital herpes was due to HSV-1

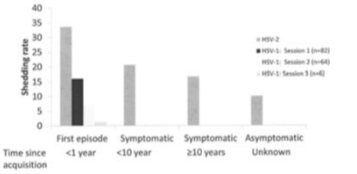
Public Health-Seattle & King County



Each decade, 52% increase in proportion of first episode genital HSV-1

Durukan STI 2019
Dabestani, STD 2019

Genital Shedding Rate: HSV-2 vs. HSV-1

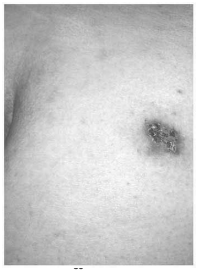


Genital Herpes: Viral Shedding

- 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



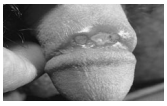
- **The patient had been to her doctor 3 times over the past 8 months with this pruritic and mildly painful rash on her right buttock. She had been told that it was an irritation from riding a bicycle.**
- **What is the key to the diagnosis?**
  - **A. the fact that lesions recurred**
  - **B. site of involvement is not unusual**
  - **C. trauma can induce reactivation**

Photo courtesy of Jeffrey Gilbert, MD

Question #2

PREVIEW QUESTION

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.

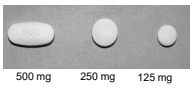


Which of the following diagnostic tests is most likely to yield the specific diagnosis?

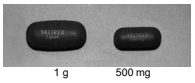
A. **Serum RPR**
B. **Serum FTA-Abs**
C. **Darkfield microscopy**
D. **Glycoprotein-G 1 serum antibodies**
E. **PCR on lesion swab**

Oral Antiviral Therapies

- **Famciclovir [Famvir®]**



- **Valaciclovir [Valtrex®]**



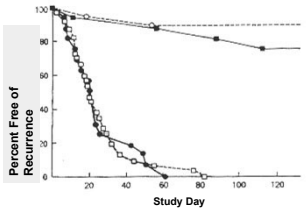
- **Acyclovir [Zovirax®]**

Valtrex® and Zovirax® are registered trademarks of GlaxoSmithKline.

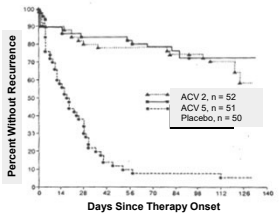
Impact of Acyclovir Therapy on Primary Genital HSV Infection

	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

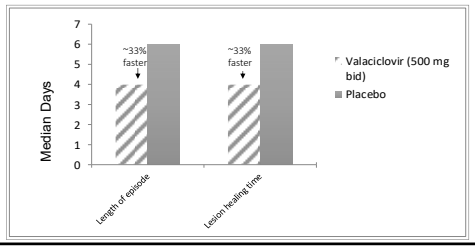
Second Generation Anti-Herpetic Medications

- Valacyclovir (prodrug of acyclovir)
- Famciclovir (prodrug of penciclovir)

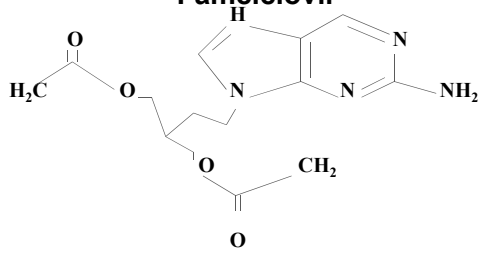
Acyclovir/Valacyclovir Kinetics

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

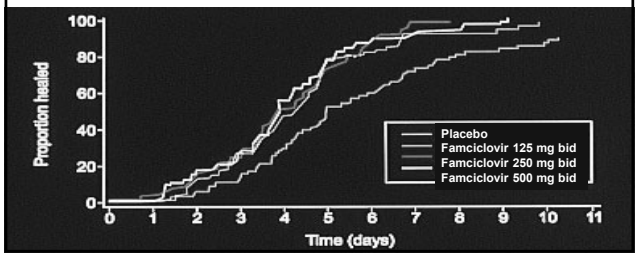
Therapy of Recurrent Genital Herpes: Duration of Disease



Famciclovir



Famciclovir Therapy of Recurrent Genital Herpes



Shorter and Shorter Therapy

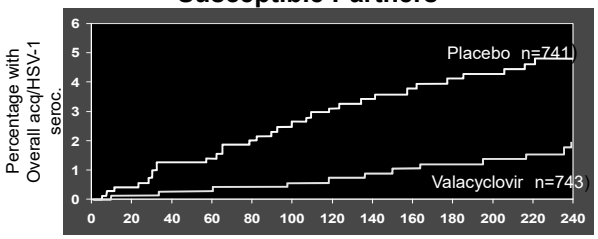
- Genital Herpes
  - Valacyclovir: three days
  - Famciclovir: one day
- Labial Herpes
  - Valacyclovir: two days
  - Famciclovir: one day

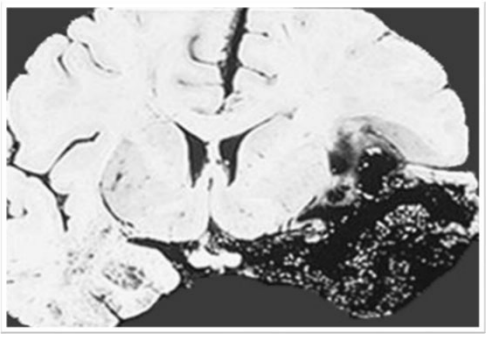
Prevention of Person-to-Person Transmission

Valacyclovir Prevention of HSV Transmission to Susceptible Partners

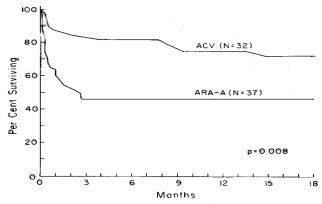
Susceptible Partner	Val-ACV N = 743	Placebo N = 741	Total
No. acquired HSV-2	14	28	42
No. acquired HSV-1	0	4	4
No. developed clinical HSV-2	4	17	21

Time to Acquisition of HSV-1 or HSV-2 in Susceptible Partners





Herpes Simplex Encephalitis Survival



Vidarabine (ARA-A) vs Acyclovir (ACV); P=0.008

HSE Morbidity

Percent Patients
Patient Normal / Mild Impairment

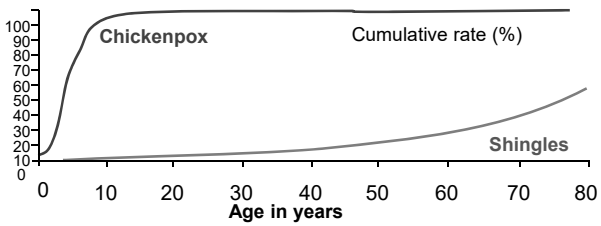
Age	Glasgow Coma Scale	
	<6	>6
<30	0	60
>30	0	36

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?

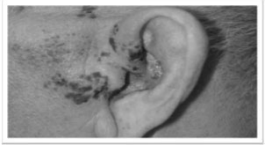
Treatment of Chicken Pox: Adults (>18 Years) < 24 Hour Duration

	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?



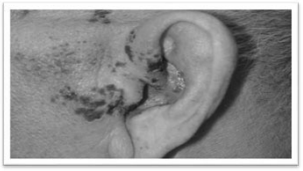
Answer

- 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 on his nose.

- **What is your most likely diagnosis?**
- **What is the name of this sign?**

www.medscape.com

Question #4

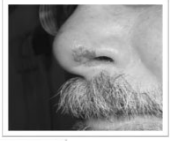
What complication is it most likely to be associated with this illness?

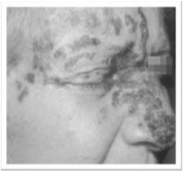
A. Deafness
B. Vertigo
C. Optic neuritis
D. Keratitis
E. Stroke

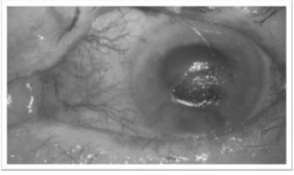
www.medscape.com

Hutchison's Sign

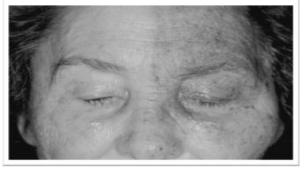
Zoster Involving nasociliary branch, Cranial Nerve VII which inervates the tip of the nose and the cornea







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**

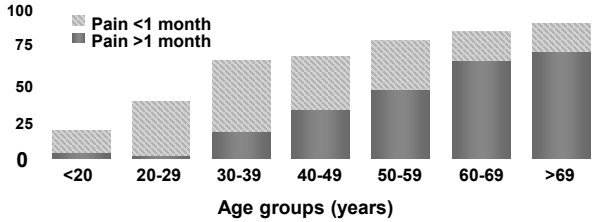
NATURAL HISTORY OF ZOSTER IN THE NORMAL HOST

- **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	• Cutaneous dissemination
• Ocular complications	• Herpes gangrenosum
• Ophthalmic zoster	• Hepatitis
• (uveitis, keratitis, scleritis, optic neuritis)	• Encephalitis
• Pneumonitis	• Motor neuropathies
• Scarring	• Myelitis
• Bacterial superinfection	• Hemiparesis (granulomatous CNS vasculitis)

Prevalence and Duration of Pain

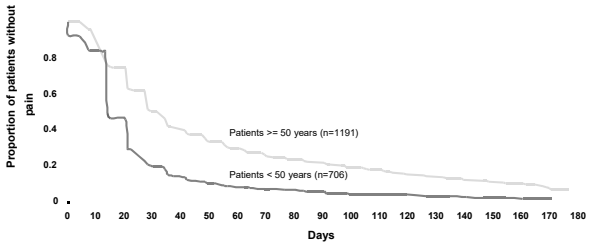


de Moragas et al. *Arch Derm.* 1957;75:193-196.

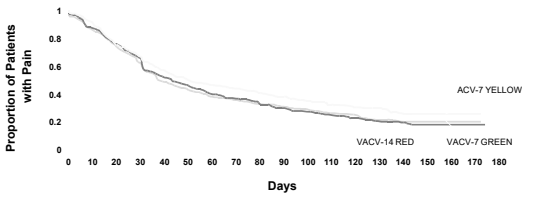
Goals of Therapy

- Accelerate cutaneous healing
- Accelerate loss of pain acute / chronic
- Prevent complications

Time to Cessation of Zoster-Associated Pain

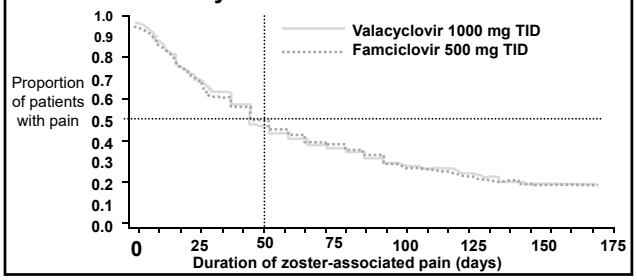


Time to Cessation of Zoster Associated Pain n = 1141



* Beutner, et al. Acyclovir versus Valacyclovir in the treatment of herpes zoster in patients > 50 years old.

Resolution of Pain in Herpes Zoster With Valacyclovir and Famciclovir



Summary of Efficacy of Concomitant Steroid Therapy with Acyclovir

- Accelerates resolution of acute neuritis
- Accelerates:
  - Return to usual activity P<0.001
  - Unaroused sleep P<0.0001
  - Cessation of analgesic use P<0.001
- Effect on chronic pain P=0.06

Question #5

What is the most likely etiologic agent?

A. HSV
B. VZV
C. CMV
D. EBV
E. HHV6

www.cdc.gov

METHODS OF PREVENTING / MODIFYING VARICELLA

Pre-exposure: Oka varicella vaccine

Post-exposure: VZIG (now available in US)

Oka varicella vaccine
(<3 days after exposure)
Acyclovir
(7-14 days after exposure)

Shingles Prevention Trial: Zostavax

Attenuated, live virus (approved 2006)

- **Efficacy but waning of immunity with time**
  - **Burden Of Illness 61.1% (51.1 – 69.1%)**
  - **Post-Herpetic Neuralgia 66.5% (47.5 – 79%)**
  - **Incidence of Herpes Zoster 51.3% (44.2 – 57.6%)**

Second Generation Vaccine: Shingrix

- **Recombinant adjuvanted vaccine**
  - **Two shots**
  - **> 50 years of age**
- **Efficacy**
  - **Both PHN and incidence of shingles**
  - **>90% for >4 years**
- **Adverse events**
  - **Local reactogenicity: redness and pain ~ 50-70%**
  - **Systemic malaise/fever: ~30%**

Thank You
rwhitley@uab.edu

Agenda Day 3: Monday, August 19, 2024

AM Moderator: Paul Auwaerter, MD					
#	Start		End	Presentation	Faculty
QP3	8:00 AM EDT	-	8:30 AM EDT	Daily Question Preview Day 3	Paul Auwaerter, MD
23	8:30 AM	-	9:00 AM	Sexually Transmitted Infections: Genital Ulcers Diseases (GUD)	Khalil Ghanem, MD
24	9:00 AM	-	9:45 AM	Fungal Diseases in Normal and Abnormal Hosts	John Bennett, MD
FC7	9:45 AM	-	10:00 AM	Faculty Q&A	Drs. Auwaerter (Moderator), Bennett, and Ghanem
25	10:00 AM	-	11:00 AM	Sexually Transmitted Infections: Other Diseases and Syndromes	Khalil Ghanem, MD
26	11:00 AM	-	11:45 AM	Nontuberculous Mycobacteria in Normal and Abnormal Hosts	Kevin Winthrop, MD
	11:45 AM	-	12:15 PM	Lunch Break	
BR3	12:15 PM	-	1:00 PM	Board Review Day 3	Drs. Auwaerter (Moderator), Bell, Bennett, Dhanireddy, Dorman, Ghanem, Klompas, and Winthrop
PM Moderator: Paul Auwaerter MD					
27	1:00 PM	-	1:45 PM	Ticks, Mites, Lice, and the Diseases They Transmit	Paul Auwaerter, MD
28	1:45 PM	-	2:30 PM	Immunizations: Domestic, Travel, and Occupational	Shireesha Dhanireddy, MD
29	2:30 PM	-	3:15 PM	Tuberculosis in Immunocompetent and Immunosuppressed Hosts	Susan Dorman, MD
FC8	3:15 PM	-	3:30 PM	Faculty Q&A	Drs. Auwaerter (Moderator), Dhanireddy, and Dorman
30	3:30 PM	-	4:00 PM	Lyme Disease	Paul Auwaerter, MD
31	4:00 PM	-	5:00 PM	Hospital Epidemiology	Michael Klompas, MD
32	5:00 PM	-	5:45 PM	Syndromes in the ICU that ID Physicians Should Know	Taison Bell, MD
33	5:45 PM	-	6:15 PM	Pneumonia	Paul Auwaerter, MD
FC9	6:15 PM	-	6:30 PM	End of the Day Faculty Q&A	Drs. Auwaerter, Bell, and Klompas

QP3

Daily Question Preview 3

Dr. Paul Auwaerter (Moderator)

Daily Question Preview: Day 3

Moderator: Paul Auwaerter, MD

7/1/2024

PREVIEW QUESTION 2024

3.1 **A pregnant patient 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.

1 of 3

PREVIEW QUESTION 2024

3.1 **Which of the following antibiotics is most appropriate?**

A) Azithromycin

B) Benzathine penicillin G

C) Ceftriaxone

D) Doxycycline

2 of 3

PREVIEW QUESTION 2024

3.2 **Formerly healthy 48M with 3 months of chronic fevers, cough, 25 lb weight loss, night sweats, presented with acute worsening on dyspnea and was found to have a high fever and diffuse lung infiltrates bilaterally. Office worker in Md. No travel. Wife healthy.**

Vitals: 39.3C, HR 97, RR 29, BP 97/54, O2: 88% on room air

Crackle all over lung, spleen tip felt.

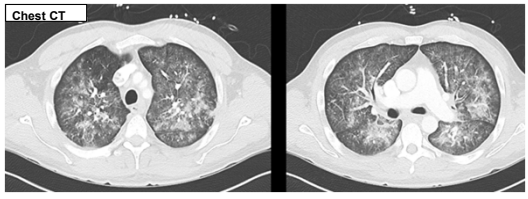
WBC: 5,300, HgB 10.1 Plt 119,000, ALP 218, ALT 43, AST54, lactate 2.5, ferritin 2418, triglycerides 250. HIV neg.

Intubation, pressors, ceftriaxone, voriconazole

1 of 4

PREVIEW QUESTION 2024

3.2



2 of 4

PREVIEW QUESTION 2024

3.2 **The preferred diagnostic procedure is:**

A) Bronchoscopy

B) Transthoracic needle lung biopsy

C) VATS lung biopsy

D) Serum antigen

E) Bone marrow

3 of 4

QP3 – Question Preview: Day 3

Moderator: Paul Auwaerter, MD

PREVIEW QUESTION INFECTIOUS DISEASE BOARD REVIEW 2024

3.3 **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.

1 of 3

PREVIEW QUESTION INFECTIOUS DISEASE BOARD REVIEW 2024

3.3 **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

2 of 3

PREVIEW QUESTION INFECTIOUS DISEASE BOARD REVIEW 2024

3.4 **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

1 of 2

PREVIEW QUESTION INFECTIOUS DISEASE BOARD REVIEW 2024

3.5 **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 (assume today is his last day of doxycycline)?

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

E) Moxifloxacin 400 mg orally daily for 7 days

1 of 2

PREVIEW QUESTION INFECTIOUS DISEASE BOARD REVIEW 2024

3.6 **72 year old female with chronic cough, normal CXR, and 1/3 sputums grow MAC.**

Which one of the following do you 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.

1 of 2

PREVIEW QUESTION INFECTIOUS DISEASE BOARD REVIEW 2024

3.7 **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.**

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

1 of 2

PREVIEW QUESTION

3.8 **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.

There is a faint maculopapular rash on extremities

1 of 3

PREVIEW QUESTION

3.8 **Which of the following is the most likely diagnosis?**

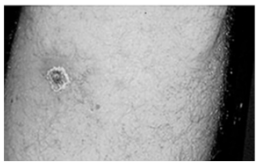
A) Human Monocytic Ehrlichiosis (HME)
B) Human Granulocytic Anaplasmosis (HGA)
C) Babesiosis
D) Rocky Mountain Spotted Fever (RMSF)
E) Tularemia

2 of 3

PREVIEW QUESTION

3.9 **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.



1 of 3

PREVIEW QUESTION

3.9 **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*

2 of 3

PREVIEW QUESTION

3.10 **38 y/o healthy physician; periodic travel to South Africa for work.**

6 years ago: pos TST; poor adherence with isoniazid preventive therapy.

Now 5 weeks of fever, chills, night sweats, 10-lb wt loss, productive cough.

CXR RUL cavitary lesion.

Sputum Xpert MTB/RIF: "MTB detected" & "Rifampin resistance not detected."

HIV negative, LFTs normal.

1 of 3

PREVIEW QUESTION

3.10 **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

2 of 3

QP3 – Question Preview: Day 3

Moderator: Paul Auwaerter, MD

PREVIEW QUESTION

3.11 **24 y/o M from Zambia, in U.S. for community college, recently tested HIV-positive, CD4 400, not yet on ART.**

Prominent anterior cervical lymph node but well-appearing, normal BMI, normal liver and renal chemistries, mild anemia.

Lymph node biopsy grows *M. tuberculosis* in culture.

1 of 3

PREVIEW QUESTION

3.11 **Best course of action regarding timing of TB therapy and HIV therapy?**

A) Start ART immediately, defer TB tx

B) Start TB tx immediately, defer ART until completes 6 months TB tx

C) Start TB tx immediately, and start ART within about 8 weeks

D) Start both TB tx AND ART immediately

2 of 3

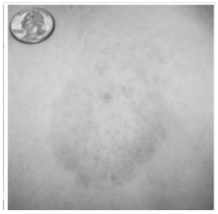
PREVIEW QUESTION

3.12 **A 56 y.o. man from southern Missouri**

Onset in July:

--Myalgia and malaise

--Rash x 2d at site of 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)

1 of 3

PREVIEW QUESTION

3.12 **Which of the following is the most likely diagnosis?**

A) Lyme disease (*Borrelia burgdorferi* infection)

B) Human Monocytic Ehrlichiosis (*Ehrlichia chaffeensis*)

C) *Borrelia mayonii*

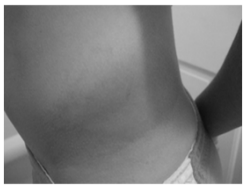
D) Southern tick-associated rash illness (STARI)

E) *B. lonestari* infection

2 of 3

PREVIEW QUESTION

3.13 **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.

1 of 3

PREVIEW QUESTION

3.13 **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* standard 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

2 of 3

QP3 – Question Preview: Day 3

Moderator: Paul Auwaerter, MD

PREVIEW QUESTION

3.14 What is the most common healthcare-associated infection?

A) Central line associated bloodstream infections
B) Catheter-associated urinary tract infections
C) Hospital-acquired pneumonia
D) Surgical site infections
E) *Clostridioides difficile*

1 of 2

PREVIEW QUESTION

3.15 A 63-year-old man with lymphoma is admitted for chemotherapy.

His course is complicated by new atrial fibrillation and hospital acquired pneumonia (treated with vancomycin, cefepime, levofloxacin).

On hospital day 12 he develops severe diarrhea and is diagnosed with *C. difficile* infection.

1 of 3

PREVIEW QUESTION

3.15 Where did the patient most likely acquire this pathogen?

A) From another patient on his ward (carried by healthcare workers' hands)
B) From the previous occupant of his bed
C) From the toilet seat of the shared bathroom in his room
D) From the food provided by the hospital
E) From the community (already colonized on admission)

2 of 3

23

Sexually Transmitted Infections: Genital Ulcers Diseases (GUD)

Dr. Khalil Ghanem

23 – 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
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Johns Hopkins University School of Medicine

7/18/2024

- **Disclosures of Financial Relationships with Relevant Commercial Interests**

  - None

NOTE

- I have tried to use patient-first language throughout. When the terms 'women' and 'men' are used, I am referring to cis-gender women and men unless otherwise specified
  - Data on the epidemiology and management of STIs in transgender populations are very limited
- 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)*
- Monkeypox

PAIN AND GUD

Which ulcers are PAINFUL?

- HSV
- Chancroid
- Monkeypox

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

23 – Sexually Transmitted Infections: Genital Ulcers Diseases (GUD)

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"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"**

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?

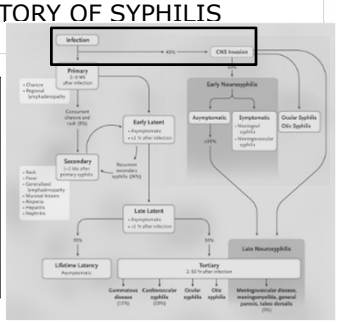
A. Serum RPR
B. Serum VDRL
C. Serum treponemal EIA
D. Darkfield microscopy on a specimen obtained from the oral ulcer
E. Darkfield microscopy on a specimen obtained from the vulvar ulcer

NATURAL HISTORY OF SYPHILIS

Sexual transmission (only occurs in early stages)
- Risk of infection after 1 exposure: 40%
- Index patient is most contagious during 1° and 2° stage, less so in early latent stage

Vertical transmission (may occur during any stage)
- ~80% transmission in the early stages
- ~10% transmission in the late stages

Rarely, transmission may occur through **blood transfusions** and **organ transplantations**



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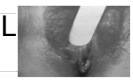
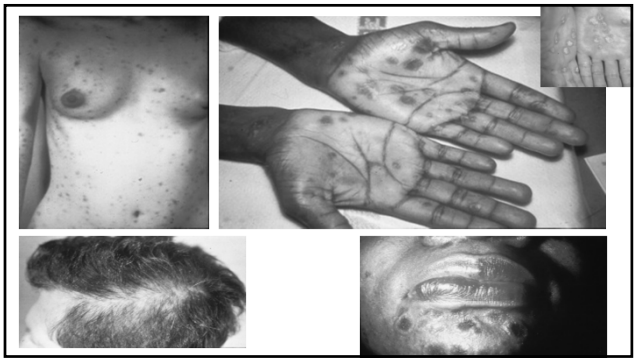
EARLY SYPHILIS: CLINICAL MANIFESTATIONS



- Incubation ~3 weeks
- Primary: chancre; LAD; resolves 3-6 weeks
- Secondary: **Systemic symptoms**: low-grade fever, malaise, sore throat, adenopathy
  - RASHES: [1]evanescent, copper-colored, macular (dry) rash; followed by [2] a red papular eruption (involving palms and soles in 60%); mucosal lesions (gray plaques or ulcers) ; condyloma lata- wart-like lesions that develop in moist areas
  - Other manifestations: Patchy alopecia, hepatitis (mild elevation of aminotransferases with disproportionately high alkaline phosphatase), gastritis, periostitis, glomerulonephritis, etc.



23 – Sexually Transmitted Infections: Genital Ulcers Diseases (GUD)

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NEUROLOGICAL MANIFESTATIONS OF SYPHILIS

- **Can occur during any stage of infection******
- **Symptomatic Early Neurosyphilis**
  - Occurs within the **first year** after infection
  - **Mainly among PWH**
  - **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

~30% of patients with cardiovascular and gummatous syphilis will have asymptomatic neurosyphilis- 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 at least 40% of cases of otic syphilis**

*****No need for a CSF examination in patients who only have ocular or otic symptoms/signs**

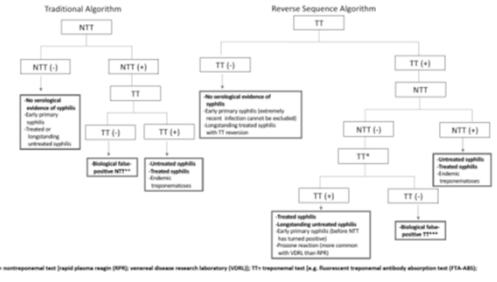
SYPHILIS SEROLOGICAL TESTING

Nontreponemal tests

- RPR (serum) or VDRL (serum or CSF)
- **False positives:** endemic treponematoses, old age, pregnancy, autoimmune disease (APS), viral infections
- **False negatives:** PROZONE effect and in early infection
- Reactive result must be confirmed with treponemal test
- 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
- **False positives:** Endemic treponemal infections (e.g. yaws, pinta, bejel); Lyme disease; rarely in autoimmune conditions
- **False negatives**: Early primary syphilis
- **Once reactive, always reactive even after appropriate therapy**
  - **Exception: ~25% of persons treated early in primary syphilis may serorevert years later**



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23 – Sexually Transmitted Infections: Genital Ulcers Diseases (GUD)

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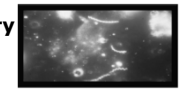
SYPHILIS: DIAGNOSTICS

- 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
  - CSF pleocytosis **most sensitive** marker
  - 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 tests

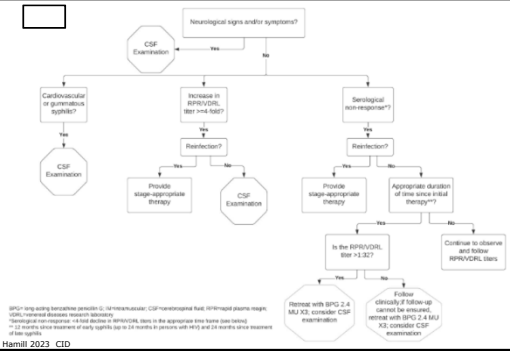
A FEW IMPORTANT CONCEPTS TO REMEMBER ABOUT NEUROSYPHILIS, OCULAR SYPHILIS, AND OTIC SYPHILIS

A normal CSF examination rules out neurosyphilis, but it does not rule out ocular or otic syphilis

A patient with ocular only or otic only signs and/or symptoms does not need a CSF examination. An immediate through clinical evaluation is warranted and if the clinical picture is consistent with ocular or otic syphilis, start antibiotic therapy

A patient with both neurological signs/symptoms and ocular or otic signs/symptoms should undergo a CSF examination. While it may not impact the treatment decision, it may impact diagnostic considerations [patients may have neurological manifestations due to something other than syphilis- you don't want to delay the diagnosis]

Who Should Have a CSF Exam?



Hamill 2023 CID

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

Serological Non-Response

Are there any neurological, ocular, or otic signs or symptoms?
- Yes → **Manage accordingly**
- No ↓

Did you wait long enough for the titers to decline?
- No → **Keep following**
- Yes ↓

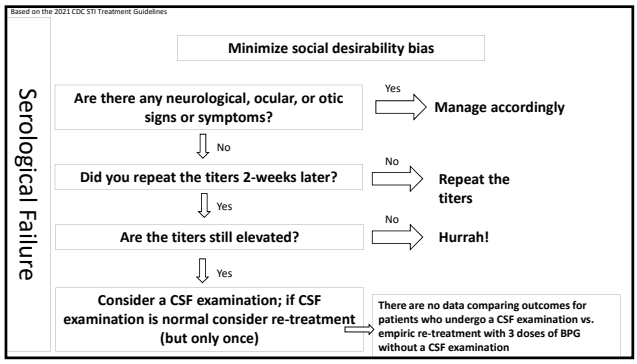
Did the patient get reinfected or is the patient pregnant?
- Yes → **Re-treat**
- No ↓

Is the titer >=1:64?
- Yes → **Consider CSF examination**
  Cai *Scientific Reports* 2017
- No ↓

Keep following the titers ⇒ **5 observational studies show no difference in intermediate-term outcomes between treatment and watchful waiting. If you feel better re-treating, do so, but only once!**

Based on the 2021 CDC STI Treatment Guidelines

Reviewed by Hamill *CID* 2023



SYPHILIS THERAPY CONTINUED

- Neurosyphilis/Ocular/Otic syphilis
  - Aqueous penicillin 18 to 24 MU IV X 10-14 days
  - Ceftriaxone 1-2g IV/IM X 10-14 days (2nd line regimen)
  - **Follow-up CSF exams are NOT necessary if patient improves clinically, serologically, and is not immunosuppressed (PWH on ART at time of diagnosis does not need a f/u CSF exam)**


Normalization of Serum Rapid Plasma Reagin Titer Predicts Normalization of Cerebrospinal Fluid and Clinical Abnormalities after Treatment of Neurosyphilis


SCIENTIFIC REPORTS

- Jarisch-Herxheimer: within 6 hours (up to 24 hours) after therapy of (usually) early syphilis; antipyretics only; **may induce early labor**

QUESTION #2

PREVIEW QUESTION

A pregnant patient 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

PREVIEW QUESTION

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 negative
- Serological response may be slower among PWH
- Follow-up is more frequent (every 3 months)

SYPHILIS & PREGNANCY

- Screen at 1st prenatal visit
- Screen higher risk patients and those living in high-prevalence areas twice in the 3rd trimester: at 28 weeks and again at the time of delivery
- Screen all those who deliver a stillborn infant after 20 weeks' gestation
- **Pregnant penicillin-allergic patients with syphilis need to be desensitized to penicillin and treated with a penicillin-based regimen. There are NO OTHER OPTIONS (not even ceftriaxone)**

23 – Sexually Transmitted Infections: Genital Ulcers Diseases (GUD)

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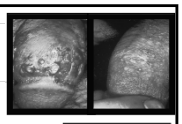
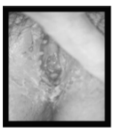
HSV





- 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 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 those who have active lesions or prodromal symptoms at the time of delivery

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**

HSV: DIAGNOSTICS IN ASYMPTOMATIC PATIENTS

- Use Glycoprotein G-based type-specific EIA assays
  - If gG2 is reactive, patient has genital herpes
    - 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)
  - If gG1 is reactive, patient either has oral herpes or genital herpes (assay has low sensitivity)
- Serologic testing **NOT** routinely recommended for screening
- **Never obtain IgM or try to interpret IgM results!**

HSV: PREGNANCY

- Risk of vertical transmission if mom acquires FIRST episode (i.e. primary infection) of herpes at time of delivery is 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: Those 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)

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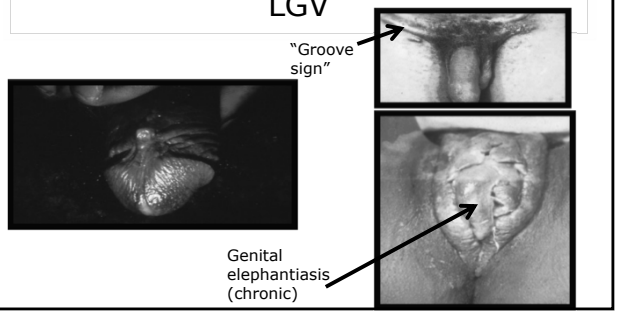
LGV

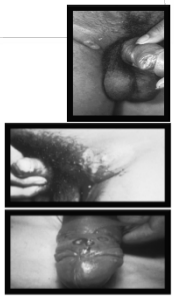


LGV DIAGNOSIS & THERAPY

- **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)
- **Patients with *C trachomatis* and a + rectal NAAT:**
  - **Mild symptoms- treat with doxycycline for 1 week**
  - **Moderate to severe symptoms- treat with doxycycline for 3 weeks**

CHANCROID

- *Haemophilus ducreyi*
  - Endemic in parts of the southern US. Rates have gone down
  - Increased risk with HIV infection and commercial sex work
- Symptoms: painful, indurated, 'ragged' genital ulcers & tender suppurative inguinal adenopathy (50%); kissing lesions on thigh; 10% of patients co-infected with syphilis or HSV; bacterial superinfection not uncommon
- Dx: culture (80% sensitive) [antigen detection and PCR not widely available]
- Rx: Azithromycin 1g PO X1 OR Ceftriaxone 250mg IM X1 (erythromycin and ciprofloxacin may also be used)
- Treat all partners in preceding 60 days

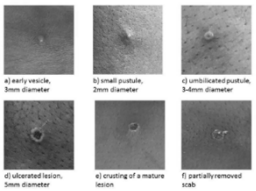


GRANULOMA INGUINALE OR DONOVANOSIS

- *Klebsiella granulomatis (Calymmatobacterium granulomatis)*
- Not endemic in US; common in SE Asia (India), & Southern Africa (recently eradicated in Australia)
- Painless, progressive (destructive), "serpiginous" ulcerative lesions, without regional LAD (pseudobuboes occasionally); beefy red with white border & highly vascular
- Dx: tissue biopsy (no culture test; PCR not FDA cleared); demonstrating the organisms in macrophages, called **Donovan bodies**, using **Wright-Giemsa** stain (NOT Gram's stain)
- Rx: Doxycycline 100mg PO BID X 3 weeks (or until resolution) OR azithromycin 1g PO q week X3 (can also use trimethoprim/sulfa)

MONKEYPOX

- Prodrome: Fever, chills, rash, or new lymphadenopathy; however, onset of perianal or genital lesions (often painful) in the absence of prodrome may occur; proctitis described
- DDx rash: Secondary syphilis, HSV, chancroid, and VZV. Consider in men who report sexual contact with other men (incubation 5-21 d) & individuals reporting a significant travel history
- Patients generally describe close, sustained physical contact with other people with monkeypox (respiratory transmission inefficient)
- Persons are infectious once symptoms begin; when all scabs have fallen off a person is no longer contagious
- Rx: Tecovirimat in patients with or at-risk for severe disease (CDC-held Emergency Access Investigational New Drug Protocol)



UK Health Security Agency

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

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Enlarged slides: 10, 18

NATURAL HISTORY OF SYPHILIS

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- Index patient is most contagious during 1º and 2º stage, less so in early latent stage

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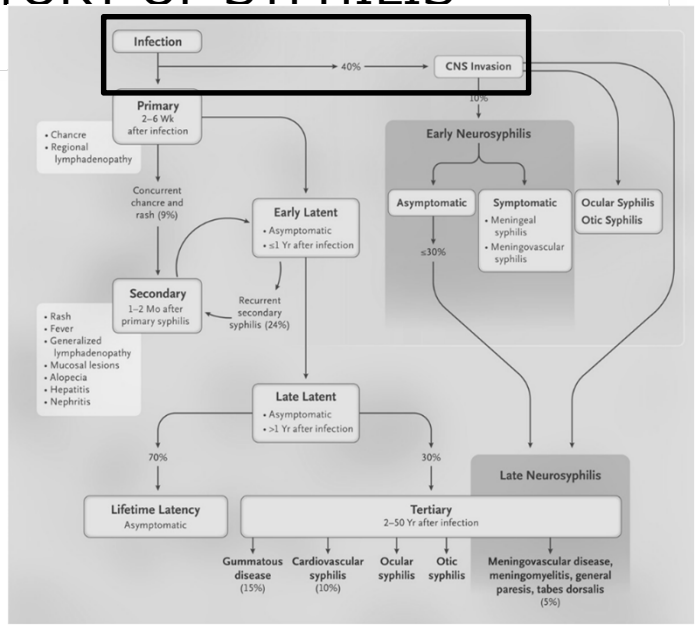
- ~10% transmission in the late stages

Rarely, transmission may occur through **blood transfusions** and **organ transplantations**



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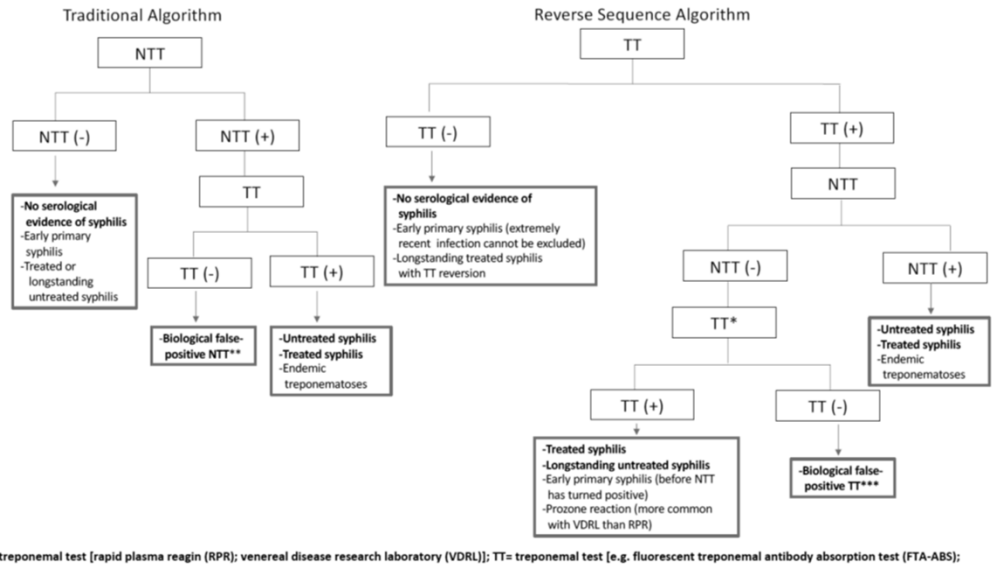

NTT= nontreponemal test [rapid plasma reagin (RPR); venereal disease research laboratory (VDRL)]; TT= treponemal test [e.g. fluorescent treponemal antibody absorption test (FTA-ABS);

* N Engl J Med 2020;382:845-854

24

Fungal Diseases in Normal and Abnormal Hosts

Dr. John Bennett

24 – Fungal Disease in Normal and Abnormal Hosts

Speaker: John Bennett, MD

IDBR INFECTIOUS DISEASE BOARD REVIEW AUGUST 17-21, 2024

Fungal Diseases in Normal and Abnormal Hosts

John E. Bennett, MD
Bethesda, Maryland

7/1/2024

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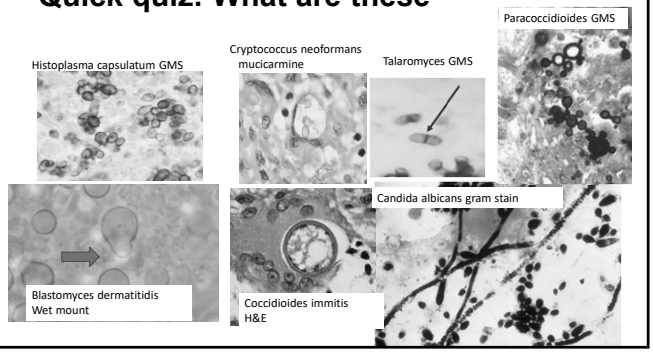
- **Disclosures of Financial Relationships with Relevant Commercial Interests**

  - None

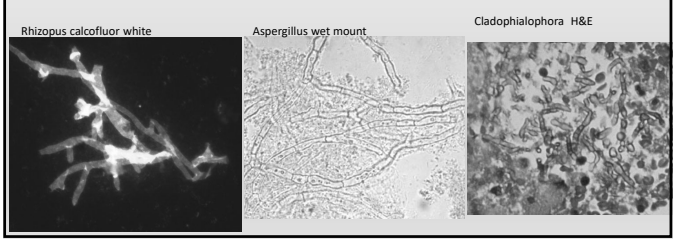
Mycology 101

- Yeasts reproduce by budding
  - All Candida have pseudohyphae in tissue except C.glabrata
  - Crypto has capsule, stains with mucicarmine
- Dimorphic fungi are round cells in tissue, hyphae in culture
  - Histoplasma, Coccidioides, Blastomyces, Sporothrix , Paracoccidioides
- Molds have hyphae in tissue and culture
  - Septate: Aspergillus, Fusarium, Scedosporium, others
  - Rare or no septae (Mucorales): Rhizopus, Mucor, Cunninghamella, others
  - Dark-walled fungi: many cause infection of skin, paranasal sinus, brain
    - Phaeohyphomycosis

Quick quiz: What are these



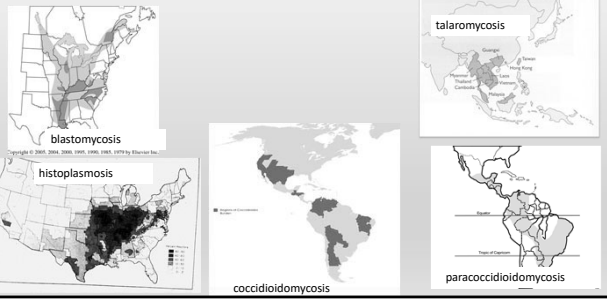
Quick Quiz: What are these?



ENDEMIC MYCOSES

- Geographically restricted
- Dimorphic (yeast in tissue,hyphae in culture)
- Infection by inhaling spores in nature
- No person to person transmission
- Cluster of cases with fever, cough after soil exposure
  - No secondary cases
  - Desert dust=cocci. Rich earth, bat guano=histo
    - Streams, rivers=blasto

What are these endemic mycoses?



CASE 1

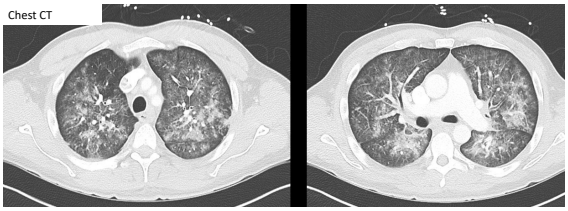
(COURTESY OF SHANAN IMMEL, MD)

PREVIEW QUESTION

- Formerly healthy 48M with 3 months of chronic fevers, cough, 25 lb weight loss, night sweats, presented with acute worsening on dyspnea and was found to have a high fever and diffuse lung infiltrates bilaterally. Office worker in Md. No travel.Wife healthy.
- Vitals: 39.3C, HR 97, RR 29, BP 97/54, O2: 88% on room air
- Crackle all over lung, spleen tip felt.
- WBC: 5,300, HgB 10.1 Plt 119,000, ALP 218, ALT 43, AST54, lactate 2.5, ferritin 2418, triglycerides 250. HIV neg.
- Intubation, pressors, ceftriaxone, voriconazole

PREVIEW QUESTION

Chest CT



The preferred diagnostic procedure:

A. Bronchoscopy
B. Transthoracic needle lung biopsy
C. VATS lung biopsy
D. Serum antigen
E. Bone marrow

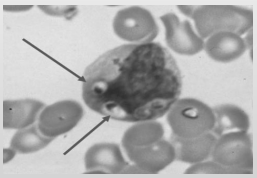
Recognizing mycoses on the board exam

Histoplasma capsulatum complex

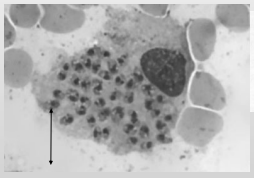
- Case clusters of acute pneumonia two weeks after soil exposure (rare: bat caves)
- Immunosuppressed patient with febrile disseminated disease
  - Cytopenias
  - Miliary lung infiltrate can look like PJP, miliary TB
  - Mucosal lesions resemble squamous carcinoma
  - Adrenal insufficiency
  - Can mimic HLH (hemophagocytic lymphohistiocytosis) or miliary TB
  - HIV patients can have IRIS after starting ARV
- Urine or serum antigen good diagnostic test
- Biopsy: small budding yeast, mold on culture
- Rx: ampho then itraconazole for disseminated
- Histoplasma duboisii (African histoplasmosis)
  - Skin and bone lesions

QUICK QUIZ: WHAT IS THE DISEASE ASSOCIATTED WITH THESE INTRACELLLAR PARTICLES?

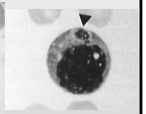
HISTOPLASMOSIS



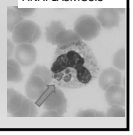
LEISHMANIASIS



EHRLICHIOSIS

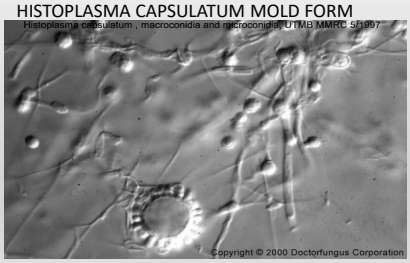


ANAPLASMOSIS

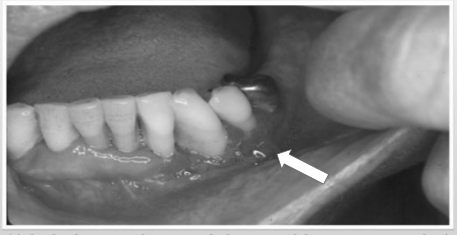


Histoplasma capsulatum growing at room temperature

- HISTOPLASMA CAPSULATUM MOLD FORM



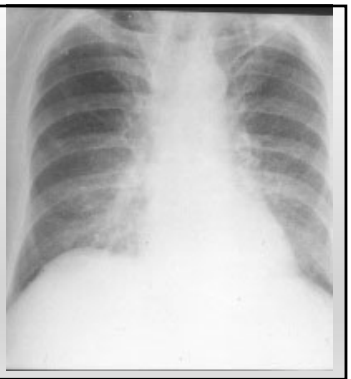
Gingival Ulcer



¼ CASES HAVE ORAL LESION IN DISSEMINATED HISTO

TONGUE AND PENILE LESIONS
MUCOSAL LESIONS CAN RESEMBLE SQUAMOUS CARCINOMA

MILIARY LUNG LESION IN DISSSEMINATED HISTOPLASMOSIS (LOOKS LIKE PJP ON IMAGING)



Case

PREVIEW QUESTION

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

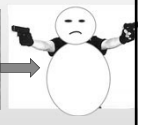
PREVIEW QUESTION

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

Crypto is a killer, not a currency

PREVIEW QUESTION



- Cryptococcus neoformans species complex:
  - Wordwide, pigeon guano,corticosteroids, transplants, HIV
- Cryptococcus gattii species complex
  - Pacific coast, trees, Australia, tropics, often previously healthy
  - Serum antibody to GM-CSF
- Chronic lymphocytic meningitis
  - Headache, confusion, cranial nerve palsies, +/- fever, vision loss
  - Rx ampho+flucytosine then fluconazole, relieve high opening pressure (LP's, shunt)
  - HIV ARV-naïve: consider delay ARV 2 weeks (IRIS)
  - Skin lesions (10%) like molluscum contagiosum
- Lung only: fluconazole alone (negative LP)
- Cryptococcal antigen in CSF, serum
  - Diagnosis, screening high risk patients

24 – Fungal Disease in Normal and Abnormal Hosts

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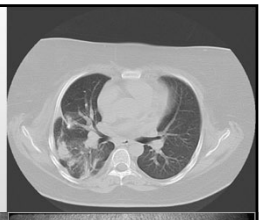
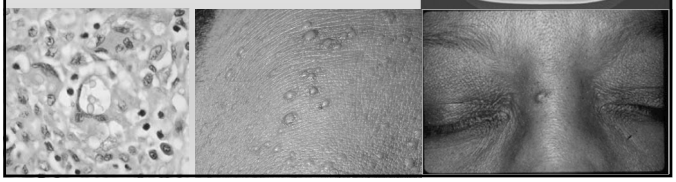
Cryptococcal lung lesions usually asymptomatic

Skin lesions can resemble molluscum contagiosum

Mucicarmine often stains crypto pink.





Case 2

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

Fusariosis

Severely immunocompromised patients
Mold, looks like Aspergillus in tissue
Red, tender skin nodules
Routine blood culture grows mold in a third to half the patients
RX: response to amph and vori poor in severe neutropenia. Experimental: PMN transfusion?, fosmanogepix (investigational)??
Note: fungal meningitis from F. solani, Mexico, epidural anesthesia.

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 4

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

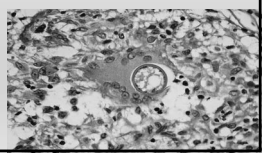
- Two species, one disease:
  - C. immitis and C. posadasii. Both serious lab hazards Southwest USA. Washington state
- Acute pneumonia 2 wks after inhalation: arthralgias or erythema nodosum may accompany. Resolves.
- Residual nodule or thin walled cavity may persist
- Dissemination: African americans, HIV, SOT, TNF inhibitors
- Bone, skin, chronic meningitis. Eosinophils
- 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 in severe disease

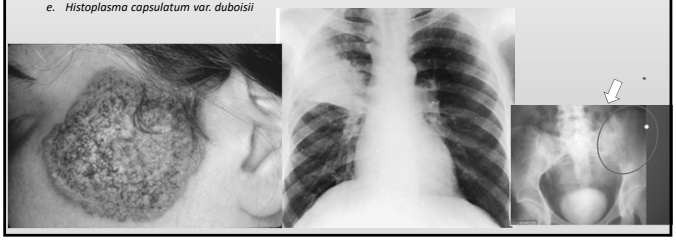
CULTURE
Routine cultures negative, fungal cultures positive. Lab hazard

BIOPSY
Distinctive non-budding spherules



CASE 5
A previously healthy 52 yr old Wisconsin man presented with a leg lesion, painful elbow swelling and 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 dermatitidis
e. Histoplasma capsulatum var. duboisii



Blastomyces dermatitidis , B. gilchristii

CENTRAL USA AND CANADA, MOLD IN NATURE
LARGE BROAD-BASED BUDDING IN TISSUE

MOIST EARTH NEAR RIVER, BEAVER DAMS.

NORMAL HOST

YEAST WITH BROAD BASED BUD, THICK WALL

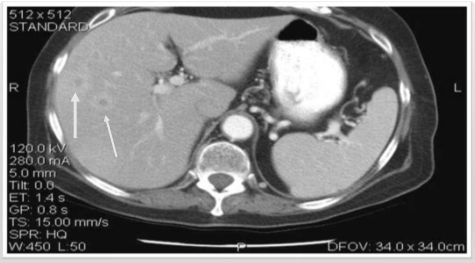
ACUTE PNEUMONIA MAY SELF HEAL

INDOLENT, PROGRESSIVE PNEUMONIA
DISSEMINATES TO SKIN, BONE, MALE GU TRACT

OFTEN PRESENTS AS SKIN LESIONS

RX: ITRACONAZOLE, AMPHO B

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

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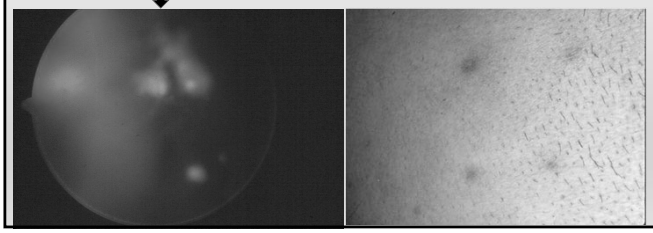
Candidiasis makes the sick get sicker

- Fundoscopy for retinal lesions in candidemia patients.
  - Intravitreal Rx may be needed
- Remove intravenous catheter with candidemia
- *Candida auris* hospital outbreaks. Spreads on hands, surfaces
- Fluconazole resistance in C. auris, C. krusei, C. glabrata
- Fungitell (1-3) beta-D-glucan positive in serum

Candida endophthalmitis:

"fluff balls" floating in the vitreous humor

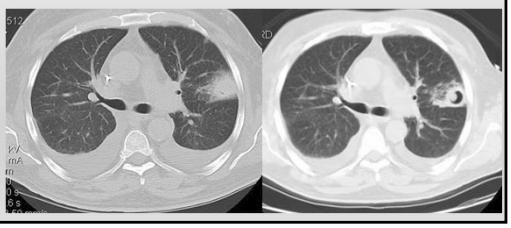
Candida lesions in a neutropenic patient



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



Aspergillus Pneumonia

Sudden onset of a dense, well circumscribed lesion in a neutropenic patient should suggest a mould pneumonia, most commonly aspergillosis, halo sign early, crescent sign later

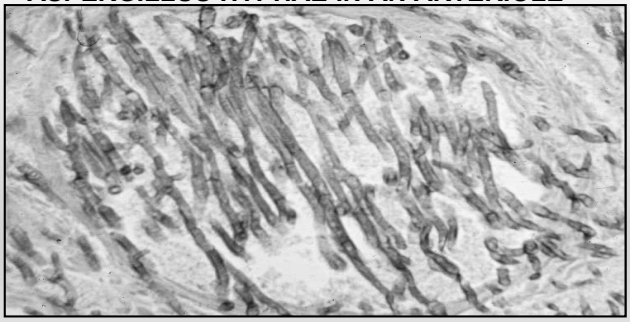
Septated hyphae invade blood vessels, infarct tissue.

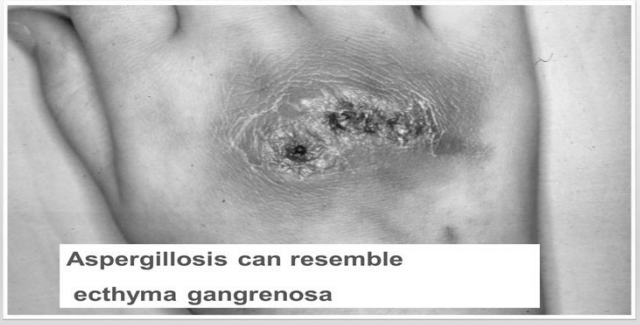
Galactomannan useful in CSF, BAL, blood

- False positives
- False negatives with azole prophylaxis

Rx. voriconazole, isavuconazole, posaconazole, ampho B

ASPERGILLUS HYPHAE IN AN ARTERIOLE





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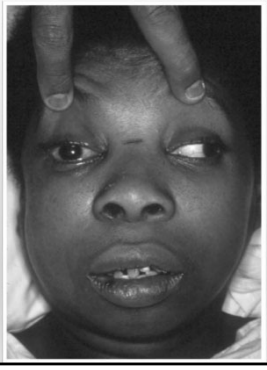
CASE 8

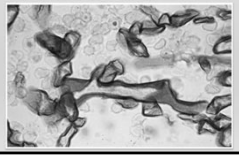
25 YR OLD FEMALE ADMITTED WITH DIABETIC KETOACIDOSIS AND BLINDNESS IN HER RIGHT EYE. ON EXAM THE RIGHT EYE WAS FIXED IN POSITION AND PROPTOTIC. CT SHOWED DENSE MASS IN ADJACENT ETHMOID SINUS WITH EXTENSION INTO THE ORBIT. SURGICAL EXPLORATION OF THE SINUS SHOWED BROAD, ASEPTATE HYPHAE. THE FUNGUS WAS LIKELY:

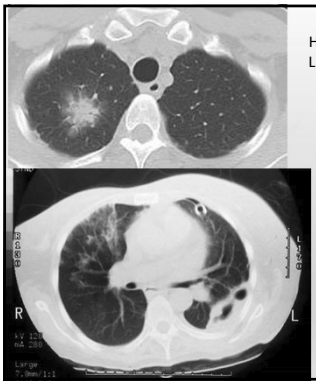
A. RHIZOPUS
B. FUSARIUM
C. ASPERGILLUS
D. SCEDOSPORIUM
E. CANDIDA



MUCORMYCOSIS

- Infection acquired by inhaling spores into lung or paranasal sinus
- Rhizopus, Rhizomucor, Mucor, Cunninghamella, Apophysomyces, Saksenaea
- Broad, flexible nonseptate hyphae right angle branching
- Rhinoorbital: poorly controlled DM2 or immunosuppression
- India: severe COVID + DM2+steroids
- Pulmonary: neutropenia, immunosuppression



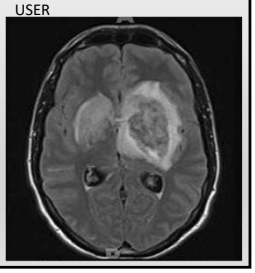


HALO SIGN IN A LEUKEMIC

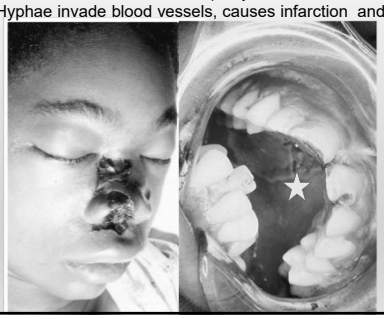
CAVITY AFTER PMN RETURN

MUCORMYCOSIS

BRAIN ABSCESS IN A HEROIN USER



Poorly controlled diabetes melitus, Prolonged neutropenia, corticosteroids
India: COVID-19+ corticosteroids+ poorly controlled diabetes mellitus
Hyphae invade blood vessels, causes infarction and necrosis.



-Rx. Ampho
Followup: Posaconazole o
Isavuconazole?

-Surgical debridement

-Control diabetes.

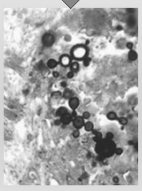
-Decrease immunosuppression.

PARACOCCIDIOIDOMYCOSIS:

- RURAL CENTRAL AND SOUTH AMERICA.

-MAY APPEAR DECADES AFTER LEAVING ENDEMIC AREA.

MULTIPLE BUDS

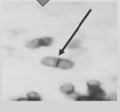


TALAROMYCOSIS (FORMERLY PENICILLIUM MARNEFFEI).

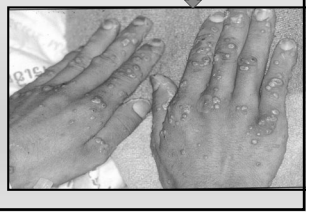
SOUTHEAST ASIA

MOSTLY AIDS

YEAST IN BIOPSY, MOLD IN CULTURE.
DIVIDES BY FISSION

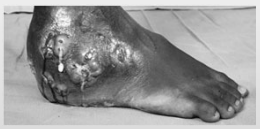


DISSEMINATED INFECTION WITH SKIN LESIONS.

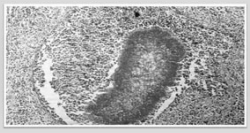


MYCETOMA (Madura foot)

MINOR TRAUMA TO FOOT OR HAND
FIRM SWELLING PROGRESSES OVER YEARS
DRAING SINUSES



GRAINS IN PUS
FUNGI OR HIGHER BACTERA



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***

THAT'S IT!

It' s all perfectly clear, isn't it?

25

Sexually Transmitted Infections: Other Diseases and Syndromes

Dr. Khalil Ghanem

25 – Sexually Transmitted Infections: Other Diseases and Syndromes

Speaker: Khalil Ghanem, MD

Sexually Transmitted Infections: Other Diseases and Syndromes

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Professor of Medicine
Division of Infectious Diseases
Johns Hopkins University School of Medicine

7/1/2024

- **Disclosures of Financial Relationships with Relevant Commercial Interests**

  - None

OF NOTE

- I have tried to use patient-first language throughout. When the terms 'women' and 'men' are used, I am referring to cis-gender women and men unless otherwise specified
- 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 (assume today is his last day of doxycycline)?

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 7 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
- Both D-K and LGV (L1-L3) cause proctitis/proctocolitis
- Longer duration of therapy (3 weeks of doxycycline) for L1-L3 serotypes **if symptomatic*****
- Association with reactive arthritis; 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 RCTs: Efficacy difference in favor of doxycycline of 20%

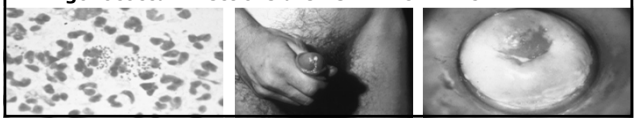
Dombrowski CID 2021; Lau NEJM 2021

GONORRHEA: TAKE-HOME POINTS

- IM ceftriaxone 500 mg is the preferred regimen for uncomplicated gonorrhea
- 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**



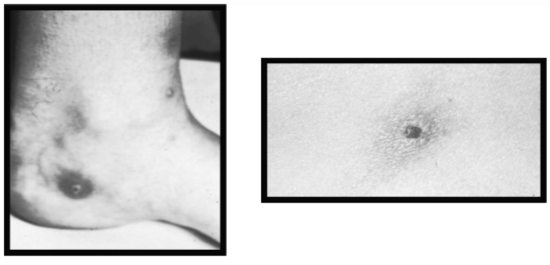
SCREENING FOR GONORRHEA

- 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) and with complement inhibitors (Eculizumab)**
- Differential diagnosis: meningococcemia, RMSF, dengue, staphylococcal endocarditis, Reiter's
- Treatment: Ceftriaxone IM/IV usually 5-7 days; longer with arthritis, meningitis, or endocarditis

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 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)
  - 7% of isolates in the US in 2021 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

St Cyr MMWR 2020

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 at the rectum but screening for only GC at 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; NEVER SCREEN!
- 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

- **DUAL antibiotic therapy is now recommended**
  - Start with one week of doxycycline 100 mg orally BID (will decrease bacterial load) followed by either:
    - Azithromycin 500mg orally X1 followed by 250 mg daily on the subsequent 3 days (if macrolide sensitivity is known) OR
    - Moxifloxacin 400mg POX 7 days (if macrolide resistant or if macrolide resistance is unknown)
  - Emerging resistance to fluoroquinolones (~15% moxifloxacin resistance)
- **NOT FOR THE BOARDS:** In persons with FQ failures you can use minocycline (100 mg PO BID X 14 d) or (if you can get it) Pristinamycin (or a clinical trial)

Int J STD AIDS. 2019;30(5):512-514
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 ceftriaxone and one week of oral doxycycline
- If the GC and CT tests are negative and the patient has persistent symptoms and signs:
  - 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 male partner is asymptomatic.

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	Male 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]
  - RCT: 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** 500 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+)
- (Monkeypox)

OTHER CAUSES

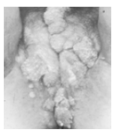
- Campylobacter
- Shigella
- Entamoeba
- CMV
- *Giardia lamblia** (mainly enteritis; especially among MSM)

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

25 – 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)

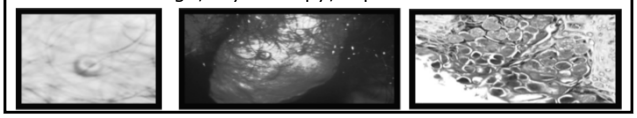
*FDA approved a supplemental biologics licensure application in 6/2020: prevention of oropharyngeal and other head and neck cancers caused by HPV types targeted by the vaccine

HPV VACCINES (CONT.)

- 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

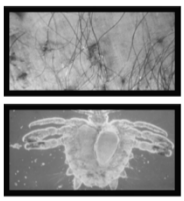
MOLLUSCUM CONTAGIOSUM

- Poxvirus
- 1 to 5mm lesions; painless papules; CENTRAL UMBILICATION
- Not necessarily sexually transmitted
- Molluscum bodies: intracytoplasmic inclusions
- Rx: curettage; cryotherapy; topical cidofovir

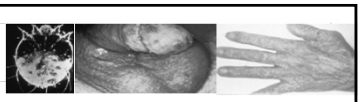


PEDICULOSIS PUBIS

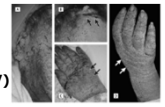
- Pediculosis pubis= pubic lice= crabs (*Pthirus pubis*)
  - Nits confined to upper shaft=old infection (no need for retreatment)
  - Maculae ceruleae (blue gray macules)
  - Permethrin 1% cream OR Pyrethrins with piperonyl butoxide (topical)
  - Resistance increasing; consider malathion 0.5% lotion 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***

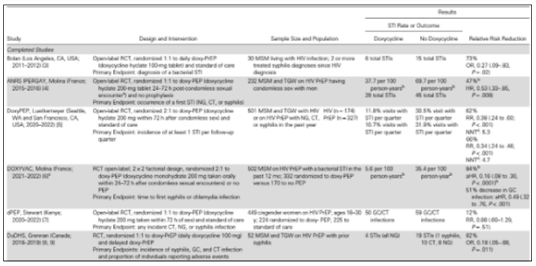


Arch Dermatol. 2007;143(5):626

PREVENTION: DOXY-PEP

- Doxycycline 200 mg within 72 hours of a sexual exposure in MSM and transgender women with >=1 STI in prior 12 months
  - Data in cis-gender women do not suggest benefit (additional studies are in progress)
  - Significant protection against syphilis and chlamydia; data on gonorrhea are less clear
  - In addition to known doxycycline toxicities, questions about emergence of antimicrobial resistance, impact on microbiome, and impact on syphilis management remain unanswered.

TRIALS ON DOXYCYCLINE AS PEP



Study	Design and Intervention	Sample Size and Population	Results: STI Rate or Outcome — Doxycycline	Results: STI Rate or Outcome — No Doxycycline	Relative Risk Reduction
Completed Studies					
Bolan (Los Angeles, CA, USA; 2011–2012) [3]	Open-label RCT, randomized 1:1 to daily doxy-PEP (doxycycline hyclate 100-mg tablet) and standard of care. Primary Endpoint: diagnosis of a bacterial STI	30 MSM living with HIV-infection; 2 or more treated syphilis diagnoses since HIV diagnosis	6 total STIs	16 total STIs	73%; OR, 0.27 (.09–.83; P = .02)
IPERGAY, Molina (France; 2015–2016) [4]	Open-label RCT, randomized 1:1 to doxy-PEP (doxycycline hyclate 200-mg tablet 24–72 h post-condomless sexual encounter[a]) and no prophylaxis. Primary Endpoint: occurrence of a first STI (NG, CT, or syphilis)	232 MSM and TGW on HIV PrEP having condomless sex with men	37.7 per 100 person-years[b]; 26 total STIs	69.7 per 100 person-years[b]; 45 total STIs	47%[c]; HR, 0.53 (.33–.85; P = .008)
DoxyPEP, Luetkemeyer (Seattle, WA and San Francisco, CA, USA; 2020–2022) [5]	Open-label RCT, randomized 2:1 to doxy-PEP (doxycycline hyclate 200 mg within 72 h after condomless sex) and standard of care. Primary Endpoint: incidence of at least 1 STI per follow-up quarter	501 MSM and TGW with HIV or on HIV-PrEP with NG, CT, or syphilis in the past year. HIV (n = 174); PrEP (n = 327)	11.8% visits with STI per quarter; 10.7% visits with STI per quarter	30.5% visit with STI per quarter; 31.9% visits with STI per quarter	62%; HR, 0.38 (.24 to .60; P < .001); NNT[d] 5.3; 66%; RR, 0.34 (.24 to .48; P < .001); NNT[d] 4.7
DOXYVAC, Molina (France; 2021–2022) [6][e]	RCT open-label, 2 × 2 factorial design, randomized 2:1 to doxy-PEP (doxycycline monohydrate 200 mg taken orally within 24–72 h after condomless sexual encounter) or no PEP. Primary Endpoint: time to first syphilis or chlamydia infection	502 MSM on HIV-PrEP with a bacterial STI in the past 12 mo; 332 randomized to doxy-PEP versus 170 to no PEP	5.6 per 100 person-years[b]	26.4 per 100 person-years[b]	MHR[f]; aHR, 0.16 (.09 to .30; P < .0001)[g]; 61% decrease in GC infection; aHR, 0.49 (.32 to .76; P < .001)
dPEP, Stewart (Kenya; 2020–2022) [7]	Open-label RCT, randomized 1:1 to doxy-PEP (doxycycline hyclate 200 mg taken within 72 h of next and standard of care. Primary Endpoint: any incident CT, NG, or syphilis infection	449 cisgender women on HIV-PrEP, ages 18–30 y; 224 randomized to doxy- PEP, 225 to standard of care	50 GC/CT infections	59 GC/CT infections	12%; RR, 0.88 (.60–1.29; P = .51)
DoDHIL Grennan (Canada; 2018–2019) [8, 9]	RCT, randomized 1:1 to doxy-PrEP (daily doxycycline 100 mg) and delayed doxy-PrEP. Primary Endpoints: incidence of syphilis, GC, and CT infection and proportion of individuals reporting adverse events	52 MSM and TGW on HIV PrEP with prior syphilis	4 STIs (all NG)	19 STIs (1 syphilis, 10 CT, 8 NG)	82%; OR, 0.18 (.05–.68; P = .011)

THE END

Thank you and good luck!

26

Nontuberculous Mycobacteria in Normal and Abnormal Hosts

Dr. Kevin Winthrop

26 – Nontuberculous Mycobacteria in Normal and Abnormal Hosts

Speaker: Kevin Winthrop, MD

Nontuberculous Mycobacteria in Normal and Abnormal Hosts

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7/1/2024

Disclosures of Financial Relationships with Relevant Commercial Interests

- **Research Grant---Insmed**
- **Consultant---Insmed, Spero, Paratek, AN2**

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, M. chimaera*
- 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
  - 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

PREVIEW QUESTION

72 year old female with chronic cough, normal CXR, and 1/3 sputums grow MAC. Which one of the following do you 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)

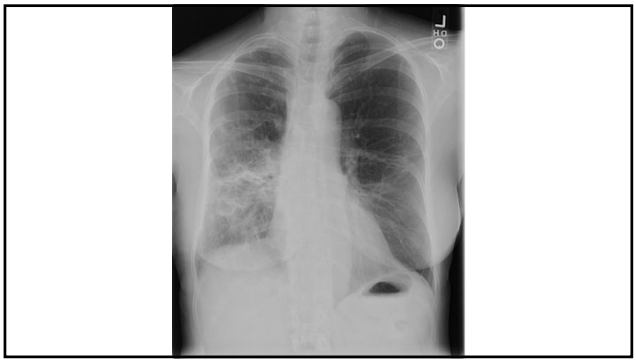
Two Types of MAC Pulmonary Diseases

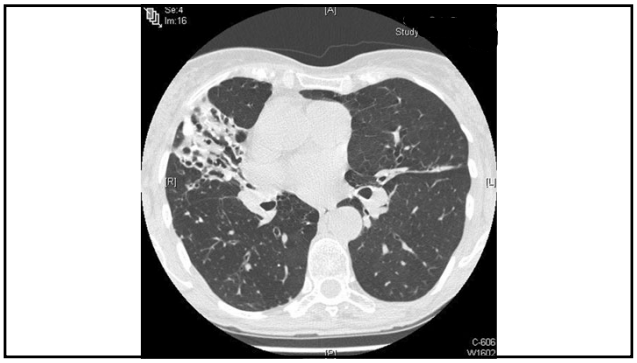
- Older male, smoker, COPD
  - Apical cavitary or fibronodular disease
  - More rapidly progressive
- Older female ("Lady-Windermere")
  - Scoliosis, thin, pectus deformities*, hypomastia
  - Nodular and interstitial nodular infiltrate
  - Bronchiectasis right middle lobe / lingula
  - Bronchiolitis ("tree and bud") on HRCT
  - Slowly progressive

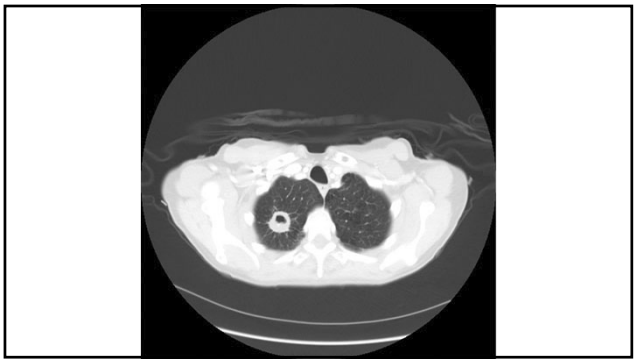
***Iseman MD et al. *Am Rev Respir Dis.* 1991**

26 – Nontuberculous Mycobacteria in Normal and Abnormal Hosts

Speaker: Kevin Winthrop, MD







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.
    - FQ or Macrolide useful in RIF resistant disease

Pulmonary M. abscessus ssp. Therapy

- *M. boletti, M. massiliense M. abscessus*
  - Inducible macrolide resistance--erm (41) gene
- "Cure" = rare
- Can be 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
  - Omadacycline 100mg QD, 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), Azithromycin 250mg QD (if suscep), Omadacycline 300mg QD
  - Surgical resection

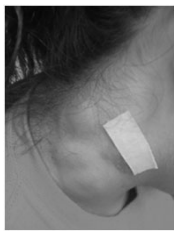
Extrapulmonary NTM

- 1. Immunocompetent settings
- 2. Immunocompromised settings

Immunocompetent settings

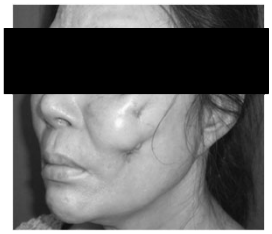
- Nail salon, trauma, surgical or injection procedures, fishtank, hot tubs
- Rapid or slow growing NTM
- Incubation period
  - Infection usually occurs 2-8 weeks after contact with contaminated water source

Children under 5 years NTM > TB



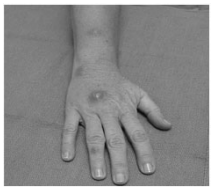
- Usually MAC
  - Males > females, age 1-2 years old
- Surgical resection alone is best therapy
- Adjunctive ABX rarely needed

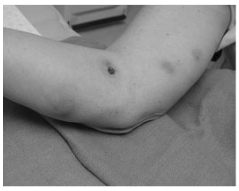
Post- plastic surgery



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

M. marinum---fish tank granuloma



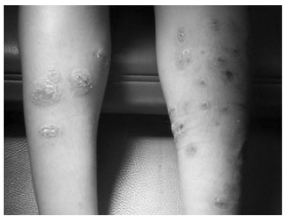


Treatment: multiple drugs

- 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

PREVIEW QUESTION

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

PREVIEW QUESTION

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?
  - Rifabutin dose adjustment with PI
  - Immune reconstitution inflammatory syndrome (IRIS)

Griffith D et al. AJRCCM 2007

TABLE 7. REGIMENS FOR TREATMENT AND PREVENTION OF DISSEMINATED *MYCOBACTERIUM AVIUM* IN HIV-INFECTED PATIENTS

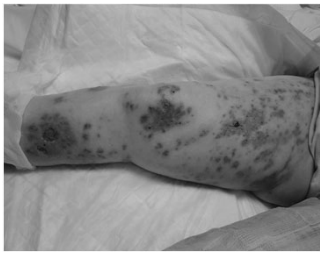
Preferred (A, I)*	Alternative (B, I)*
Treatment	
Clarithromycin 500 mg orally twice daily + Ethambutol 15 mg/kg orally daily ± Rifabutin† 300 mg orally daily	Azithromycin 500 mg daily + Ethambutol 15 mg/kg daily + Rifabutin† 300–450 mg orally daily
Prevention‡	
Azithromycin 1,200 mg orally weekly	Clarithromycin 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

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

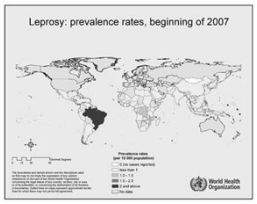
Length of treatment for disseminated infection
3 drugs (including 1 IV) X 4-6 months
Depends on immunosuppression reversal

M. chimaera

- Slow growing. M. avium complex
  - Pulmonary disease
- Extrapulmonary disease
  - 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: forever?

Hansen's Disease (Leprosy)

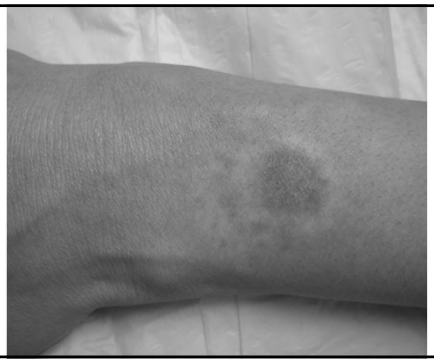
- Rare in US (100-200 cases per year)
  - Armadillos and gulf region
  - Rest imported
- Most humans resistant
  - Household contacts at risk (low risk)
  - Nasopharyngeal transmission?
- *M. leprae* does not grow in culture

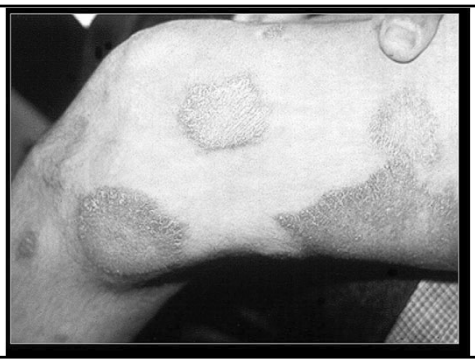


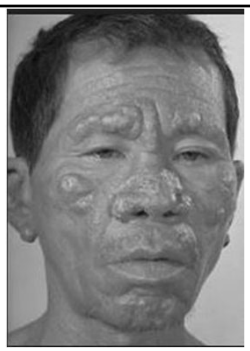
Leprosy Disease Classification

- 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 (6-12 months)
  - Dapsone 100mg daily
  - Clofazimine 50mg daily
  - *Rifampin 600mg once monthly
  - (US guidelines are daily RIF and no Clofaz for 12 months)
- MB (12-24 months)
  - Dapsone 100mg daily
  - Clofazimine 50mg daily
  - Rifampin 600mg daily

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

BR3

Board Review Session 3

Drs. Auwaerter (Moderator), Bell, Bennett, Dhanireddy, Dorman, Ghanem, Klompas, and Winthrop

Board Review: Day 3

Moderator: Paul Auwaerter, MD
Faculty: Drs. Bell, Bennett, Dhanireddy, Dorman, Ghanem, Klompas, and Winthrop

7/1/2024

BOARD REVIEW DAY 3 2024

#27 **A 55-year-old man presents for outpatient evaluation of subjective fevers and recurrent pruritic skin eruption.**

He is currently asymptomatic.

He notes that over the last 6 months he has had >5 episodes of hives that resolve with Benadryl.

He has felt hot during these episodes but has not taken his temperature.

1 of 4

BOARD REVIEW DAY 3 2024

#27 **There are no additional symptoms, and he is not aware of any precipitating factors.**

The patient owns a tree nursery and is frequently outdoors. He lives in Kentucky and denies travel.

He recalls multiple tick bites over the last year prompting his PCP to send tick serologies. *Rickettsia rickettsii* antibodies are negative.

An IFA for *Ehrlichia chaffeensis* is elevated at 1:256.

2 of 4

BOARD REVIEW DAY 3 2024

#27 **What is the most appropriate next step in management for this patient?**

A) Doxycycline

B) Convalescent *Ehrlichia* serologies

C) Prednisone dose pack

D) Dietary modification

E) Stool O&P

3 of 4

BOARD REVIEW DAY 3 2024

#28 **You've been charged with leading a program to decrease ventilator-associated pneumonia (VAP) rates in the medical intensive care unit.**

You gather a multidisciplinary team with nurses, doctors, respiratory therapists, pharmacists, physical therapists, and the unit clerk.

1 of 3

BOARD REVIEW DAY 3 2024

#28 **Which of the following initiatives is most likely to lower VAP rates and improve outcomes for patients on mechanical ventilation?**

A) Begin bathing patients twice daily with povidone iodine

B) Provide oral care with 0.12% chlorhexidine solution twice daily

C) Switch to using silver coated endotracheal tubes for all patients

D) Introduce a protocol to minimize sedation and increase patient mobility

E) Put patients in the Trendelenburg position in order to encourage drainage of respiratory secretions away from the lungs

2 of 3

BOARD REVIEW DAY 3 INFECTIOUS DISEASE BOARD REVIEW 2024

#29 **A 50-year-old-woman with psoriatic arthritis presented with two weeks of cough, dyspnea, fever, and malaise.**

She had been treated with prednisone and methotrexate for several years.

She was started on infliximab about 10 months prior to this illness.

1 of 6

BOARD REVIEW DAY 3 INFECTIOUS DISEASE BOARD REVIEW 2024

#29 **On physical exam, she appeared short of breath.**

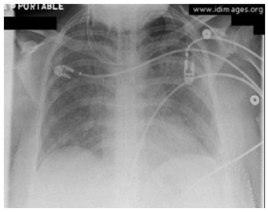
Her respiratory rate was 32 and her oxygen saturation was 96% on 100% FiO_2 supplemental 0_2.

Her lungs had coarse rales bilaterally, decreased breath sounds at bases.

2 of 6

BOARD REVIEW DAY 3 INFECTIOUS DISEASE BOARD REVIEW 2024

#29 **Her CXR showed bilateral pulmonary infiltrates, and she underwent lung biopsy.**

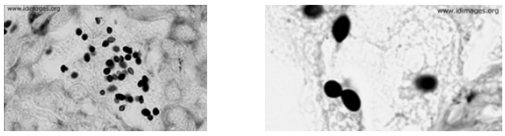


3 of 6

BOARD REVIEW DAY 3 INFECTIOUS DISEASE BOARD REVIEW 2024

#29 **Lung Biopsy**

Silver stain: organisms 2-5 microns in size, narrow based budding



4 of 6

BOARD REVIEW DAY 3 INFECTIOUS DISEASE BOARD REVIEW 2024

#29 **Which one of the following is the most likely diagnosis?**

A) Histoplasmosis

B) Pneumocystis pneumonia

C) Coccidioidomycosis

D) Cryptococcosis

E) Blastomycosis

5 of 6

BOARD REVIEW DAY 3 INFECTIOUS DISEASE BOARD REVIEW 2024

#30 **A primary care physician asks you about TB testing for one of her patients.**

Her patient is a 30-year-old accountant in a midwestern United States city who has never traveled outside the United States.

The accountant is in excellent health, takes no medications, and has no known exposures to tuberculosis.

The accountant has never been tested for latent TB.

1 of 3

BOARD REVIEW DAY 3 INFECTIOUS DISEASE BOARD REVIEW 2024

#30 **What would you advise regarding testing this patient for latent tuberculosis?**

A) PPD skin test

B) Interferon gamma release test (IGRA)

C) IGRA: if negative, follow up with a PPD

D) No testing

2 of 3

BOARD REVIEW DAY 3 INFECTIOUS DISEASE BOARD REVIEW 2024

#31 **A 62-year-old woman with no medical issues, normal BMI, who is vegetarian and does regular yoga asks if she should get the RSV vaccine.**

1 of 3

BOARD REVIEW DAY 3 INFECTIOUS DISEASE BOARD REVIEW 2024

#31 **What do you tell her about this vaccine?**

A) Given that it is approved for her age cohort, she should get it if she wants it

B) Those most likely to benefit from this vaccine include those with comorbidities or who are over the age of 75 years; given that she does not have any of those risk factors, she may wish to consider waiting

C) Her brother's history puts her at higher risk for Guillain-Barre syndrome after vaccination

D) It is a relatively new vaccine, and you are not recommending it for anyone

2 of 3

BOARD REVIEW DAY 3 INFECTIOUS DISEASE BOARD REVIEW 2024

#32 **A 24-year-old transgender woman presents for evaluation of rectal discharge.**

She has engaged in unprotected receptive anal intercourse on several occasions over the last few months.

She takes cabotegravir injections every 2 months for prevention of HIV, as well as citalopram for generalized anxiety.

1 of 4

BOARD REVIEW DAY 3 INFECTIOUS DISEASE BOARD REVIEW 2024

#32 **She has no known medication allergies.**

A rectal swab for nucleic acid amplification testing (NAAT), is positive for *Neisseria gonorrhea* and negative for *Chlamydia trachomatis*.

2 of 4

BOARD REVIEW DAY 3 INFECTIOUS DISEASE BOARD REVIEW 2024

#32 **Which of the following describes the recommended management of this patient, according to the Centers for Disease Control and prevention (CDC) guidelines?**

A) Doxycycline 100 mg by mouth twice daily for 10 days

B) Cefixime 500 mg po single dose

C) Ceftriaxone 500 mg single dose via intramuscular injection

D) Ceftriaxone 500 mg single dose via intramuscular injection, plus azithromycin 2 grams orally in a single dose

E) Azithromycin 2 grams orally in a single dose

3 of 4

BOARD REVIEW DAY 3 INFECTIOUS DISEASE BOARD REVIEW 2024

#33 **A distraught nurse pages you to report that she just got splashed in the eye while irrigating a deep sacral wound in a patient with hepatitis C.**

There was visible blood in the wound.

The patient's hepatitis C viral load is over 3 million copies/ml.

The nurse advises you that she is pregnant.

1 of 3

BOARD REVIEW DAY 3 INFECTIOUS DISEASE BOARD REVIEW 2024

#33 **How will you advise this nurse?**

A) Start post-exposure prophylaxis with sofosbuvir-velpatasvir now

B) Start post-exposure prophylaxis with sofosbuvir-velpatasvir as soon as the nurse delivers her baby

C) Get a hepatitis C viral load now. If negative, nothing more needs to be done

D) Get an HCV antibody test now, in 3-6 weeks, and in 4-6 months. If negative, nothing more needs to be done

E) Get an HCV antibody test now, a hepatitis C viral load in 3-6 weeks, and an antibody test again in 4-6 months. If negative, nothing more needs to be done

2 of 3

BOARD REVIEW DAY 3 INFECTIOUS DISEASE BOARD REVIEW 2024

#34 **A 56-year-old white male with cavitary pulmonary disease due to *Mycobacterium abscessus* is transferred to your care. He is thought to be failing therapy.**

He is currently being treated with azithromycin, clofazimine, and moxifloxacin.

He started this regimen 6 weeks ago with intravenous amikacin but had sudden onset of tinnitus and the amikacin was stopped a month ago.

1 of 4

BOARD REVIEW DAY 3 INFECTIOUS DISEASE BOARD REVIEW 2024

#34 **His antibiotic susceptibility testing reports "susceptibility" to each of the medications within the current regimen except the moxifloxacin which has an MIC of 4.0.**

Tigecycline and linezolid were tested as possible additional agents for this patient and were found to be in "susceptible" range.

2 of 4

BOARD REVIEW DAY 3 INFECTIOUS DISEASE BOARD REVIEW 2024

#34 **Which of the drugs being tested may fail because of induced resistance in an isolate that appears susceptible on routine testing?**

A) Clofazimine

B) Tigecycline

C) Moxifloxacin

D) Azithromycin

E) Linezolid

3 of 4

BOARD REVIEW DAY 3 INFECTIOUS DISEASE BOARD REVIEW 2024

#35 **In July, an 18-year-old girl in rural northern Louisiana presented with a 5 cm diameter fiery red, round, well-demarcated macular lesion on the back of her left knee.**

The lesion had been present for at least 2 days, accompanied by moderate headache and malaise but not fever. The lesion was not painful or pruritic.

1 of 4

BOARD REVIEW DAY 3 INFECTIOUS DISEASE BOARD REVIEW 2024

#35 She had removed a tick from the area of the lesion.

No inguinal adenopathy was palpable.

Routine laboratory work was normal.

2 of 4

BOARD REVIEW DAY 3 INFECTIOUS DISEASE BOARD REVIEW 2024

#35 Which tick would be the most likely vector for this illness?

A) *Dermacentor andersoni*

B) *Ixodes pacificus*

C) *Amblyomma americanum*

D) *Ixodes scapularis*

E) *Ornithodoros parkeri*

3 of 4

BOARD REVIEW DAY 3 INFECTIOUS DISEASE BOARD REVIEW 2024

#36 A 59-year-old male is being treated for MSSA sternal osteomyelitis after undergoing coronary artery bypass grafting.

He has been home receiving outpatient parenteral antimicrobial therapy (OPAT) with IV oxacillin.

Two weeks after discharge, fever develops.

1 of 4

BOARD REVIEW DAY 3 INFECTIOUS DISEASE BOARD REVIEW 2024

#36 On OPAT laboratory surveillance, the following results are noted:

WBC: 18.4
neutrophils: 32%
eosinophils: 18%
HCT: 31.3
PLT: 512
BUN: 24
Creatinine: 1.4 (baseline 1.1)
AST: 380
ALT: 475
Alk Phos: 166
Bili: 1.0

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

2 of 4

BOARD REVIEW DAY 3 INFECTIOUS DISEASE BOARD REVIEW 2024

#36 What is the best management option?

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

B) Start cefazolin and IV diphenhydramine; continue outpatient monitoring

C) Start vancomycin; hospitalize and consider corticosteroid therapy

D) Test dose cefazolin; if tolerated start IV cefazolin

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

3 of 4

BOARD REVIEW DAY 3 INFECTIOUS DISEASE BOARD REVIEW 2024

#37 A patient with HIV Infection on dolutegravir, emtricitabine, tenofovir alafenamide was recently found to have converted his PPD to positive and was placed on daily isoniazid plus pyridoxine since he thought he could remember a daily regimen and did not want to take rifampin or rifapentine due to fear of drug interactions with psychotropic medications he was taking.

1 of 4

BOARD REVIEW DAY 3 INFECTIOUS DISEASE BOARD REVIEW 2024

#37 **He has no comorbidities or concurrent medical issues.**

His evaluation for active TB was negative.

He comes back after two months and admits that he never takes his pyridoxine.

2 of 4

BOARD REVIEW DAY 3 INFECTIOUS DISEASE BOARD REVIEW 2024

#37 **What toxicity is most likely to occur if he fails to take pyridoxine?**

A) Encephalopathy

B) Peripheral neuropathy

C) Hepatitis

D) Dermatitis

E) Microcytic anemia

3 of 4

BOARD REVIEW DAY 3 INFECTIOUS DISEASE BOARD REVIEW 2024

#38 **An 18-year-old woman is considering the desirability of getting HPV vaccine.**

She asks about the advantages of 9 valent HPV vaccine for her and her male sexual partners.

Among the information you might consider telling her is that vaccine has a high rate of protection against acquiring cervical HPV, cervical dysplasia, and likely developing cervical cancer.

1 of 3

BOARD REVIEW DAY 3 INFECTIOUS DISEASE BOARD REVIEW 2024

#38 **Which of the following limitations of the 9 valent vaccine is correct?**

A) Will not prevent her developing HPV associated anogenital warts

B) Will not prevent transmitting infection to her male sexual partner

C) Will not prevent her from developing HPV associated oropharyngeal cancer

D) Will only prevent HPV infection for 2-5 years

E) Will not eradicate an existing infection

2 of 3

BOARD REVIEW DAY 3 INFECTIOUS DISEASE BOARD REVIEW 2024

#39 **A medical products vendor approaches you as the head of your hospital's infection control committee to share data with you on a promising new endotracheal tube design.**

The vendor describes a randomized controlled trial in which they were able to demonstrate that the new endotracheal tube was associated with a 32% decrease in ventilator-associated pneumonia (VAP) rates. You're intrigued but want to know more.

1 of 3

BOARD REVIEW DAY 3 INFECTIOUS DISEASE BOARD REVIEW 2024

#39 **Which of the following questions is most likely to help you better understand the potential benefits of this new technology and whether you ought to advocate for its adoption in your hospital?**

A) What country was the study performed in?

B) What was the impact of the intervention on duration of mechanical ventilation?

C) What kind of ICU was the study performed in?

D) How large was the study population?

E) Did the study include post-operative patients?

2 of 3

27

Ticks, Mites, Lice, and the Diseases They Transmit

Dr. Paul Auwaerter

27 – 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

7/1/2024

- **Disclosures of Financial Relationships with Relevant Commercial Interests**
  - **Consultant: Gilead, Shionogi**
  - **Research Grant: Pfizer**
  - **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
Tick vectors
- Ticks cause 95% of vector borne disease in the US
- Co-infections in some patients

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.

27 – Ticks, Mites, Lice and The Diseases They Transmit

Speaker: Paul Auwaerter, MD

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 burnetti
- Tularemia
  - (< 10% tickborne)
- Other Borrelia
  - B. miyamotoi
  - B. mayonii

Ticks: arachnids, not insects

- **Number of species**
  - **>900 species or subspecies world wide**
    - **90 species in North America, handful cause most human infections**
- **Hematophagous arthropods**
  - **parasitize every class vertebrates ≅ entire world**
- **Two major families**
  - **Ixodidae, >700 species (hard ticks, attach & engorge)**
  - **Argasidae, >190 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
Eisen, Ticks Tick Borne Dis 2022;12(6):102025

Top Ticks in North American That Transmit Human Pathogens (Ixodidae)

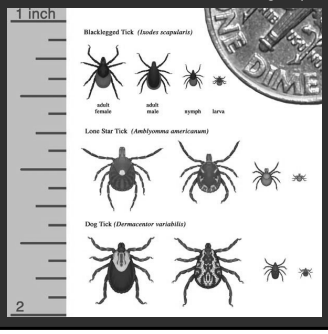
#1 Ixodes scapularis

#2 Amblyomma americanum

#3 Dermacentor variabilis

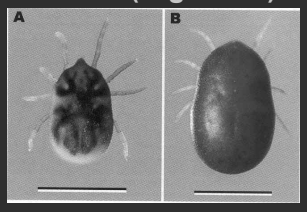
#4 Ixodes pacificus (Western black-legged tick)

#5 Dermacentor andersoni (Rocky Mt wood tick)



Eisen, Ticks Tick Borne Dis 2022;12(6):102025

Ornithodoros Hermsi nymphal Tick Soft tick (Argasidae)



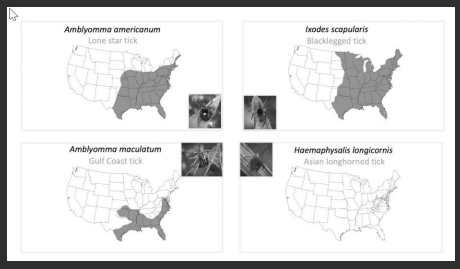
A: shows the nymph before its infective blood meal (from California)

B: shows it after feeding

These are soft ticks that feed briefly at multiple spots—DO NOT remain attached

Scale bars = 2 mm

Expanding Range and Ticks New to the US



I. scapularis
-Ticks that carry B. burgdorferi and bite humans mostly northern tick populations

H. longicornis
May carry multiple pathogens, participation in transmitting to Humans occurs but uncertain to what degree

Molaei, JID 2022;226(3):370-373

Selected Tickborne Diseases in the US

Home | Data Summary | Cases by Year | Cases by Month

Tickborne Disease Surveillance Data Summary

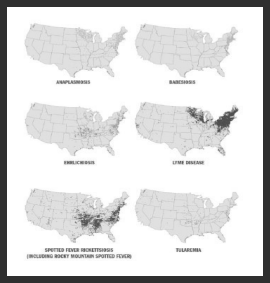
Total Reported Cases by Tickborne Disease, 2019-2022

Disease	2019	2020	2021	2022
Lyme disease	34,945	18,010	24,611	62,551
Anaplasmosis	5,655	3,639	6,744	5,633
Spotted fever rickettsioses	5,207	1,175	1,278	1,271
Ehrlichia chaffeensis ehrlichiosis	2,093	1,180	1,347	1,557
Babesiosis	2,418	1,827	1,915	
Tularemia	274	150	162	167
Undetermined ehrlichiosis/anaplasmosis	185	50	77	95
Powassan virus disease	43	21	24	47
Ehrlichia ewingii ehrlichiosis	43	21	19	25
Total	**50,863**	**26,073**	**36,177**	**71,346**

← New 2022 CDC Surveillance Definition for Lyme disease

CDC, https://www.cdc.gov/ticks/data-research/facts-stats/tickborne-disease-surveillance-data-summary.html#:~:text=During%202019%202022%2C%20state%20and,to%20CDC%20over%20the%20years. (accessed 6/22/24)

New regions for Common Tickborne Infections



Range expanding for
- Lyme disease
  - Upper Midwest
  - South along Appalachians
- Babesiosis
  - Expanding w/i Lyme disease range
- Ehrlichioses
  - E. chaffeensis, northward

CDC, https://www.cdc.gov/ticks/tickbornediseases/overview.html
Accessed 1/16/23

Question #1: PREVIEW QUESTION

62M living in an exurb of Phoenix, Arizona presents in early September with a three day history of fever, myalgia, headache and rash.

He works as a lineman for a utility company. He lives with his family in an older adobe home with dogs. There is a faint maculopapular rash on extremities

Which of the following is the most likely diagnosis?

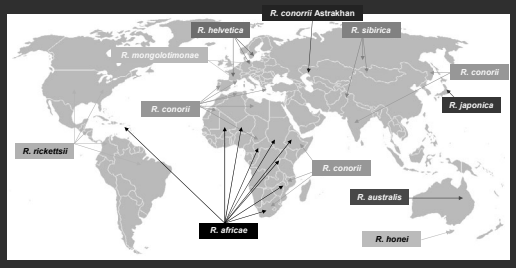
A. Human Monocytic Ehrlichiosis (HME)
B. Human Granulocytic Anaplasmosis (HGA)
C. Babesiosis
D. Rocky Mountain Spotted Fever (RMSF)
E. Tularemia

Rickettsial species: two major groups (not a comprehensive rickettsial 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

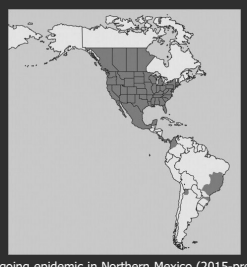
Tick-borne Rickettsia World Wide: many species



- 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



See in all lower 48 states

Mexico

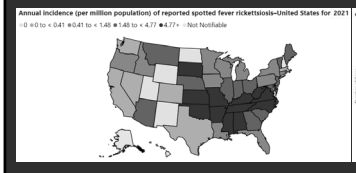
Parts of Canada

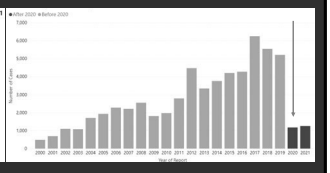
Central and South America

Ongoing epidemic in Northern Mexico (2015-present)

Alavarez-Hernandez, Lancet ID 2017;17(6):e189-196
Tinoco-Gracia, EID 2018;24(9):1723-25

CDC Changes:
--2010: RMSF to "spotted fever rickettsioses" 2010 due to lack of serologic specificity includes RMSF, *R. parkeri*, Pacific Coast tick fever, Rickettsialpox, and others
--2020: SFG criteria changes w/ IFA titer raise to ≥ 1:128 from 1:64 to raise specificity, elimination of IFA IgM ELISA





Source: CDC https://www.cdc.gov/rocky-mountain-spotted-fever/data-research/facts-stats/index.html (accessed 6/22/24)

SFR in the United States

Incidence/Case Fatality 1920-2019

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

https://www.cdc.gov/rocky-mountain-spotted-fever/data-research/facts-stats/index.html (accessed 6/22/24)

Am J Trop Med Hyg 2012;86:713-9

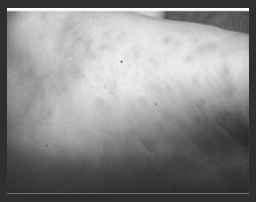
Rocky Mountain Spotted Fever Signs and Symptoms

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%

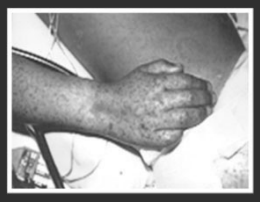
Adapted from Helnick CG et al. *J Infect Dis* 150:480, 1984

Rocky Mountain Spotted Fever

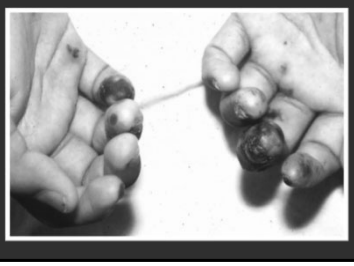
Early: rash absent or maculopapular
Starts on extremities



Later rash: petechial



Fulminant RMSF Gangrenous features (usually seen with multi-organ Failure)



RMSF diagnosis and treatment

- Start treatment upon suspicion: DON'T WAIT
  - Mortality 4% if doxycycline w/i 5d of symptom onset; 35% if > 5d.
- 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)

Jay R. J Vector Borne Dis 2020;57(2):114-120

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

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.
      - IgG is best to confirm
        - IgM with low specificity
- DON'T USE AS FEVER SCREENING TEST
- False positives (especially IgM) common
  - Georgia blood donor study 11.1% IgG > 1:64, but only 28% fit case definition for SFGRb[Strally 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

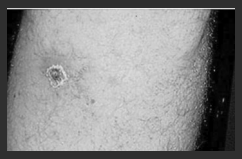
Question #2: PREVIEW QUESTION

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

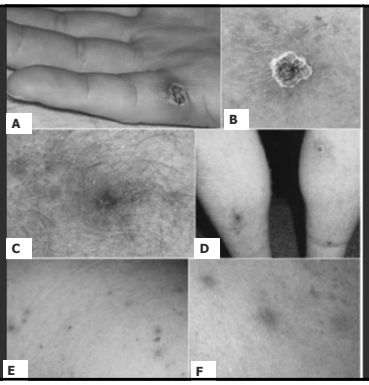


"American Boutonneuse Fever" Rickettsia parkeri

- Transmission: Lone Star or Gulf Coast ticks (*A. maculatum*)
  - Southeastern US, Gulf Coast
- AKA "Maculatum fever"
  - Also seen in Central and South America including Argentina, Uruguay, parts of Brazil
- Symptoms 2-10d post-bite
  - 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
Scott, Trends in Micro 2022;30(5):511-512

Examples of R. parkeri-associated rashes



Source: CDC

Green: Lone star tick range; Yellow: A. maculatum tick found; Red dots: R. parkeri
Note: Overlap of Lone star and Gulf coast tick range (Cohen SB. Emerg Infect Dis 2009; 15(9)

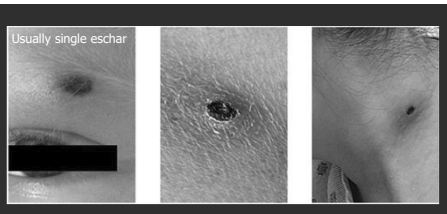
Pacific Coast Tick Fever

Rickettsia philippii (Rickettsia 364D)
Described in 2008

Transmitted by Pacific Coast tick (*Dermacentor occidentalis*)

Northern Baja → Southern Oregon, Most cases

Common symptoms:
Eschar
Fever
Headache
Usually mild infection



Dermacentor occidentalis

Pladgett K
PLOS Neg Trop Dis 2016

Question #3

22M upstate NY July c/o HA and fever x 3d now confused. No known tick bite but an outdoorsman. Exam without meningism or rash. Labs normal.

Admitted, doxycycline, CTX, vancomycin started. Head CT: normal

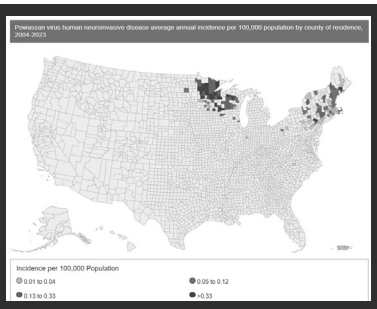
LP: WBC 130 60%P, 40%L, glucose: nl, protein 65 mg/dL (elevated).

Which of the following is the most likely etiologic agent?

A. Anaplasma phagocytophilum
B. Ehrlichia chaffeensis
C. Heartland virus
D. Powassan virus
E. Borrelia miyamotoi

POWV:
>Report cases mostly neuroinvasive
>Tick-borne flavivirus infection

- Mostly present in Spring-Summer
  - But can be year round
  - Related to nymphal *Ixodes scapularis*
- All ages, median 62 years, 72% male
- Clinical Syndromes
  - Neuroinvasive (90%)
    - Encephalitis (72%)
    - Meningitis (16%)
    - Other neurologic (2%)
  - Non-Neuroinvasive (10%)
- Hospitalized (90%)
- Death (11%, most > 50 years)



Krow-Lucal ER. Vect Borne Zoo Dis 2018; 18(6):286-290
https://www.cdc.gov/powassan/data-maps/historic-data.html (accessed 6/22/24)

Powassan virus Diagnosis & Care

- Antibody testing best sensitivity
  - CT or MRI may be normal; severe cases often with cerebellar changes (70%)
  - CSF: IgM POWV
    - Commercial, State Public Health labs & CDC
    - Needs confirmation by plaque-reduction neutralizing test to r/o cross-reactivity with other flaviviruses
- Other:
  - Viral RNA serum, CSF, tissue
    - Performs best early in illness
  - Immunohistochemistry, fixed tissue
- Treatment: supportive care
- Prognosis: mortality ~ 10%, neurologic sequelae 50%

Piantadosi A. Inf Dis Clin N Am 2022;36(3):671-688

Question 4

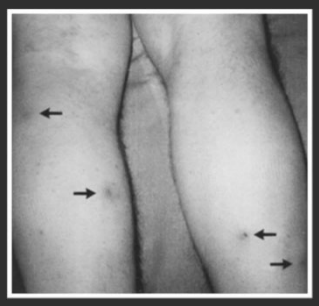
28F presents 8d after from a safari in Tanzania

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)

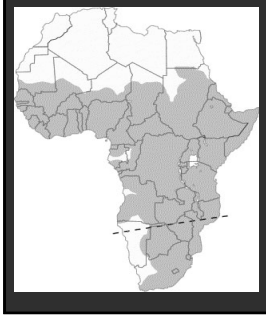


Question #4 Continued:

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. 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: 280 travelers (1996-2008)
- Spotted fever group (83.5%)
  - 87.5% acquired in sub-Saharan Africa

Others
- Scrub typhus (5.7%)
- Q fever (3.6%)
- Typhus group (2.5%)
- Human granulocytic ehrlichiosis (0.4%)

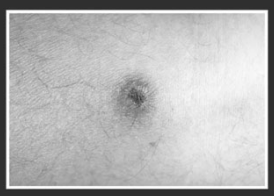
Jensenius M, EID 2009;15(11)

Question #5:

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 #5:

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

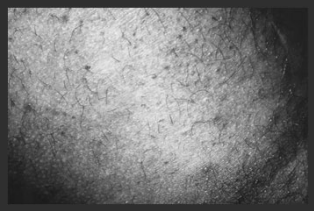
Rickettsialpox

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
  mpox
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

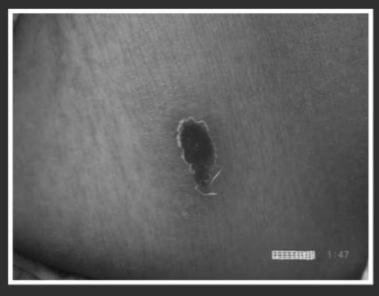
Scrub Typhus

Organism
- O. tsutsugamushi (> 70 strains)

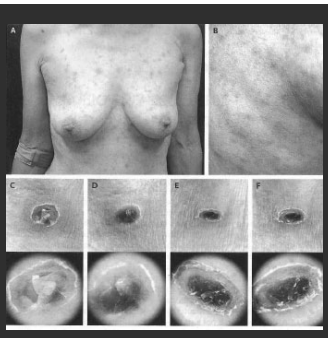
Vector
- Trombiculid mite (chiggers)

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%

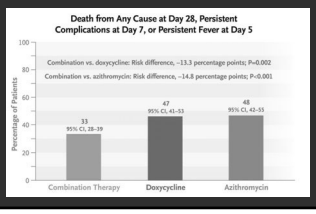


Eschar is often associated with regional lymphadenitis



Scrub Typhus Treatment

Treatment
- Doxycycline x 7 days, relapses common
  - Alt: azithromycin (AAC 2014;58:1488-93)
- Combination: appears superior, and safe
  - Doxycycline 200 mg twice daily day 1, then 100 mg twice daily x 6d PLUS Azithromycin 500 mg PO twice daily d1, then 500 mg daily x 6d [Varghese, NEJM 2022]



Question #6:

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.

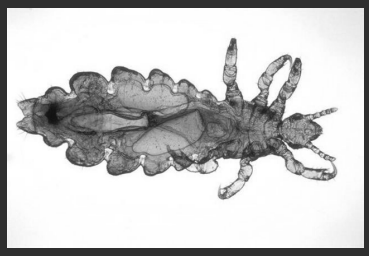
Exam is notable only for fever (39.6^0; no rash), tachycardia (P110)

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 you read a question with a "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) in N America, so not "epidemic" but sporadic
Most with flying squirrel exposure (Glaucomys volans)



Body louse: infestation = pediculosis
Pediculus humanus humanus

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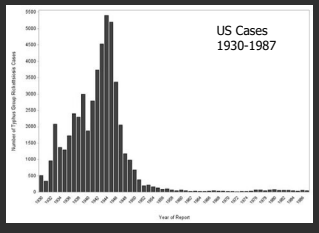
Typhus: Two Forms

	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	Usually milder, some fatalities
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
- Agent: *Rickettsia typhi*
- Infected cat/rat flea feces → skin
- Most don't recall fleabite
- Usually non-specific febrile infection
  - Underdiagnosed
  - ~50% with rash
  - Occasional severe disease:
    - Meningoencephalitis
    - Pneumonitis
    - Shock

Historically, decline w/ better sanitation
No longer reportable since 1987



Dittrich, Lancet Global Health 2015;3:e104; Blanton Am J Trop Med 2017;96(1):53 CDC, accessed 7/6/2023 https://www.cdc.gov/typhus/murine/history.html

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CDC Centers for Disease Control and Prevention
CDC 24/7: Saving Lives, Protecting People™
Search

Morbidity and Mortality Weekly Report (*MMWR*)

Fleaborne Typhus–Associated Deaths — Los Angeles County, California, 2022

Weekly / August 4, 2023 / 72(31);838–843

Incidence:
2010: 1
2022: 171
Deaths 3 (autopsies)
-HLH
-Myocarditis
-Septic shock
>late or no doxycycline

Case fatality usually < 1.0%
LA Series: 1.8%

Suspect: exposure to rodents, cats
Homeless

→Doxycycline

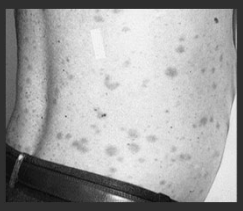
Murine (or endemic) typhus

- Consider especially febrile illness: CA, TX, Gulf coast
- 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

Flea-borne typhus (*R. felis*)



- Found globally; underdiagnosed
- Discovered 1990
  - Cat fleas
- Often lumped in with murine typhus
- Usually mild illness but can be severe
  - Fever, headache
  - Rash variable (macular)
  - Eschar in 12%
- Dx:
  - RMSF serology is often reactive
    - Acute/convalescent R. typhi serology
  - PCR (tissue)
- Treatment: doxycycline

Martinez MAC, Resp Rep Trop Med 2021;12:1-15

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 #7:

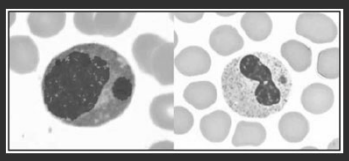
- 43F visited southern Missouri on vacation, returns 7d later with fever, headache and diffuse myalgia x 3d
- Physical examination: no findings
- Laboratory evaluation :
  - WBC: 2.1/mm³ (80% PMNs, 10% lymphocytes, 8% monocytes
  - Hemoglobin: 7.0 g/dL, hematocrit: 24%
  - Platelets: 105,000/mm³
  - AST: 364 U/L, ALT: 289 U/L
  - renal function: normal

Question #7

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

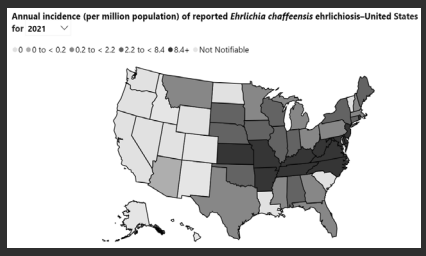
Morulae



HME HGA

Human Monocytic Ehrlichiosis (HME)

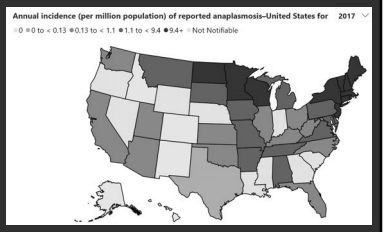
- E. chaffeensis
- Vector: Lone star tick
- Rash: ~30%
  - Maculopapular or petechial
- Labs: LFTs ↑, leukopenia, thrombocytopenia
- Mortality 2.7%
- Diagnosis
  - PCR
  - Morulae (2-38%)
  - Serology: acute/convalescent
  - Treatment: doxycycline



Source: CDC https://www.cdc.gov/ehrlichiosis/data-research/facts-stats/index.html (accessed 6/22/24)

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 most Southern state representation

Source: CDC https://www.cdc.gov/anaplasmosis/hcp/statistics/index.html (accessed 6/22/24)

Other Ehrlichia (less common)

Organism	Vector	Geography	Risk	Mortality
E. ewingii (aka 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 [EML] agent)	Deer tick	Wisconsin, Minnesota	Elderly, immune compromised	Low

Question #8:

- 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 #8:

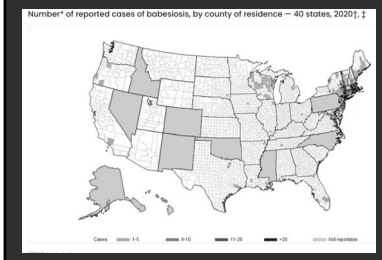
- The best recommended next step:

A. Check Babesia duncani 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

Babesia in the US



- Not reportable in all states
- Occurs within Lyme disease Geography
- Vector: *Ixodes scapularis*
- 1500-2500 cases/ yr

https://www.cdc.gov/babesiosis/maps-graphs (accessed 6/23/24)

Babesia species

- Malaria-like parasite, resides in RBCs
- Geography: Babesia microti (most cases in U.S.)
  - Nantucket, Martha's Vineyard, Long Island, Mid-Atlantic/New England, upper Midwest (similar to Lyme disease)
- Range of illness: Asx to "flu-like" to fatal

Was a common cause of blood transfusion-related infection in US
- Though decreasing through screening
  - But question may still appear on the boards

Severe Babesiosis

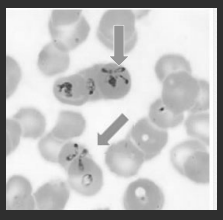
- n=34, Long Island NY
- Clinical manifestations
  - 41% Multi-organ failure
    - ARDS, DIC, CHF, ARF
- Risk factors:
  - age >60
  - splenectomy,
  - immunosuppression (e.g., HIV, rituximab)
- Labs
  - increased LTFs,
  - thrombocytopenia
  - anemia (Hb<10),
  - parasitemia (>10%)

Immunocompromised mortality
- > 20%

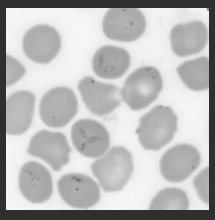
Hatcher JC, et al. Clin Infect Dis 2001; 32:1117-25

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 (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

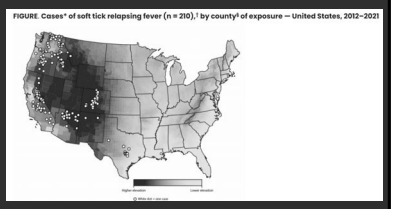
Krause, et al CID 2021; 72 (2) e49-65

Tickborne Relapsing Fever US

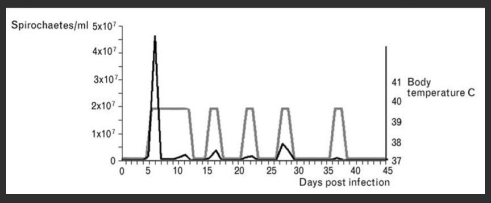
Borrelia spp. (mainly B. hermsii)
- **Ornithodorus soft ticks (brief, painless)**

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,**
  - **Dx: blood microscopic exam, PCR**
- **Rx: PCN, doxycycline**
  - **Jarisch Herxheimer reaction in 54%**

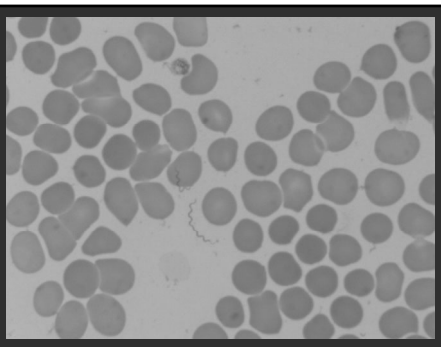


Beeson AM MMWR 2023;72(23):777-781



Relapsing Fever: recurrent bacteremia (black line) correlates with sudden fever (grey).

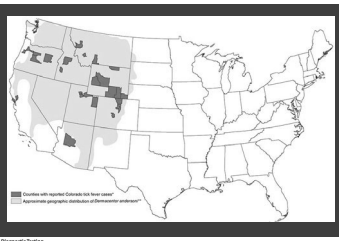
After initial bacteremia, relapses are lower and fever duration somewhat shorter.



Diagnosis: observation of spirochetes in blood film

Colorado Tick Fever

- Transmission D. andersoni
  - 4,000-10,000 feet
- Agent: Coltivirus
- Sx range from
  - Mild febrile flu-like illness
    - May include rash: maculopapular or petechial
  - Rare: severe illness multi-system, neuroinvasive disease
- Labs:
  - ↓ WBC, atypical lymphocytes
  - ↓ plt
- Dx: samples to state lab, some commercial lab testing
  - Not a reportable illness



Diagnostic Testing

Preliminary diagnosis of Colorado tick fever (CTF) is based on signs and symptoms, places and dates of travel, activities, and history of potential tick exposure. Acute samples should be tested by reverse-transcriptase polymerase chain reaction (RT-PCR) to detect viral RNA as antibody production is delayed until 14–21 days after onset of symptoms.

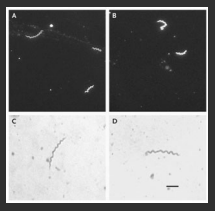
Timing of specimen collection	Specimens	Preferred Test
≤14 days after symptom onset	Serum (CSF if suspected CNS involvement)	RT-PCR for viral RNA
≥14 days after symptom onset	Serum (CSF if suspected CNS involvement)	Antibody testing*; consider RT-PCR for samples from days 14-21

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

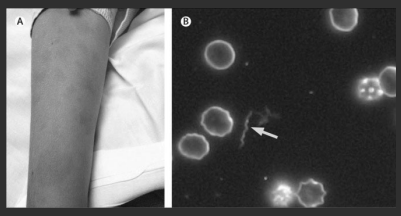


Spirochetes in CSF

Telford, Clin Microbiol Infect 2015

Gugliotta, NEJM 2013

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 #9:

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

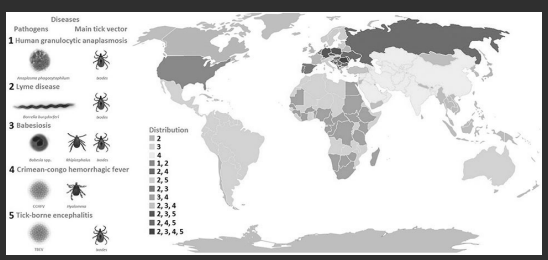
Suspect ehrlichiosis (but no morulae on blood smear)

Question #9:

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

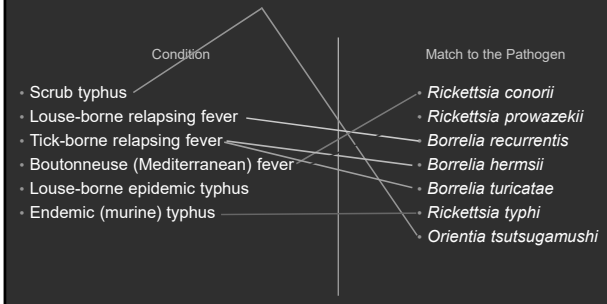
Tick-borne infections: some testable points?

- Babesia:
  - 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.

B. mayonii Spirochete in Culture

Pritt, Clin Micro and Inf 2022

28

Immunizations: Domestic, Travel, and Occupational

Dr. Shireesha Dhanireddy

28 – Immunizations: Domestic, Travel, and Occupational-I, II

Speaker: Shireesha Dhanireddy, MD

Immunizations:
Domestic, Travel, and Occupational

Shireesha Dhanireddy, MD
Professor, Allergy & Infectious Diseases
University of Washington

7/1/2024

- **Disclosures of Financial Relationships with Relevant Commercial Interests**

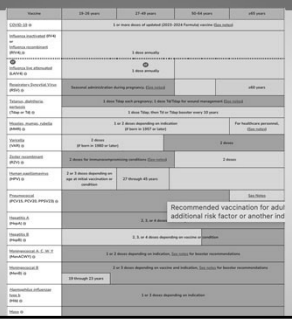
  - None

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

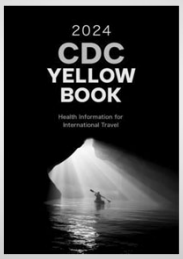


*

https://www.cdc.gov/vaccines/schedules/hcp/adult.html

Key Sources

Only CDC guidance from yellow book for travel vaccines will be 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

28 – Immunizations: Domestic, Travel, and Occupational-I, II

Speaker: Shireesha Dhanireddy, MD

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

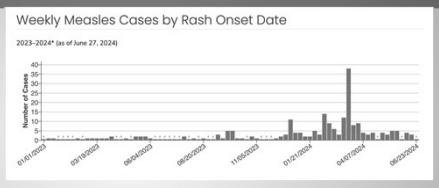
U.S. Cases in 2024

Total cases

159

Age
Under 5 years: **73 (46%)**
5-19 years: **36 (23%)**
20+ years: **50 (31%)**

Vaccination Status
Unvaccinated or Unknown: **84%**
One MMR dose: **11%**
Two MMR doses: **5%**



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

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.

28 – Immunizations: Domestic, Travel, and Occupational-I, II

Speaker: Shireesha Dhanireddy, MD

Question: Pneumococcal Vaccine

A 37 year-old man recently diagnosed with HIV presents to clinic for routine care after starting antiretroviral therapy 3 months ago. He has not received pneumococcal vaccination. Which of the following is most accurate?

A. He does not need pneumococcal vaccination as he is under 65
B. He needs a PCV20 alone
C. He needs a PCV20 followed 1 year later by a PPSV23
D. He needs a PCV15 followed by PPSV23 1 year later and again in 5 years

Pneumococcal Disease

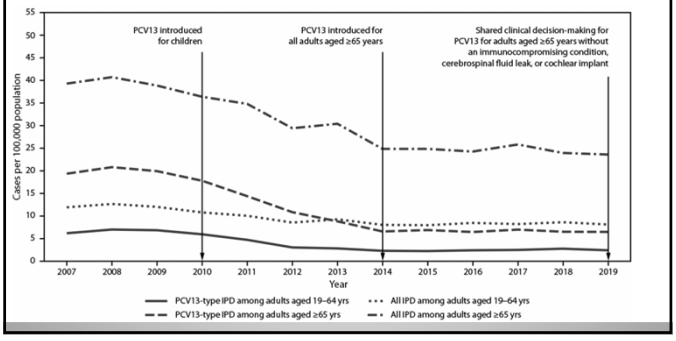
Age (years)	Disease Incidence Cases/100,000 (number of cases)	Death Rate Deaths/100,000 (number of deaths)
<1	17.7 (702)	0.20 (8)
1	12.6 (500)	0.20 (8)
2–4	5.07 (606)	0.13 (16)
5–17	1.23. (659)	0.00 (0)
18–34	2.33 (1,757)	0.08 (60)
35–49	6.48 (3,982)	0.46 (284)
50–64	14.8 (9,326)	1.47 (932)
65–74	18.0 (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

FIGURE. Incidence of all invasive pneumococcal disease and 13-valent pneumococcal conjugate vaccine-type* invasive pneumococcal disease among adults aged ≥19 years, by invasive pneumococcal disease type and age group — United States, 2007–2019†



Updated Guidelines October 2022

- CDC ACIP recommended PCV20 or PCV15 to all individuals ≥ 65 years who have not received PCV before or if unknown
- For people with HIV, individuals with asplenia and others at increased risk, Give PCV20 or PCV15 at age 19-64
  - If PCV15 given, then give PPSV23

Pneumococcal Vaccine in People with HIV

Adults 19–64 years old with specified immunocompromising conditions
Complete pneumococcal vaccine schedules

Prior vaccines	Option A	Option B
None*	PCV20	PCV15 → ≥8 weeks → PPSV23
PPSV23 only	≥1 year → PCV20	≥1 year → PCV15
PCV13 only	≥1 year → PCV20	≥8 weeks → PPSV23 → ≥5 years → PPSV23 Review pneumococcal vaccine recommendations again when your patient turns 65 years old.
PCV13 and 1 dose of PPSV23	≥5 years → PCV20	≥5 years† → PPSV23 Review pneumococcal vaccine recommendations again when your patient turns 65 years old.
PCV13 and 2 doses of PPSV23	≥5 years → PCV20	**No vaccines** recommended at this time. Review pneumococcal vaccine recommendations again when your patient turns 65 years old.

Pneumococcal Vaccine in People with HIV

Adults ≥65 years old
Complete pneumococcal vaccine schedules

Prior vaccines	Option A	Option B
None*	PCV20	PCV15 → ≥1 year† → PPSV23
PPSV23 only at any age	≥1 year → PCV20	≥1 year → PCV15
PCV13 only at any age	≥1 year → PCV20	≥1 year† → PPSV23
PCV13 at any age & PPSV23 at <65 yrs	≥5 years → PCV20	≥5 years† → PPSV23

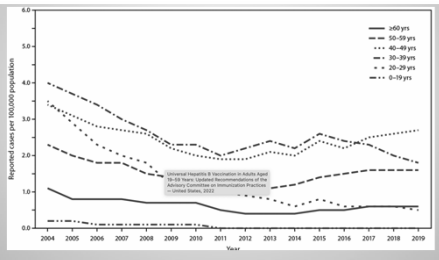
Question: Hepatitis B Vaccine

A 40 year-old software engineer presents to establish care. She has no medical problems. She is in a mutually monogamous relationship with a cis-male partner. She denies any upcoming foreign travel. She reports she has not received Hep B vaccine in the past. Which of the following is most accurate regarding Hep B vaccination?

A. She should start the series today
B. She should only receive if she has risk factors for Hep B
C. Hep B vaccine is not recommended in individuals her age

Hepatitis B

FIGURE. Rates of reported acute hepatitis B virus infection, by age group — United States, 2004–2019



Hepatitis B Vaccine: Current Recommendations

- All infants
- All persons < 19 years
- All adults 19-59 years
- Adults ≥ 60 years with risk factors for Hep B
- Adults ≥ 60 without known risk factors may receive vaccine

Hepatitis B Risk Factors

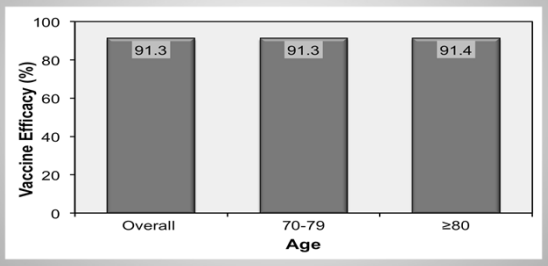
- Sexual exposure
  - Partners with Hep B
  - More than 1 sex partner in last 6 months
  - Getting STI testing or treatment
  - MSM
- Percutaneous exposure (IDU, household contacts, healthcare, public safety, patients on HD or those working with HD patients)
- International travelers
- People with HIV
- Incarceration
- Chronic liver disease (including HCV)

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. What do you recommend regarding the zoster vaccine?

A. Vaccine not indicated given her history of zoster
B. Check VZV titer to confirm history. If negative, proceed with vaccination
C. Recommend recombinant zoster vaccine

RZV Efficacy Against First Episode of Zoster in Immunocompetent Patients ≥50



Cunningham AL, et al. N Eng J Med. 2016;375:1019-32.

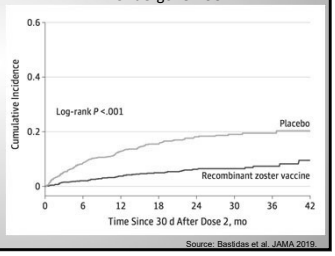
ACIP Recommendations for Zoster Vaccine

- 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

ACIP Recommendations for Zoster Vaccine in Immunocompromised Persons

- RZV recommended for all IC adults 18+
- 2 doses – 2-6 months apart
  - May give 2nd dose early (1-2 months) if anticipating more immunosuppression
  - If second dose early, then repeat dose given at least 4 weeks later
- For those without h/o VZV, RZV not indicated

Efficacy of RZV in Preventing Incident Herpes Zoster in Patients Who Had Undergone HSCT



Source: Bastidas et al. JAMA 2019.

28 – Immunizations: Domestic, Travel, and Occupational-I, II

Speaker: Shireesha Dhanireddy, MD

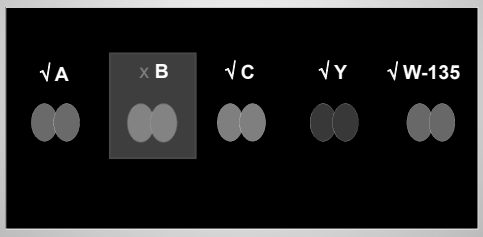
Question: Meningococcal Vaccine

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 quadrivalent conjugate vaccine
B. Give meningococcal B vaccine only
C. Give both quadrivalent conjugate and meningococcal B vaccines

Meningococcal Quadrivalent Vaccines

Serogroups Included in Vaccine: A, C, Y, W-135

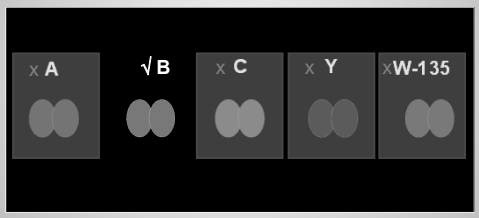


Meningococcal Quadrivalent Vaccines

Serogroups Included in Vaccine: A, C, Y, W-135

- ~~*Menactra* (MenACWY-D)~~
  ~~- Conjugate vaccine~~
  ~~- Approved for ages 9 months to 55 years~~
- *Menveo* (MenACWY-CRM)
  - Conjugate vaccine
  - Approved for ages 2 to 55 years
- *MenQuadFi* (MenACWY-TT)
  - Polysaccharide tetanus toxoid conjugate vaccine
  - Approved for ages 2 to 55 years

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

Speaker: Shireesha Dhanireddy, MD

ACIP Meningococcal B Vaccine Recommendation Adolescents and Young Adults

- Recommended for people 16-23 years of age at increased risk, preferred age 16-18:
  - Meningococcal B outbreak
  - Asplenia
  - Complement deficiency
  - Use of complement inhibitors (ie eculizumab)
  - Microbiologist with potential exposure to *Neisseria meningitidis*
- For others age 16-23, shared decision making recommended
- Same vaccine should be used for all doses

CDC. MMWR. 2020;69:1-41

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

Pentavalent Meningococcal Vaccine

- MenACWY-TT/MenB-FHbp
- FDA approved 10/2023 for persons age 10-25
- ACIP recommendations:
  - –Healthy persons 16-23, when shared decision making favor giving MenB and both vaccines are due
  - –For persons age ≥ 10 years at increased risk of disease
    - Subsequent MenB vaccine should be the same (ie MenB-FHbp (*Trumenba*)

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, except in immunocompromised hosts
  - No clear correlate of immunity

Hepatitis A Vaccination in Adults

- **Any person not fully vaccinated who requests vaccination**
- 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**

Travel Medicine: Scope

- ~20% of all Americans travel abroad per year
- 38 million travel to developing countries per year
- Destinations and itineraries increasingly ambitious
- Average 3 days lost to illness per 14-day trip
- Some of these illnesses may be preventable …

Question: Travel

51 year-old man is planning a 3-week vacation to South Africa, Tanzania, and Kenya in mid August. Prior international travel to Brazil for vacation 11 years ago. Vaccine history - received all childhood vaccines as well as routine adult vaccines. Yellow fever vaccine 11 years ago. He is very concerned about becoming ill during travel and would like all recommended vaccines. Which of the following vaccines are recommended?

A. Yellow fever, Hep A, Typhoid, meningococcal, Japanese encephalitis, cholera, polio
B. Hep A, Typhoid, meningococcal, cholera, polio
C. Hep A, Typhoid
D. Yellow fever, Hep A

Yellow Fever

Yellow Fever Vaccine

- Recommended for ≥ 9 months traveling to or living in areas of risk or countries requiring vaccine for entry
- In 2014, WHO concluded that single dose fellow fever vaccine provides lifelong protection and no booster needed
  - Exceptions if ongoing risk and the following
    - pregnant when initially vaccinated
    - underwent HSCT after initial vaccine
    - HIV+

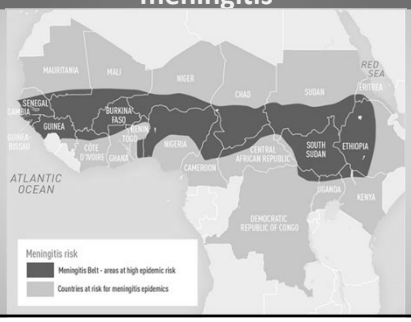
Yellow Fever Vaccine

As of April 5, 2021, Yellow Fever Vaccine (YF-VAX®) is available again in US

28 – Immunizations: Domestic, Travel, and Occupational-I, II

Speaker: Shireesha Dhanireddy, MD

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 and older --> MenACWY (conjugate vaccine) recommended
- Meningitis B vaccine not recommended for travel
- Approx 7-10 days after vaccine for the development of protective antibody levels

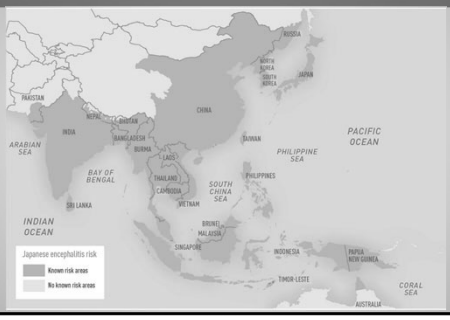
Meningococcal Vaccine and Travel for Umrah or Hajj

- Travelers to Saudi Arabia for Umrah or Hajj are required to provide documentation of meningococcal vaccination at least 10 days before arrival
  - No more than 3 years before for polysaccharide vaccine
  - No more than 9 years before for conjugate

Typhoid Vaccine

- Highest risk for travelers to South Asia (6-30 x more than other destinations)
- Increased risk in West Africa, particularly in rural areas
- 2 vaccines available in US
  - Oral, live attenuated (given at least 1 wk before travel); age 6 and above, q 5 years if ongoing risk or travel
  - IM, polysaccharide (given at least 2 wks before travel); age 2 and above, q 2 years if ongoing risk or travel
  - Both 50-80% effective
- Indicated in travelers
- Delay vaccine >72 hrs after antibacterial medications

Japanese Encephalitis



JEV

- 35,000-50,000 cases/year
- 20-30% mortality
- 30-50% with neurologic sequelae
- Very low risk in travelers *(< 1 case per million travelers)*
- Risks are extended travel > 1 month, rural areas, irrigated areas (rice paddies), or going to an outbreak area
- Vaccine 2 doses, 28 days apart. 2nd dose should be given at least a week prior to travel
- 2 months or older
  - Smaller dose for children under 3
  - ? Booster dose for ≥ 17 years if risk and > 1 year since prior vaccine

28 – Immunizations: Domestic, Travel, and Occupational-I, II

Speaker: Shireesha Dhanireddy, MD

Cholera Vaccine

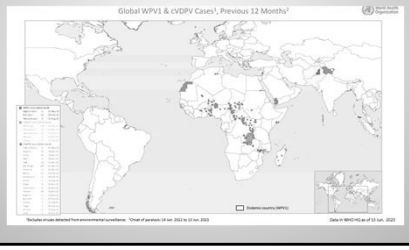
- Approved in 2016
- Single-dose vaccine recommended for adults 18-64 years travelling to an area of active transmission (where cases have been reported in the past year)
- Cholera in travelers is extremely rare
- Risk factors: aid workers in outbreak settings
- Vaccine 90% effective in preventing severe diarrhea (declined to 80% after 3 months)

Hepatitis A

- "The most frequent vaccine-preventable disease in international travelers"
- 2 doses, at least 6 months apart
- Minimum age: 12 months
- Lifetime protection

Polio

- Decreased over 99% since 1988 (350,000 cases)
- One dose after age 18 years in addition to the pediatric series of 4 doses if going to area with polio



www.polioeradication.org

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*.

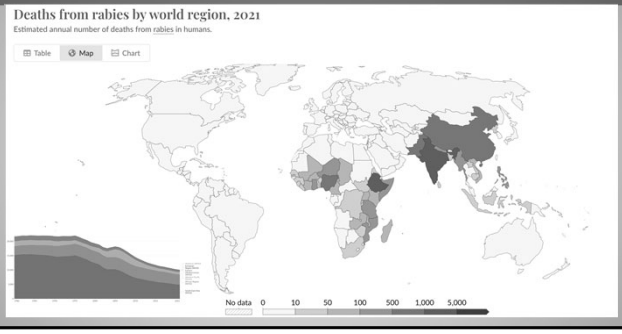
What do you recommend?

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
- 25 cases between 2009-2018
- **5 cases in US so far in 2022**

Human Deaths Attributed to Rabies, 2021



Rabies Vaccine

- Pre-exposure prophylaxis – updated February 2021
  - Vaccination on day 0, 7, ~~and 21 OR 28 days~~

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

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

28 – Immunizations: Domestic, Travel, and Occupational-I, II

Speaker: Shireesha Dhanireddy, MD

Exposure: Anthrax

If exposure to aerosolized *Bacillus anthracis* spores

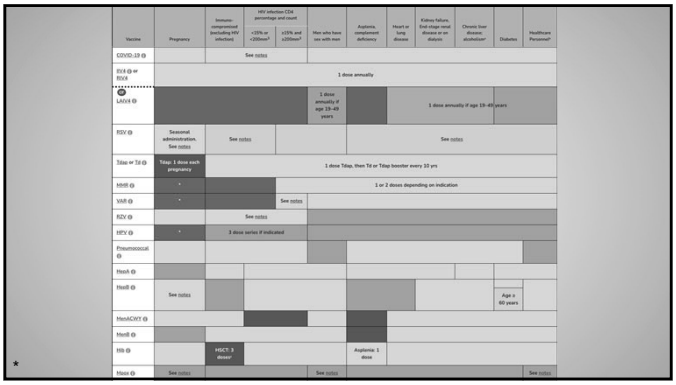
- 60 days of antimicrobial prophylaxis +
- 3 doses of anthrax vaccine

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

<u>If CD4 count > 200</u>

Inactivated influenza
Tdap
Pneumococcal
Meningococcal
HBV
HPV
MMR
Varicella

<u>If CD4 count < 200</u>

Inactivated influenza
Tdap
Pneumococcal
Meningococcal
HBV
HPV
~~MMR~~
~~Varicella~~

Vaccinations for Persons with HIV

- Meningococcal vaccine
  - 0, 8 weeks; then q5 years thereafter
- Pneumococcal vaccine age 19-64
  - PCV20 or PCV15 once, if PCV15 given, then PPSV23 at least 8 weeks later, no recommendation for repeat doses
- Recombinant zoster vaccine (2 doses, 0 and 8 weeks) recommended for all persons with HIV age 18+

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)
  - PCV20 or PCV15 once as adult, if PCV15 given then PPSV23 at least 8 weeks later
- Above vaccines should be given at least 2 weeks prior to elective splenectomy, if possible

Speaker: Shireesha Dhanireddy, MD

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

Resources

- www.cdc.gov/vaccines/recs/ACIP/default.htm
- www.immunize.org/acip

29

Tuberculosis in Immunocompetent and Immunosuppressed Hosts

Dr. Susan Dorman

29 – Tuberculosis in Immunocompetent and Immunosuppressed Hosts

Speaker: Susan Dorman, MD

IDBR INFECTIOUS DISEASE BOARD REVIEW AUGUST 17-21, 2024

Tuberculosis in Immunocompetent and Immunosuppressed Hosts

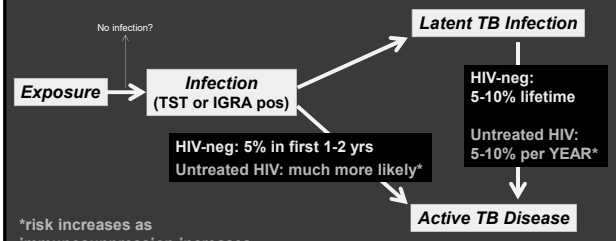
Susan Dorman MD
Professor of Medicine
Medical University of South Carolina

7/1/2024

IDBR INFECTIOUS DISEASE BOARD REVIEW AUGUST 17-21, 2024

- **Disclosures of Financial Relationships with Relevant Commercial Interests**
  - **None**

Overview of TB Epidemiology



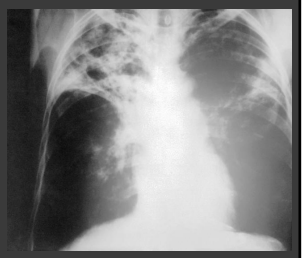
*risk increases as immunosuppression increases

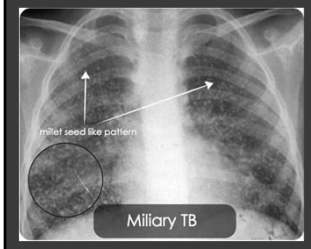
Risk Factors for Active TB Disease

Epi risk factors for TB INFECTION	Medical risk factors for PROGRESSION TO TB DISEASE	
Exposure to person w/ active TB	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 healthcare, corrections	End stage renal dz	
Injection drug use	Diabetes	
	Silicosis	

Active TB disease: clinical presentations

- **Fever, sweats, wt loss**
- **Cough if pulmonary**
- **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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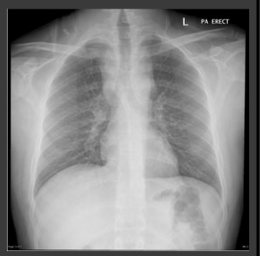


Tuberculous mediastinal lymphadenopathy

http://images.radiopaedia.org/images/5440907/ba7efaf8df7333e5eef8f4a964dd8e_jumbo.jpg

29 – Tuberculosis in Immunocompetent and Immunosuppressed Hosts

Speaker: Susan Dorman, MD

Active TB disease: clinical presentations

Extrapulmonary

- **CNS** (meningitis, focal tuberculomas)
- **Lymphadenitis**
- **Bone and joint**
  - Vertebral (thoracic, lumbar, anterior wedging, +/- psoas abscess)
  - Consider TB in DDx of chronic osteomyelitis, arthritis
- **Pleural** (lymphocytic effusion, low bacillary burden, obtain pleural bx)
- **Pericardial** (lymphocytic effusion, low bacillary burden, obtain pericardial bx)
- **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, d/o of IFN-gamma/IL-12/TNF axis
- Can present as sepsis
- Mycobacterial blood cultures, obtain respiratory specimens, other tissue specimens

Active TB disease: diagnosis

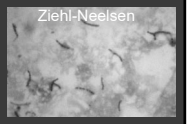
Smear microscopy	nucleic acid amplification tests	culture
		
LOD: 10,000 cfu/ml	100 cfu/ml	1-10 cfu/ml
Sensitivity: LOW	MEDIUM (currently)	HIGH

ADJUNCTIVE:
IGRA, TST: do not distinguish latent from active; NEG test does not rule out active TB
CXR, 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 AFB

- ***NEG SMEARS DO NOT EXCLUDE A DX OF ACTIVE TB***
- Low sensitivity: takes 10,000 cfu/ml bacilli to make a smear pos
- Overall 50-60% sensitive for pulmonary TB
- Less sensitive in advanced HIV (30-50%)
- In pulmonary TB, the yield of smear microscopy increases if multiple specimens obtained
- Not specific for MTB (mycobacteria look alike)
- Good PPV in TB endemic settings



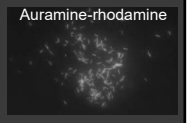


Image credits:
1. CDC/Dr. George P. Kubica
2. https://laboratoryinfo.com/auramine-rhodamine-staining-for-afb-principle-procedure-reporting-and-limitations/

Active TB disease: diagnosis

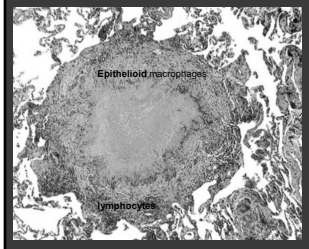
Nucleic Acid Amplification Tests

- E.g. 'Xpert MTB/RIF'
- Sensitivity of available NAATs 'in between' that of smear and culture
- **A negative NAAT does not rule out TB**
- **High specificity for *M. tuberculosis* (by design)**
- Xpert MTB/RIF detects MTB & rifampin resistance (NO info about INH)
- Procedures designed for, validated for sputum
  - Can use for other specimens but test can be falsely negative due to inhibitors

Active TB disease: diagnosis

Mycobacterial Culture

- The **most sensitive method** but SLOW (3-6 weeks)
- Once growth observed, 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



Typical caseating granuloma

Immunodeficient patients:
(e.g. advanced HIV; use of TNF alpha inhibitors)

- Caseation may not be apparent
- Granulomas may lack structure

Image credit: http://pathhsw5m54.ucsf.edu/overview/tb.html

29 – Tuberculosis in Immunocompetent and Immunosuppressed Hosts

Speaker: Susan Dorman, MD

Question 1

PREVIEW QUESTION

38 y/o healthy physician; periodic travel to South Africa for work.
6 years ago: pos TST; poor adherence with isoniazid preventive therapy.
Now 5 weeks of fever, chills, night sweats, 10-lb wt loss, productive cough.
CXR RUL cavitary lesion.
Sputum Xpert MTB/RIF: "MTB detected" & "Rifampin resistance not detected".
HIV negative, LFTs 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

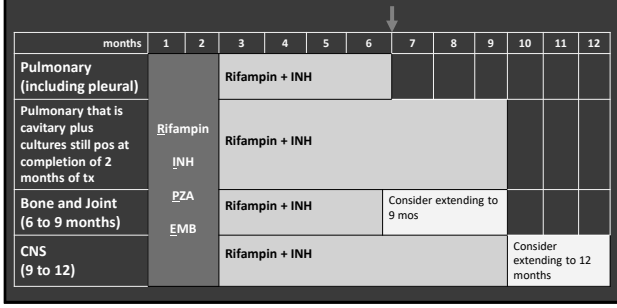
Extend continuation phase therapy for

- Pulmonary dz if cavitation & cx pos at end of tx month 2 (9 months total)
- CNS TB (9-12 months total duration)
- Bone and joint TB (6-9 months total duration)

Corticosteroids: indicated for TB meningitis

- Pericardial TB: probably reduce the risk of constrictive pericarditis
  - Most experts use for patients at high risk for inflammatory complications, e.g.
    - Large effusion, high levels of inflammatory cells in fluid, early constriction

Active TB disease: treatment durations



Question 2

The 38 y/o physician is started on rifampin, isoniazid, PZA, ethambutol (plus pyridoxine) for presumed pulmonary TB.
3 weeks later the culture grows *M. tuberculosis*, susceptible to those drugs.
4 weeks into TB treatment develops nausea, anorexia, abdominal pain.
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 = Vit B6)**
- **Retrobulbar neuritis: ethambutol (acuity, color vision)**
- Arthralgias: PZA

RIFAMPIN CHEWS UP SOME OTHER DRUGS*

Oral anticoagulants	HIV PIs
Hormonal contraceptives	HIV NNRTIs
Methadone	HIV INSTIs
Corticosteroids	HIV CCR5 inhibitors
Fluconazole	TAF*

*Induces hepatic cytochromes & uridine diphosphate gluconyltransferase, resulting in increased metabolism (and decreased serum levels, potential decreased efficacy, potential need for increased doses) of other drugs metabolized by those enzymes

**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*

Question 3

53F recently arrived in US from Ukraine. Reports 3 months of cough. CXR with RUL cavity. Sputum Xpert result "MTB detected" and "Rifampin resistance detected". Additional molecular testing shows mutation in *katG* associated with high-level INH resistance. No mutations in *gyrA* or *gyrB* (ie no molecular evidence of FQ resistance). What is the best treatment approach?

A. Start RIPE plus moxifloxacin, plus amikacin given daily
B. Start RIPE plus moxifloxacin, plus amikacin given 3x/week
C. Start moxifloxacin, amikacin, cycloserine, linezolid, ethionamide
D. Start bedaquiline, pretomanid, linezolid, moxifloxacin

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 bedaquiline or linezolid**
- Treat with multiple agents against which the isolate is susceptible
- Do not add single drug to a failing regimen
- WHO/FDA: BPaL(M) = Bedaquiline + Pretomanid + linezolid (+/- moxifloxacin)
- **Bedaquiline (Sirturo™): novel drug, novel target (MTB ATP synthase); QT prolongation; half-life 4 months**
- **Pretomanid: inhibits mycolic acid synthesis; elevated LFTs**

Question 4

PREVIEW QUESTION

24 y/o M from Zambia, in U.S. for community college, recently tested HIV-positive, CD4 400, not yet on ART.

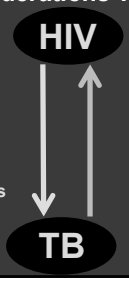
Prominent anterior cervical lymph node but well-appearing, normal BMI, normal liver and renal chemistries, mild anemia.

Lymph node biopsy grows *M. tuberculosis* in culture.

Best course of action regarding timing of TB therapy and HIV therapy?

A. Start ART immediately, defer TB tx
B. Start TB tx immediately, defer ART until completes 6 months 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 & 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 including 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 (RIF)**
  - 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
    - PI-based regimens: Do not use rifampin
    - Cabotegravir and cabotegravir/rilpivirine: do not use rifampin
- **RIFABUTIN (RBT)**
  - Weaker enzyme inducer than rifampin
  - A CYP450 substrate (rifabutin metabolism affected by NNRTIs and PIs)
  - OK with DTG, RAL at standard doses
  - OK with cabotegravir but not with rilpivirine
  - 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 5

30y/o F with HIV, CD4=20, viral load >1 million copies/mL (new dx).
Microbiologically confirmed pulmonary TB (new dx).
RIPE TB treatment started immediately; tolerated well.
12 days later starts DTG-based ART with appropriate bid dosing of DTG.
Four weeks after ART started she reports new headaches, RUE paralysis.
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 active 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: Transplant recipients

- **Transplantation-associated immunosuppression increases risk of active TB disease if the person is infected with MTB**
- **'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
- **RIFAMPIN DDI** with 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: People on 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)

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, M. marinum, M. szulgai* can cause false pos IGRA
- Sensitivity approx same as that of TST
  - Can be negative in immunosuppressed
- As for TST, adjunctive in diagnostic eval for active TB
- 'issues' around performance in clinical care; not fodder for board Q's

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 (recall of waned CMI):
  - Some people infected with MTB may have neg rxn to a TST if many years have passed since Mtb infection. However, the TST PPD stimulates immune response to Mtb antigens, and a subsequent TST can be positive.
  - "Booster effect" can be mistaken for TST conversion
  - Use 2-step TST for individuals who may be tested periodically (e.g. HCW)

Latent TB infection (LTBI): classification of tuberculin skin test results

≥ 5 mm is POS	≥ 10 mm is POS	≥ 15 mm is POS
HIV-infected	Recent arrival (w/in 5 years) from TB high prevalence area	Persons with no known risk factors for TB infx or progression
Recent TB contact	Injection drug use	
CXR with fibrotic changes	Residents & employees of high-risk settings (HWC, corrections, homeless shelters)	
Transplantation	Mycobacteriology lab staff	
Prednisone ≥ 15 mg/d x 1 month or more	Children < 5 years old	
TNF-α antagonists	Medical conditions: diabetes, silicosis, end-stage renal dz, gastrectomy or small bowel resection, CA head & neck	

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) — OK with DTG 50 mg qd
- 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

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 & Good luck!

Susan Dorman [DORMAN@MUSC.EDU]

30

Lyme Disease

Dr. Paul Auwaerter

30 – Lyme Disease

Speaker: Paul Auwaerter, MD

IDBR INFECTIOUS DISEASE BOARD REVIEW AUGUST 17-21, 2024

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

7/1/2024

IDBR INFECTIOUS DISEASE BOARD REVIEW AUGUST 17-21, 2024

- **Disclosures of Financial Relationships with Relevant Commercial Interests**
  - **Consultant: Gilead, Shionogi**
  - **Research Grant: Pfizer**
  - **Ownership Interest: Johnson & Johnson**

Question # 1

PREVIEW QUESTION

A 56 y.o man from southern Missouri
Onset in July:
--Myalgia and malaise
--Rash x 2d at site of tick bite 1 week ago

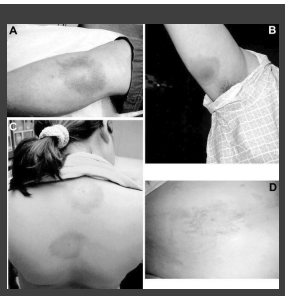
Exam: T 37.0°C
Annular "bulls-eye" ~6 cm
(same area that engorged tick was removed earlier in the week)

Question # 1

PREVIEW QUESTION

Which of the following is the most likely diagnosis?

A. Lyme disease (*Borrelia burgdorferi* infection)
B. Human Monocytic Ehrlichiosis (*Ehrlichia chaffeensis)*
C. *Borrelia mayonii*
D. Southern tick-associated rash illness (STARI)
E. B. lonestarii infection



CDC

STARI

Rash variable

Usually single lesion

Multiple described

Maybe Bull's eye-like

STARI

No infection yet convincingly documented *B. lonestarii* (single case)

Appears to occur after bite of Lone star tick

Symptoms can include fever, headache and Musculoskeletal pains

B. burgdorferi tests including serology negative --no diagnostic test for STARI. Clinical diagnosis

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
Wormser GW, Clin Infect Dis 2005;41:958-65
CDC, STARI, (accessed 6/22/24)

30 – 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* (uncommon)
      - 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

Borrelia burgdorferi sensu lato

USA

- *Borrelia burgdorferi*
  - Geographically localized
    - 90% cases in 15 states
    - Estimates 300,000-476,000 cases/yr
    - Especially coastal, lake and river environs
      - New England
      - Mid-Atlantic
      - Upper Midwest

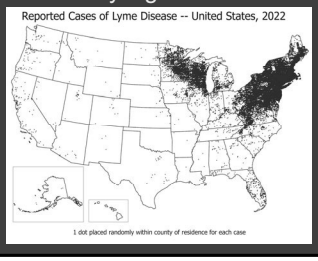
Europe (+ other genospecies)

- *Borrelia afzelii* > *B. garinii* >> *Borrelia burgdorferi sensu stricto, B. bavariensis*
- Occasionally others
- Genus name: changing to *Borreliella?*

(to distinguish from relapsing fever Borrelia spp.)

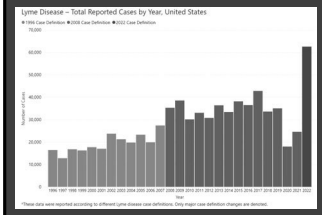
Most common vector-borne infection in US: A mostly regional disease

Newer States
Ohio
Michigan
Indiana
Iowa
Virginia
North Carolina



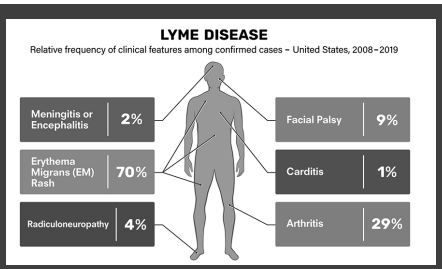
Source: CDC accessed 6/23/24

CDC Case Definition (Revised 2020*)



- 2022 ↑ Lyme disease cases = 1.7 x '17-'19
- High incidence states report based on serology only (w/o clinical information)
- Low incidence states require clinical information

*First applied in year 2022 report
As of 2022, high-incidence jurisdictions (15): CT, DE, DC, ME, MD, MA, MN, NH, NJ, NY, PA, RI, VT, VA, WV and WI.



(based on 62% of 311,561 confirmed cases reported--probably favoring later presentations, Source CDC)
http://www.cdc.gov/lyme/stats/chartstables/casesbysymptom.html

Lyme Disease Presentations

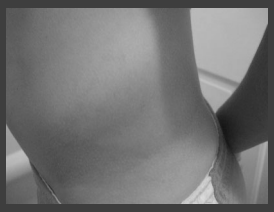
- Early, localized
  - Rash: erythema migrans
- Early, disseminated
  - Rash: multiple erythema migrans
  - Cardiac
  - Neurologic
- Late
  - Lyme arthritis
  - Neurologic (rare)
  - Dermatologic (Europe)
- Overlapping presentations possible

30 – Lyme Disease

Speaker: Paul Auwaerter, MD

Question # 2

PREVIEW QUESTION



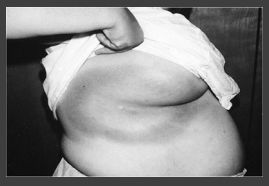
July, 18M living in suburban Maryland, with this rash growing to ~12 cm, first noted 4d, ago, asymptomatic. Landscaper, had tick bite 10d ago. PCP gave cephalexin 2d ago.

Which of the following is true

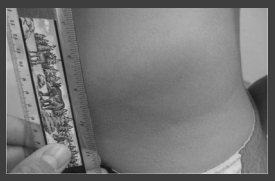
A. Lack of response to cephalexin is consistent with erythema migrans
B. Lack of systemic symptoms makes this unlikely to be Lyme disease
C. Ordering *B. burgdorferi* standard 2-tier serology will likely confirm Lyme disease
D. Whole blood *B. burgdorferi* PCR is superior to serology in early infection
E. Tick should be submitted for detection of *B. burgdorferi* by PCR

Early, localized LD: Erythema migrans

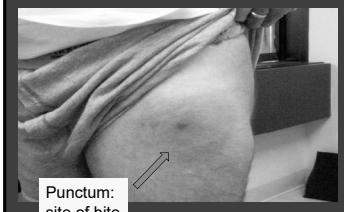
Classic: "bull's eye" with central clearing upon expansion



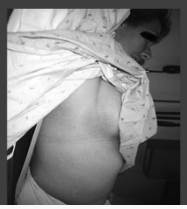
Most common: homogeneous, pink-red ovoid



Typical Erythema Migrans

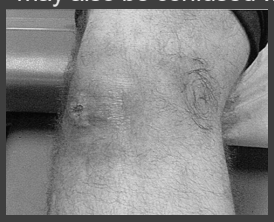


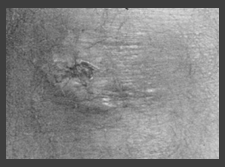
Punctum: site of bite



Lesions: occur typically below neck and above knees & elbows

Spider bite?: differential diagnosis may also be confused with MRSA, cellulitis



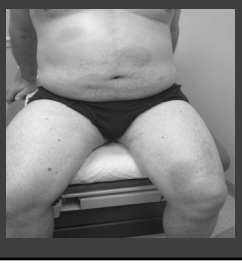


Less typical erythema migrans: skin punch biopsy *B. burgdorferi* culture positive (research labs only)

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)

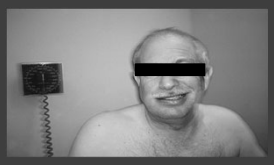


- Multiple Erythema Migrans
  - Often smaller and less red than primary lesion
  - Always ill:
    - Fever
    - Flu-like symptoms
    - Headache

30 – Lyme Disease

Speaker: Paul Auwaerter, MD

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

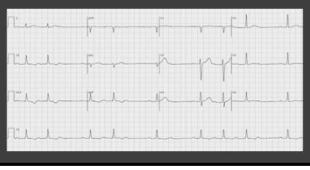
Diagnosis – Facial Palsy

- 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

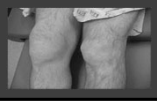
Question # 3

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. No prior arthritis history. (-) new sexual contacts

PMH: HTN, hyperlipidemia
PE: afebrile, mildly warm knee, moderate effusion, reduced ROM

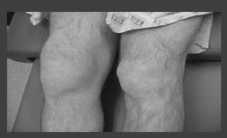
Labs: nl CBC



Which of the following is usually true for Lyme arthritis?

A. Knee swelling doesn't remit without arthrocentesis
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

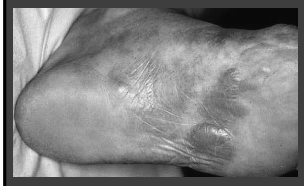
Late Lyme disease (2): Neurologic

- 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

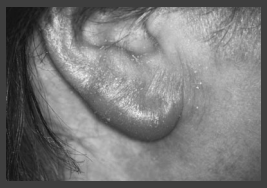
Halperin JJ. Brain 2022;145(8):2635-2647
Wormser GW. Diagn Micro Biol Infect Dis 2017;87(2):163-167

Late Lyme disease (3): Dermatologic

Acrodermitis chronica atrophicans (Europe)
Distal extremities most commonly seen



Borrelia Lymphocytoma (Europe)
Earlobes, nipples, genitals favored sites



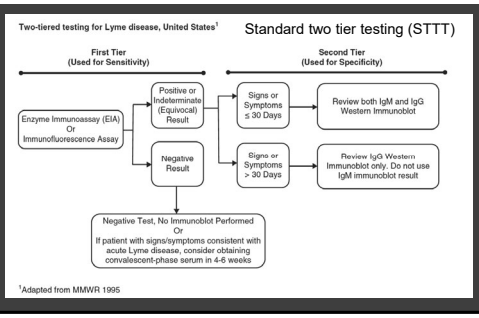
Question # 4

- 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. Borrelia burgdorferi PCR (whole blood)
E. Neither additional Lyme disease testing nor treatment

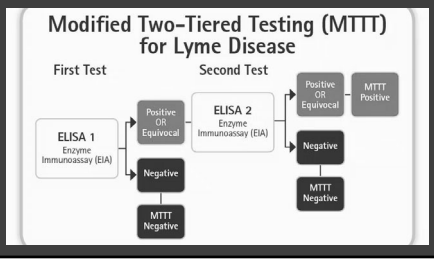


Laboratory testing

- Two tier serology: not needed for erythema migrans
  - First: total Ab screen – ELISA or EIA (for sensitivity)
  - If positive, second tier reflexes to immunoblots (IB, for specificity)
    - 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

MTTT: Faster, Cheaper, Better (early LD)



Modified Two-tier (2-EIA) vs. STTT

- Technically easy, quick
- Less cost
- Appears to provide similar sensitivity/specificity
- Better in early disease

Pooled LD USA	Standard 2-tier	Modified 2-tier	C6 only
Specificity (%)	98.3-100	98.3-100	96.5-100
Sensitivity (%) --Early LD	28-54	38-61	64-68
--Late LD	96-100	98-100	98-100

Branda et al. Clin Infec Dis 2018;66(7):1133-1139

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

FYI: Stats on Lyme disease presentations and routine diagnostics

Table1: Sensitivity and specificity of assays for the diagnosis of Lyme disease

Assay	Specimen type	Clinical manifestation	Sensitivity (%)	Selected References	Specificity (%)	Selected References
Standard two-tiered testing	Serum	Early localized	< 40% (acute) 27% (convalescent) 61% (convalescent)	[32] [33] [97] [33] [32]	~99%	[36]
	Serum	Early disseminated	86% (carditis) 90% 42–87%	[32] [98] [99]	~99%	[98]
	Serum	Neuroborreliosis	90%	[32]	96–100%	[39]
	Serum	Late disseminated	100% (arthritis) 97–100%	[32] [99]	99–100%	[24] [39]
Modified two-tiered testing	Serum	Early localized	53% (acute) 58% (acute) 88% (convalescent) 67% (convalescent)	[37] [33] [25] [37] [33] [25]	~99% 96–100%	[36] [39]
	Serum	Early disseminated	71-86% (carditis)	[100]	96–100%	[39]
	Serum	Neuroborreliosis	96–100%	[22] [37] [100]	96–100%	[22] [37] [39]
	Serum	Late disseminated	~100% (arthritis)	[24] [100]	96–100%	[24] [39]
Polymerase chain reaction	Serum and/or skin Serum/Plasma	Early localized	64–81% 62%	[97] [101]	~100%	[102]* [103] [104]
	Serum	Early disseminated	29% (carditis)	[32]		
	CSF	Neuroborreliosis	25–38% 73%	[102]* [99]		
	Synovial fluid	Late disseminated	85% (arthritis) 83% (arthritis)	[102]* [99]		

*

Kobayashi, Auwaerter. Inf Dis Clinics N Am Sept 2022

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: both STTT & MTTT
  - C6 or VlsE (variable major protein-like sequence expressed)
  - Offers better sensitivity and specificity than whole cell lysate assays
- 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 Ceftroxime axetil	10 14 14
Meningitis/radiculopathy	Oral	Doxycycline	14-21
	IV[c]	Ceftriaxone	14-21
Cranial nerve palsy	Oral	Doxycycline	14-21
Encephalomyelitis	IV[c]	Ceftriaxone	14-28
Carditis	Oral	Doxycycline or Amoxicillin or Ceftroxime axetil	14-21
	IV[c]	Ceftriaxone	14-21
Arthritis	Oral	Doxycycline or Amoxicillin or Ceftroxime 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.

Some key points
1. 10d doxy ok for early EM
2. Neuroborreliosis
   Oral doxy = IV CTX
   Do not need CTX
3. Lyme carditis
   Once improved → oral

Lantos et al, IDSA/AAN/ACR Lyme Guideline, 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 patients

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. Sjöwall, 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

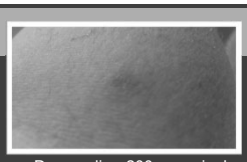
PA2

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 for patients w/ symptoms > 1 month
- Late Lyme arthritis: always seropositive (IgG)
  - 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

31

Hospital Epidemiology

Dr. Michael Klompas

31 – Hospital Epidemiology
Speaker: Michael Klompas, MD

Hospital Epidemiology

Michael Klompas MD, MPH, FIDSA, FSHEA
Professor, Harvard Medical School
Hospital Epidemiologist, Brigham and Women's Hospital

7/1/2024

- **Disclosures of Financial Relationships with Relevant Commercial Interests**

Grant funding:
- Centers for Disease Control and Prevention
- Agency for Healthcare Research and Quality
- Mass Department of Public Health

- **Royalties:**
  - UpToDate

Question #1

PREVIEW QUESTION

What is the most common healthcare-associated infection?

A. Central line associated bloodstream infections
B. Catheter-associated urinary tract infections
C. Hospital-acquired pneumonia
D. Surgical site infections
E. Clostridioides difficile

The Most Common Hospital Acquired Infections

CDC point-prevalence survey of healthcare-associated infections in 2015, 199 hospitals, 10 states

	Frequency per 100 patients
Pneumonia	0.9
Surgical site infections	0.7
Gastrointestinal infections including *C. difficile*	0.6
Bloodstream infections	0.4
Urinary tract infections	0.3
Any healthcare-associated infection	3.2

Magill, *N Engl J Med* 2018;379:1732-1744

The Most Common Hospital Acquired Pathogens

CDC point-prevalence survey of healthcare-associated infections in 2015, 199 hospitals, 10 states

	Frequency per 100 healthcare-associated infections
C. difficile	15%
Staphylococcus aureus	11%
Escherichia coli	10%
Candida species	6%
Enterococcus species	5%
Enterobacter species	5%
Pseudomonas aeruginosa	5%
Klebsiella species	5%

Magill, *N Engl J Med* 2018;379:1732-1744

Question #2

A surgical colleague calls you because 2 of his patients developed *Candida albicans* surgical site infections following spine surgery. You review the hospital's microbiology records and confirm that this is very unusual. What are potential sources for this cluster?

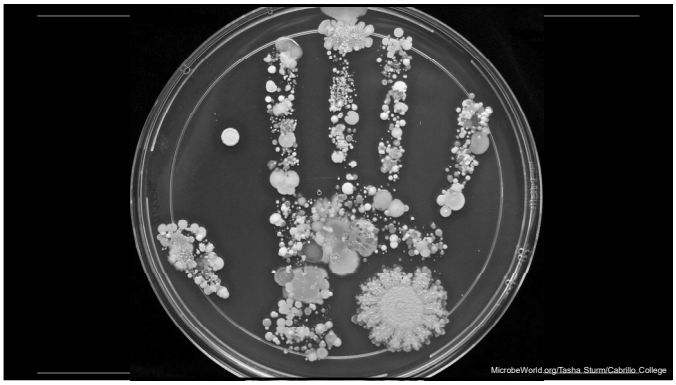
A. Scrub nurse wearing artificial nails
B. Disruption of laminar airflow in the operating room
C. Contamination of intravenous fluids used during surgery
D. Failure of peri-operative blood glucose control
E. Use of broad-spectrum antibiotics for peri-operative prophylaxis

Nail Add-Ons & Blemishes Can Harbor Pathogens

etsy.com/dk-en/listing/598625946/nurse-nail-art-decals

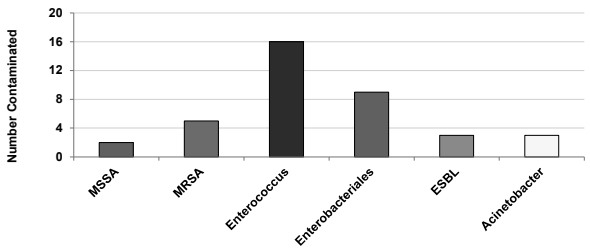
- **Nail add-ons can act as reservoirs for potentially pathogenic organisms; can persist despite cleaning with an antiseptic**
- **Multiple clusters linked to healthcare workers with artificial nails & infected nails**
  - NICU patients with ESBL *Klebs pneumo* infections
  - Serratia bloodstream infections in dialysis patients linked to RN opening heparin vials with fake nails
  - NICU patients with *Pseudomonas* infections linked to healthcare workers with artificial & infected nails
  - Laminectomy surgical site infections with *Candida albicans* traced to scrub tech with artificial nails
  - Sternal wound infections with *Pseudomonas* traced to OR nurse with onychomycosis
  - Sternal wound infections with Pseudomonas traced to cardiac surgeon with onychomycosis

Gupta, *ICHE* 2004;25:210-215 | Parry, *Clin Infect Dis* 2001;32:553-7
Gordon, *ICHE* 2007;28:743-744 | Michel, *Clin Infect Dis* 2001;33:317-323
Foca, *N Engl J Med* 2000;343:695-700 | Mermel, *ICHE* 2003;24:749-52



Organisms Recovered from Physicians' Hands Following a Single Physical Exam

Standardized exams of 56 patients, hand hygiene & sterile gloves prior to exam



Tschopp, *Infection Control & Hospital Epidemiol* 2016;37:673-679

Essential Hand Hygiene Practices

SHEA The Society for Healthcare Epidemiology of America

Promote healthy hand skin & fingernails

- Fingernails should be short, healthy, and natural
- Perform hand hygiene per the WHO's Five Moments
  1. Before touching patient
  2. Before clean procedure
  3. After touching patient
  4. After touching body fluids
  5. After touching patient environment
- Alcohol-based hand rub typically preferred over soap & water
- Facilitate primary and secondary prevention of dermatitis

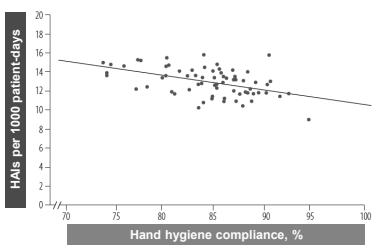
Ensure hand hygiene supplies are always readily accessible

- Widespread, convenient alcohol-based hand rub dispensers

Infection Control & Hospital Epidemiology 2023;44:355-376

Better Hand Hygiene, Fewer Healthcare Associated Infections

Monthly hand-hygiene compliance and HAI incidence, Oulu University Hospital, Finland 2013-2018



Ojanpera, *Bull World Health Organ* 2020;98:475-483

Question #3

A 43-year-old man is brought to the hospital after being found unconscious. Vomitus and feces were on the patient. His airway was suctioned, he was intubated for airway protection, and then transferred to the ICU. An LP was performed. Gram stain showed gram negative diplococci. Which healthcare workers should be offered post-exposure prophylaxis?

A. The scribe who documented the patient's emergency care
B. The respiratory therapist that suctioned the patient's vomitus
C. The medicine intern that did an admission physical in the ICU
D. The radiology technician that did a portable chest x-ray in the ED
E. The nurse that placed his IV in the ED (difficult stick, 3 attempts)

Neisseria transmission to healthcare workers

Comprehensive search for occupational Neisseria infections in healthcare workers in England and Wales 1982-1996

Case 1

Provider: Doctor

Full clinical exam of 9 yo with meningitis, including fundoscopy during which **patient coughed into doctor's face**

0.5-2h contact time

Incubation period: 4d

Case 2

Provider: EMS worker

Transported 16 yo with meningitis to hospital. Care included **airway insertion and delivery of oxygen while patient seizing** in ambulance

0.5-2h contact time

Incubation period: 7d

Case 3

Provider: Nurse

Nursed a 7mo with sepsis while baby being prepared for transfer to referral hospital; **in close contact while child crying and coughing for at least 5h**

5-6h contact time

Incubation period: 5d

Estimated 0.8 infections per 100,000 healthcare worker contacts with meningococcal patients

Gilmore, Lancet 2000;356:1654-1655

Antimicrobial Prophylaxis for *Neisseria meningitidis*

- **Indicated for close contacts of patients with invasive disease***
  - Household members (risk: 4 in 1000)
  - Childcare center contacts
  - Anyone directly exposed to patient's oral secretions
    - Kissing, mouth-to-mouth resuscitation
    - Endotracheal intubation, suctioning oral secretions without respiratory protection

*not indicated if Neisseria only isolated from sputum, nasopharynx, conjunctiva, etc.

- **Exposure window**
  - From 7 days before symptom onset through 24h after starting treatment
- **Prophylaxis options**
  - Rifampin 600mg PO q12h x 2d
  - Ciprofloxacin 500mg PO x 1
  - Ceftriaxone 250mg IM x 1

Cohn, MMWR Recomm Rep 2013;62(RR-2):1

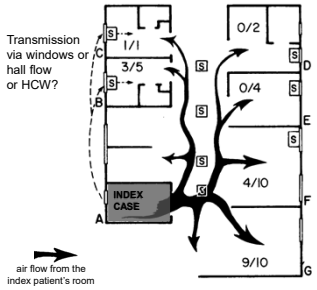
Question #4

A 69-year-old man is admitted to hospital with fatigue, weight gain, and edema. He is found to have nephrotic syndrome and ultimately diagnosed with amyloidosis. On hospital day 7, a nurse notes a vesicular rash on his left flank and right chest. The patient is placed on Airborne precautions. PCR of fluid from a vesicle is positive for VZV. Who of the following requires VariZIG?

A. Unvaccinated seronegative nurse looking after the patient in the next room
B. Unvaccinated seronegative respiratory therapist on rituximab for SLE
C. Patient's pregnant nurse, 2 doses varicella vaccine as child. She is VZV IgG-
D. Hospital roommate, 75 yo poorly controlled diabetes, unknown vax status
E. The dermatologist that unroofed a vesicle for testing. She is VZV IgG+.

Varicella Outbreak!

Cluster of 15 varicella cases, attributed to child with varicella pneumonia, Boston Children's Hospital, 1970s



0% attack rate
Distance and fresh air leading to dilution

0% attack rate
Distance and fresh air leading to dilution

40% attack rate
HVAC unit operational

90% attack rate
HVAC unit not working, rendering the room negative pressure relative to the hall

Leclair, NEJM 1980;302:450-453

Varicella Transmission

- **Person-to-person spread**
  - Direct contact with active lesions
  - Airborne spread from a person with respiratory involvement
  - Aerosolization from skin lesions or bedsheets (both rare but reported)
- **Incubation period:**
  - 8-21 days (usually 14-16 days)
- **Infectious period:**
  - From 24-48h before rash onset until all skin lesions crusted
- **Highly contagious if not immune:**
  - Varicella household transmission rate among susceptible individuals 85%
  - Herpes zoster household transmission rate ~25%
  - Breakthrough infections and transmissions relatively common but attenuated

Menkhaus, *Lancet* 1990;336:1315 (airborne spread)
Lopez, JID 2008;197:646-653 (skin lesions, linens)

Management of Varicella Exposure

- **Definition of exposure**
  - >15-60mins in same room as person with primary varicella or disseminated zoster involving the respiratory tract, or skin-to-skin contact with exposed varicella lesions
  - No exposure if HCW immune and wearing a mask or respirator
- **Management of Exposures**

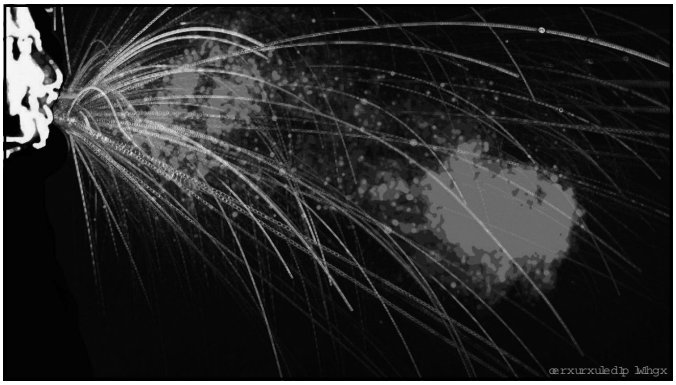
Immune Status	Vaccinate?	VariZIG?	Furlough d8-21?	Monitor d8-21?
Fully vaccinated, seropositive, or prior Dx	No	No	No	Yes
Partially vaccinated	Yes	No	Depends[2]	Yes
Unvaccinated & seronegative	Yes	No	Yes	Yes
Unvaccinated & unable to vaccinate[1]	No	Yes[3]	Yes[4]	Yes

[1] Vaccine contraindicated if pregnant or immunocompromised
[2] Furlough if vaccine was given >5d after first exposure
[3] Or valacyclovir d7-13 if VariZIG not available
[4] Furlough d8-28 if given VariZIG

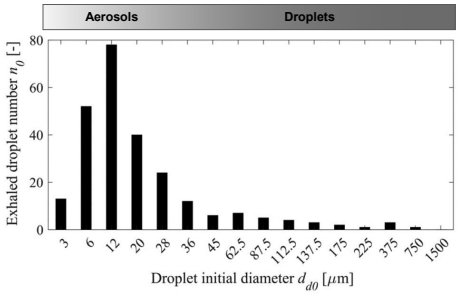
Question #5

A 64-year-old man with coronary disease is admitted with unstable angina. He is treated medically and referred for urgent catheterization. He's found to have a flow limiting lesion in the circumflex. A stent is placed. He initially improves but 3 days later develops fever, cough, and recurrent chest pain. His workup is positive for recurrent MI and influenza. The interventional cardiologist who did his procedure discloses that he had mild sniffles at the time but no fever and he wore a procedure mask at all times. Did the cardiologist infect the patient?

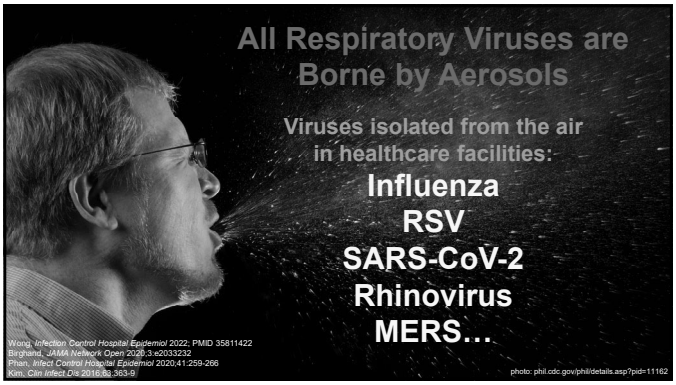
A. No, surgical masks provide excellent protection/control for respiratory viruses
B. No, sniffles alone without fever cannot be influenza
C. No, procedure rooms have excellent ventilation
D. Yes, surgical masks only provide moderate protection/control for respiratory viruses
E. Yes, surgical masks do not provide any control against respiratory viruses



People Produce Respiratory Particles in a Range of Sizes

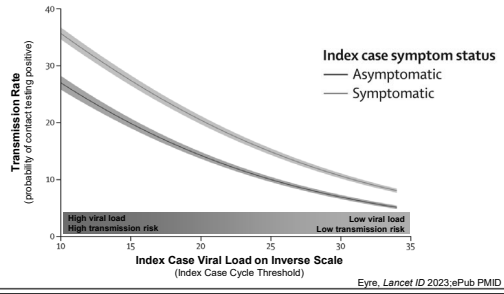


Chen, *Building and Environment* 2020;176:106859



Viral Load Predicts Transmission Risk

Secondary attack rates amongst 1,173,643 contacts of 6,263,786 index cases, UK, Jan 2021-Jan 2022



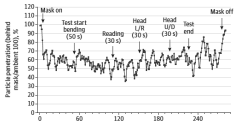
Eyre, *Lancet ID* 2023;ePub PMID 37001541

How good is your surgical mask?

Filtration Efficiency: Surgical Mask vs N95 Respirator

Surgical Mask with Ear Loops

Particle Penetration Behind Mask

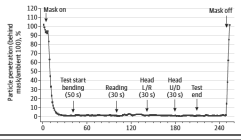


Filtration Efficiency

38.1%

N95 Respirator

Particle Penetration Behind Mask

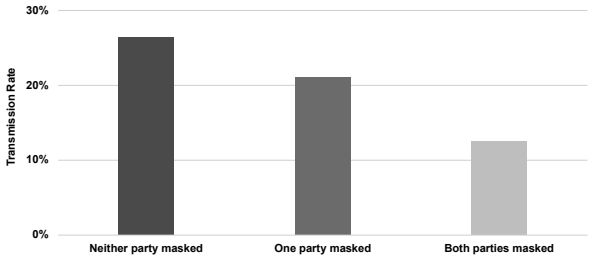


98.5%

Sickbert-Bennett, *JAMA Internal Med* 2020; 180:1607-1612

Masking Effectiveness in Practice

Transmission rates amongst 969 close contacts of 431 people with Covid-19, Johnson County Public Health, Iowa



Riley, *Emerging Infectious Disease* 2021; doi: 10.3201/eid2801.211591

Surgical Masks Decrease TB Transmission Risk Too!

17 patients with TB randomized to wear masks on alternate days. Ward air funneled to two groups of guinea pigs. One group only exposed on mask days. One group only exposed on non-mask days.

Odd days
Patients masked
Ward air ported to guinea pig group 1

Even days
Patients unmasked
Ward air ported to guinea pig group 2

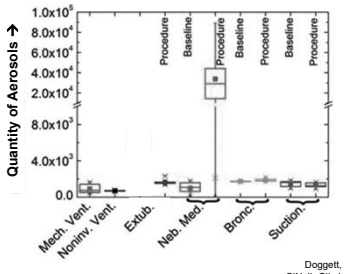
36/90 (40%) Infected

69/90 (77%) Infected

Masking patients associated with 56% decrease in TB transmission to guinea pigs

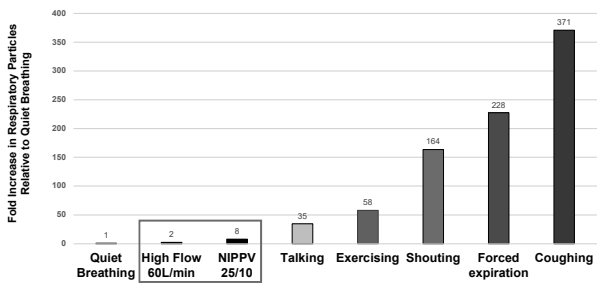
Dharmadhikari, *AJRCCM* 2012;185:1104-1109

Most "Aerosol Generating Procedures" Do Not Generate Aerosols



Doggett, *Chest* 2020; 158:2467-2473
O'Neil, *Clin Infect Dis* 2017;65:1342-1348
Li, *Open Forum Infect Dis* 2017;4(Suppl 1):S34

Impact of High Flow O2 on Respiratory Emissions



Wilson, *Anaesthesia* 2021;76(11):1465-1474

Risk & Protection Exists on a Continuum

Factors That Increase Risk

- High community incidence
- Higher viral load
- Symptoms
- Proximity
- Longer exposure
- Poor ventilation
- Lack of masking
- Lack of vaccination

Factors That Decrease Risk

- Low community incidence
- Lower viral load
- Lack of symptoms
- Distance
- Brevity
- Good ventilation
- Mask on patient
- Mask on provider
  - N95 > KN95 > facemask
- Vaccination

Question #6

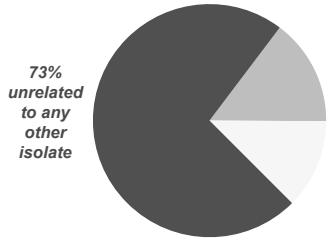
PREVIEW QUESTION

A 63-year-old man with lymphoma is admitted for chemotherapy. His course is complicated by new atrial fibrillation and hospital acquired pneumonia (treated with vancomycin, cefepime, levofloxacin). On hospital day 12 he develops severe diarrhea and is diagnosed with *C. difficile* infection. Where did the patient most likely acquire this pathogen?

A. From another patient on his ward (carried by healthcare workers' hands)
B. From the previous occupant of his bed
C. From the toilet seat of the shared bathroom in his room
D. From the food provided by the hospital
E. From the community (already colonized on admission)

Where do patients get *C.difficile*?

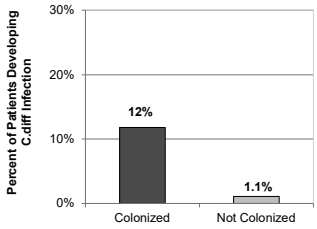
Whole genome sequencing of 1,250 C. diff isolates from symptomatic inpatients & outpatients, Oxfordshire, UK, 2007-2011



Eyre, *N Engl J Med* 2013;369:1195-1205

C.diff Colonization in ICU Patients and Progression to Infection

548 ICU patients at Johns Hopkins screened for C. difficile carriage on admission



Infect Control Hospital Epidemiol 2015;36:1324-1329

So Where Do Inpatients Get *C.diff* From?

1. Present on admission
- Patient colonized prior to arrival, disease activates in the setting of exposure to antibiotics, antacids, immunosuppressants, and frailty

2. Transmission from symptomatic patients
- Spores carried patient to patient via staff hands & clothing, equipment, the environment

3. Transmission from asymptomatic patients
- Spores carried patient to patient via staff hands & clothing, equipment, the environment

Risk of *C.diff* Acquisition Higher if Prior Room Occupant had *C.diff*

Medical ICU, University of Michigan Health System, 2005-2006

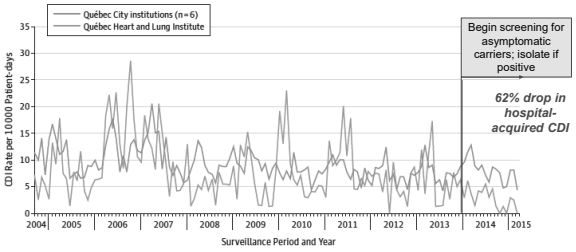
Prior Room Occupant Flagged for *C.diff*	**11.0%**
Prior Room Occupant Not Flagged for *C.diff*	**4.6%**

Adjusted Hazard Ratio **2.4** (95% CI 1.2-4.5)

Infection Control Hospital Epidemiology 2011;32:201-206

Impact of *C.diff* Screening & Isolation on *C.diff* Infections

Quebec Heart and Lung Institute began screening admissions for asymptomatic C.diff carriage in 2014; assessed impact on hospital-acquired C.diff infections relative to other Quebec City hospitals



Longtin, *JAMA Internal Med* 2016;176:796-804

Essential Practices to Prevent *C.difficile* in Hospitals

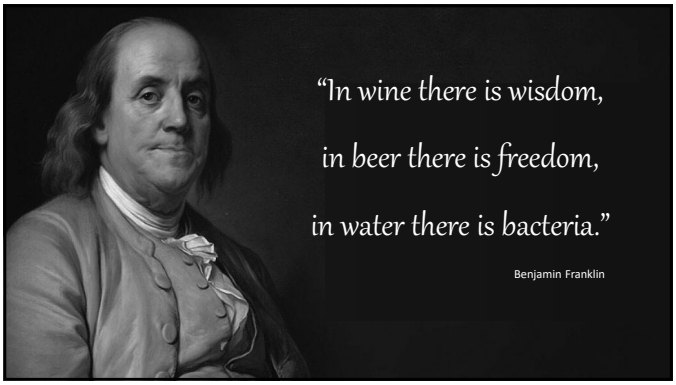
- Encourage appropriate use of antimicrobials through implementation of an antibiotic stewardship program
- Implement diagnostic stewardship to assure appropriate use and interpretation of *C.difficile* testing
  - Guide or limit use of PCR, aid in interpretation
  - Avoid testing patients if no significant diarrhea, recent positive test, or age <1 year
- Use contact precautions, single room preferred
- Adequately clean and disinfect equipment and the environment
  - Use dedicated equipment when possible (e.g. stethoscope, BP cuff, thermometer…)
- Assess the adequacy of room cleaning
  - Consider using sporicidal agents if cleaning adequate but ongoing *C.diff* transmission
- Create lab-based alerts for clinicians and infection control re new cases
- Conduct surveillance for *C.diff* infections and report to stakeholders
- Educate clinicians, enviro services, administrators, & patients about *C.difficile*
- Measure compliance with contact precautions and hand hygiene

Infection Control & Hospital Epidemiology 2023;44:527-549

Question #7

The MICU attending calls you because she's noticed 4 patients with new *Burkholderia cepacia* complex infections in her unit over the last 6 months. The patients were hospitalized during different periods. All Burkholderia isolates were first detected >7 days after admission.
What potential sources will you investigate?

A. Are providers consistently washing their hands between patients?
B. Are providers wiping down stethoscopes & phones between patients?
C. Did all the patients receive care from a common healthcare worker?
D. Were there any common devices amongst patients (e.g. ventilators, ECMO, bronchoscopes, ultrasound probes, etc.)?
E. Did all the patients visit the same operating room?



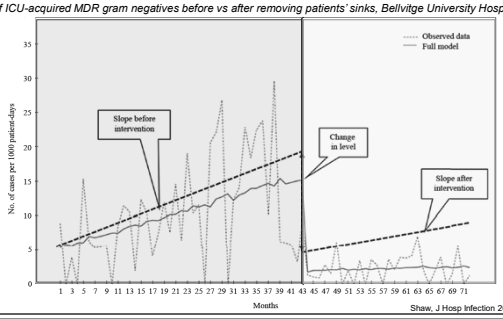
Water Avid Pathogens

Pseudomonas spp.
Legionella pneumophilia
Burkholderia cepacia
Sphingomonas spp
Stenotrophomonas maltophilia
Acinetobacter baumannii
Aeromonas spp
Elizabethkingia anophelis
Enterobacter cloacae
Nontuberculous mycobacteria
Yeasts *(Candida spp.)*
Free living amoeba

- Normal inhabitants of water systems
- Promoters of persistence:
  - Biofilm forming
  - Relative resistance to disinfectants
- When clusters occur think:
  - Respiratory care equipment
  - Heating & cooling devices
  - Contaminated IV solutions & meds
  - Decorative water displays
  - Contaminated sink drains
  - etc.

Drop in MDR Gram Negatives After Sink Removal

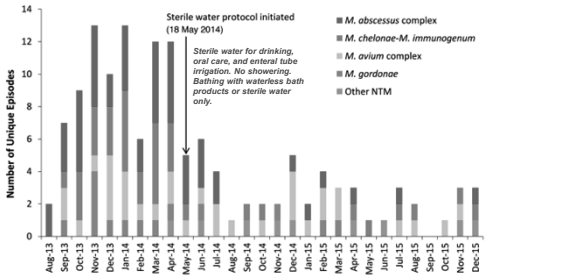
Incidence of ICU-acquired MDR gram negatives before vs after removing patients' sinks, Bellvitge University Hospital, Barcelona



Shaw, J Hosp Infection 2018;98:275-281

Eliminating tap water associated with drop in NTM infections

Count of patients with new non-tuberculous mycobacteria cultures, 3 ICUs & 1 step-down, Duke University Hospital



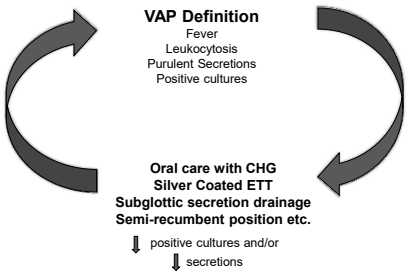
Baker, *Clin Infect Dis* 2021;73:524-527

Question #8

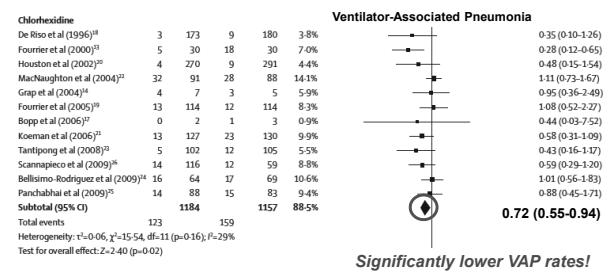
The CEO calls you to express her concern that ventilator-associated pneumonia rates in your hospital are double those of a competing hospital. Which of the following measures are advised to reduce ventilator-associated pneumonia rates and improve patient outcomes?

A. Silver coated endotracheal tubes
B. Oral care with chlorhexidine
C. Daily toothbrushing
D. Placing patients in the lateral Trendelenburg position
E. Probiotics

Circularity Between VAP Prevention Practices and the VAP Definition

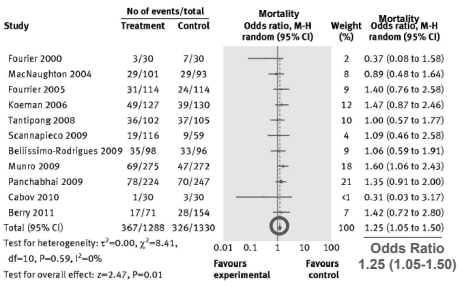


Oral Care with Chlorhexidine: Significantly *Lower* VAP Rates



Lancet Infectious Disease 2011;11:845

Oral Care with Chlorhexidine: Significantly *Higher* Mortality Rates



Study	No of events/total: Treatment	Control	Mortality Odds ratio, M-H random (95% CI)	Weight (%)	Mortality Odds ratio, M-H random (95% CI)
Fourier 2000	3/30	7/30		2	0.37 (0.08 to 1.58)
MacNaughton 2004	29/101	29/93		8	0.89 (0.48 to 1.64)
Fourrier 2005	31/114	24/114		9	1.40 (0.76 to 2.58)
Koeman 2006	49/127	39/130		12	1.47 (0.87 to 2.46)
Tantipong 2008	36/102	37/105		10	1.00 (0.57 to 1.77)
Scannapieco 2009	19/116	9/59		4	1.09 (0.46 to 2.58)
Bellissimo-Rodrigues 2009	35/98	33/96		9	1.06 (0.59 to 1.91)
Munro 2009	69/275	47/272		18	1.60 (1.06 to 2.43)
Panchabhai 2009	78/224	70/247		21	1.35 (0.91 to 2.00)
Cabov 2010	1/30	3/30		<1	0.31 (0.03 to 3.17)
Berry 2011	17/71	28/154		7	1.42 (0.72 to 2.80)
Total (95% CI)	367/1288	326/1330		100	1.25 (1.05 to 1.50)

Test for heterogeneity: τ^2=0.00, χ^2=8.41, df=10, P=0.59, I^2=0%

Test for overall effect: z=2.47, P=0.01

0.01 0.1 1 10 100

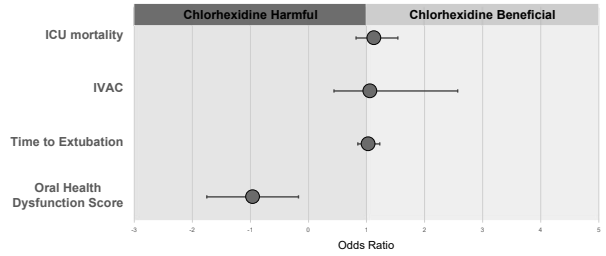
Favours experimental | Favours control

Odds Ratio
1.25 (1.05-1.50)

BMJ 2014;348:g2197

Chlorhexidine De-Adoption Cluster Randomized Trial

Cluster randomized trial of replacing oral CHG with an oral care bundle vs continuing oral care with CHG in 6 Canadian ICUs (N=3260). Oral care bundle included twice daily toothbrushing plus mouth and lip moisturization



Dale, Intensive Care Med 2021;47:1295-1302

Toothbrushing: lower mortality, shorter LOS

Meta-analysis of 15 randomized trials of oral care with vs without toothbrushing

	Studies	Patients	Meta-Analysis	
Hospital-acquired pneumonia* *12 of the 14 studies in ventilated patients	14	2557	Risk Ratio 0.68 (95% CI 0.57-0.82)	*Lower!*
Ventilator Days	7	1285	-1.2 days (95% CI -2.4 to -0.1)	*Lower!*
ICU Length of Stay	6	1284	-1.8 days (95% CI -2.9 to -0.7)	*Lower!*
ICU Mortality	6	1331	Risk Ratio 0.81 (95% CI 0.69-0.95)	*Lower!*

Ehrenzeller, *JAMA Internal Med* 2024;184(2):131-142

Essential Practices to Prevent VAP in Adults

- Avoid intubation and prevent reintubation
  - Use high flow nasal oxygen or non-invasive positive pressure ventilation whenever safe and feasible
- Minimize sedation
  - Avoid benzodiazepines
  - Use a protocol to minimize sedation
  - Implement a ventilator liberation protocol
- Maintain and improve physical conditioning
- Elevate the head of the bed to 30-45 degrees
- Provide oral care ***with*** toothbrushing but ***without*** chlorhexidine
- Provide early enteral nutrition
- Change the ventilator circuit only if visibly soiled or malfunctioning

Infection Control & Hospital Epidemiology 2022;43:687-713

Question #9

You are part of a multidisciplinary team working to prevent central line associated bloodstream infections in your hospital. Interventions to date include education, daily patient bathing with chlorhexidine, line insertion checklists, insertion kits, and maximal sterile barrier precautions during insertion. What additional steps should you consider implementing?

A. Create a standing order for vancomycin for all patients with central lines
B. Replace all central lines every 7 days
C. Preferentially site all lines in the internal jugular vein whenever possible
D. Require "double antiseptic" skin preparation with povidone-iodine-chlorhexidine before all insertions
E. Require "double antiseptic" skin preparation with alcohol-chlorhexidine before all insertions

Essential Practices to Prevent Line Infections

Before insertion

- Disseminate indications for evidence-based central line use to minimize unnecessary use
- Provide education and perform competency assessments
- Daily bathing with chlorhexidine

Infection Control & Hospital Epidemiology 2022;43:553-569

Essential Practices to Prevent Line Infections

At insertion

- Use a checklist to assure all steps followed
- Perform hand hygiene
- Subclavian site preferred
- Use a catheter-placement kit with all necessary supplies
- Use ultrasound guidance to place the catheter
- Use maximal sterile barrier precautions
- Use an alcohol-chlorhexidine antiseptic for skin prep

Infection Control & Hospital Epidemiology 2022;43:553-569

Essential Practices to Prevent Line Infections

After insertion

- Ensure appropriate nurse:patient ratio and limit use of float nurses in ICUs
- Use chlorhexidine-containing dressings for central lines
- Change transparent dressings and perform site care with a chlorhexidine-based antiseptic q7d (or immediately if soiled)
- Disinfect catheter hubs, connectors, ports before each use
- Remove non-essential catheters promptly
- Replace administration sets q7d or less
- Routinely measure line infection rates and report back to unit staff & hospital leaders

Infection Control & Hospital Epidemiology 2022;43:553-569

Question #10

A 66 yo gent with poorly controlled diabetes is admitted with fever and a swollen left knee. He underwent elective knee replacement 3 weeks ago. Knee aspirate gram stain shows gram positive cocci in clusters. Culture is positive for Staph aureus (methicillin-susceptible). The patient is taken to the OR, the prosthesis is removed, and an antibiotic spacer is placed. The patient is devastated by the setback to his recovery and the need for more surgery. He asks what more could have been done to prevent this infection?

A. Obtain a urine culture before surgery to rule out occult bacteriuria
B. Screen all patients before arthroplasty to identify *Staph aureus* carriers and decolonize them with chlorhexidine washes + nasal mupirocin
C. Prescribe 4 weeks of antibiotic prophylaxis for all arthroplasty patients
D. Only provide arthroplasty to patients with hemoglobin A1C's <7
E. Ensure all knee surgeries are performed with therapeutic hypothermia

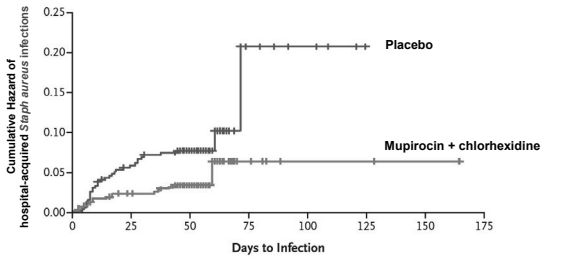
Where do *Staph aureus* infections come from?

80% of hospital acquired *Staph aureus* infections are attributable to patients' own flora (endogenous)

***Staph* Bacteremia**	**Surgical Site Infections**
Nasal isolates compared to blood isolates in 219 patients with *Staph aureus* bacteremia. 82% matched	Nasal isolates compared to wound isolates in 39 patients with *Staph aureus* SSIs. 85% matched
von Eiff, NEJM 2001;344:11-16	Perl, NEJM 2002;346:1871-77

Staph aureus screening & decolonization

917 hospitalized patients with positive Staph aureus nasal screens randomized to decolonization vs placebo
~90% of enrolled patients were on surgical services. Greatest benefit cardiac > ortho > vascular > GI



Bode, NEJM 2010;362:9-17

Targeted vs Universal Decolonization in the ICU

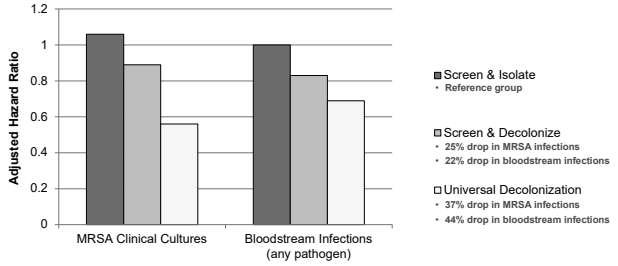
REDUCE MRSA cluster-randomized trial, 74 ICUs, 43 hospitals, 74,256 patients

Screen and Isolate	**Screen and Decolonize**	**Universal Decolonization**
Nasal MRSA screen If positive, isolate	Nasal MRSA screen If positive, isolate & decolonize with CHG baths x 5 days *+ mupirocin x 5 days*	No screening Decolonize **all** patients with CHG baths throughout ICU stay *+ mupirocin x 5 days*

Huang et al. NEJM 2013:368:2255-65

Targeted vs Universal Decolonization in the ICU

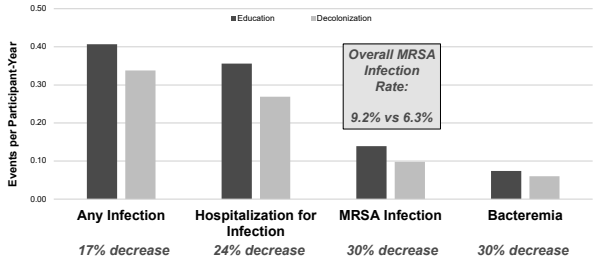
REDUCE MRSA cluster-randomized trial, 74 ICUs, 43 hospitals, 74,256 patients



Huang et al. *NEJM* 2013:368:2255-65

Should we decolonize patients after discharge?

1063 discharged patients colonized with MRSA randomized to education + decolonization vs education alone. Decolonization protocol: CHG mouthwash, CHG body wash, and BID nasal mupirocin x 5d twice a month x 6mo



Huang, *NEJM* 2019;380:638-50

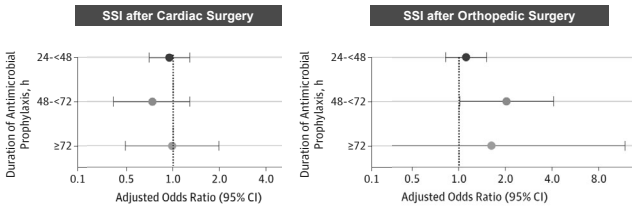
Question #11

An obese 62 yo female smoker with COPD is admitted for elective resection of adenocarcinoma of the left upper lobe. She weighs 132kg. She is intubated and undergoes left upper lobe lobectomy. Cefazolin 3g IV is administered 30mins before incision and every 4 hours during surgery. A chest tube is place on the left side. After surgery she is admitted to the ICU for recovery. How long should cefazolin be continued post-operatively?

A. O-hours – prophylaxis should be stopped after surgery
B. 12-hours
C. 24-hours
D. Until the chest tube is removed
E. Until the patient is extubated

Extending antibiotics beyond surgery does not prevent infections…

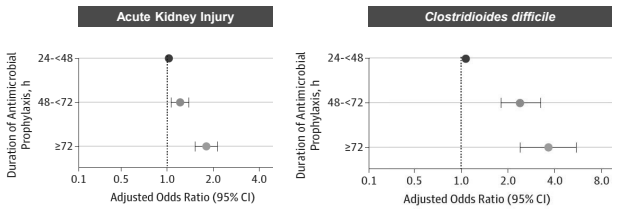
Retrospective analysis of association between duration of peri-operative antibiotic prophylaxis and adverse events in 79,058 patients who underwent orthopedic, colorectal, and vascular procedures, VA hospitals, 2008-2013



Branch-Elliman, *JAMA Surgery* 2019;154:590-598

…but extending antibiotics beyond surgery may be harmful

Retrospective analysis of association between duration of peri-operative antibiotic prophylaxis and adverse events in 79,058 patients who underwent orthopedic, colorectal, and vascular procedures, VA hospitals, 2008-2013



Branch-Elliman, *JAMA Surgery* 2019;154:590-598

Essential Practices to Prevent Surgical Site Infections – Part I

- Administer antimicrobial prophylaxis according to evidence-based practices and standards
- Use parenteral and oral abx prophylaxis before colorectal surgery
- Decolonize patients with an anti-Staphylococcal agent before cardiac and orthopedic procedures (+/- those with prosthetic implants)
- Use an anti-septic vaginal prep for cesareans & hysterectomy
- Do not remove hair at the operative site (unless it interferes with surgery)
- Use skin prep containing a combination of alcohol + an antiseptic
- Maintain normothermia during perioperative period
- Use impervious plastic wound protectors for GI and biliary tract surgery
- Perform intraoperative antiseptic wound lavage
- Control blood-glucose level in the post-operative period

Infection Control & Hospital Epidemiology 2023;44:695-720

Essential Practices to Prevent Surgical Site Infections – Part II

- Perform surveillance for surgical site infections (SSIs)
- Use a checklist and/or bundle to encourage best practices
- Increase the efficiency of surveillance by utilizing automated data
- Provide ongoing SSI rate feedback to surgical and periop personnel
- Measure & provide feedback on compliance with process measures
- Educate surgeons and periop personnel about SSI prevention measures
- Educate patients and their families about SSI prevention as appropriate
- Align SSI prevention practices with evidence-based standards, rules & regulation, and manufacturers' instructions for use
- Observe and review operating room personnel and the environment of care in the operating room and central sterile reprocessing

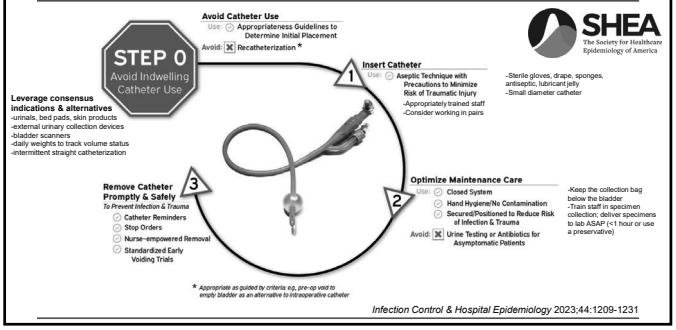
Infection Control & Hospital Epidemiology 2023;44:695-720

Question #12

A 55 year old woman is emergently transferred to your hospital after falling and sustaining a spinal cord injury complicated by paraplegia. She is admitted to the intensive care unit following neurosurgery. Which of the following steps is most likely to reduce her risk of developing a catheter-associated urinary tract infection?

A. Start prophylactic fosfomycin
B. Screen for colonization to inform targeted antibiotic prophylaxis
C. Change the urinary catheter every 7 days
D. Empty the catheter drainage bag before transporting her off the unit
E. Check a urinalysis daily and start pre-emptive antibiotics if she develops pyuria

Essential Practices to Prevent Catheter-Associated UTIs



Infection Control & Hospital Epidemiology 2023;44:1209-1231

Accepted Indications:

- Perioperative use in selected surgeries
- Acute urinary retention or obstruction
- Accurate measurement of urinary output in critically ill patients
- Strict immobilization for trauma or surgery
- Severe perineal and sacral wounds in incontinent patients
- Hospice/comfort care/palliative care

Question #13

A 52 yo woman is admitted to hospital with intermittent epigastric pain. Labwork is notable for elevated ALK, Tbili, and lipase. CT with contrast shows a thickened and dilated gall bladder with stones in the common bile duct. A foley is placed. The patient goes to ERCP for sphincterotomy and gallstone retrieval. Two days later she develops fever and delirium. Blood cultures are positive for carbapenem-resistant Enterobacterales. What sources will you consider for this infection?

A. Healthcare workers with poor hand hygiene
B. The hospital's decorative water fountain
C. A contaminated duodenoscope
D. Contaminated intravenous contrast
E. Failure to remove a foley catheter in a timely fashion

Duodenoscopes

- Notoriously difficult to sterilize
- Meta-analysis of 15 studies sampling duodenoscopes after reprocessing (925 scopes):
  - **16%** still **culture positive** after high level disinfection performed per manufacturers' instructions
  - **9%** still culture positive after **double reprocessing** or gas sterilization
- Many clusters reported

Larsen, *EClinicalMedicine* 2020;25:100451
Forbes, *JAMA Internal Med* 2023;183:191-200

Outbreak Word Associations

Pathogen	Potential Sources
Legionella	Decorative water fountains, cooling units
Pseudomonas	Respiratory care equipment, drains & sinks
Burkholderia	Water heaters & coolers (e.g. ECMO)
Carbapenem-resistant Enterobacterales	Duodenoscopes
Candida auris	Temperature probes
Mycobacterium abscessus	Ice & water machines, other water sources
Mycobacterium chimaera	Cardiac bypass heater-cooler devices
Aspergillus sp.	Construction, plants & flowers

Summary

- Pneumonia is the most common HAI; *C. difficile* the most common pathogen
- Equipment, hands, and clothing are commonly contaminated by bacteria
- Hand hygiene rates are inversely associated with HAI rates
- All respiratory viruses are spread by aerosols. Risk highest with high viral load, proximity, sustained exposure, poor ventilation. Surgical masks decrease risk by ~50%. N95 respirators decrease risk by ~95%+
- Most aerosol generating procedures do not generate aerosols
- Most *C. difficile* is endogenous; activated during medical care in setting of antibiotics, immunosuppressants, frailty. Some hospital transmission too.
- Decolonize *Staph aureus* carriers with lines, before surgery, in the ICU
- Give antibiotic prophylaxis within 60mins before incision; stop after surgery
- Contaminated water, drains, respiratory equipment, and meds can spread water-based pathogens. Leading ICUs working on decreasing water-based care.

32

Syndromes in the ICU that ID Physicians Should Know

Dr. Taison Bell

32 – Syndromes in the ICU that ID Physicians Should Know

Speaker: Taison Bell, MD

Syndromes in the ICU that Infectious Disease Physicians Should Know

Taison D. Bell, MD, MBA
Associate Professor of Medicine, UVA School of Medicine
Division of Pulmonary and Critical Care Medicine
Division of Infectious Diseases and International Health

7/29/2024

- **Disclosures of Financial Relationships with Relevant Commercial Interests**

  - None

Question 1: What proportion of patients in the ICU develop fever during their stay?

A. Less then 5%

B. Between 15-25%

C. Over 50%

D. Everyone. Absolutely everyone

Exam Blueprint: Critical Care Topics ~8-10%

Critical Care Medicine

- Systemic inflammatory response syndrome (SIRS) and sepsis
- Ventilator-associated pneumonias
- Noninfectious pneumonias (eosinophilic and acute respiratory distress syndrome [ARDS])
- Bacterial pneumonias Viral pneumonias
- Hyperthermia and hypothermia
- E-cigarette or vaping product use–associated lung injury (EVALI)

Medical Content Category	% of Exam
Bacterial Diseases	27%
Human Immunodeficiency Virus (HIV) Infection	15%
Antimicrobial Therapy	9%
Viral Diseases	7%
Travel and Tropical Medicine	5%
Fungi	5%
Immunocompromised Host (Non-HIV Infection)	5%
Vaccinations	4%
Infection Prevention and Control	5%
Internal Medicine and Non-Infectious Syndromes	18%
	100%

Question 2

- You are asked to see a 35 year-old woman with a history of seizure disorder 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

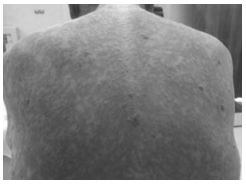
B. Stevens–Johnson syndrome (SJS)/toxic epidermal necrolysis (TEN)

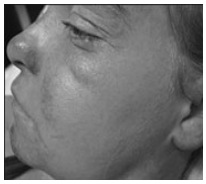
C. DRESS (drug-induced hypersensitivity syndrome)

D. Erythema Multiforme

E. Neuroleptic Malignant Syndrome (NMS)

Morbilliform Rash with Facial Edema and Eosinophilia





32 – Syndromes in the ICU that ID Physicians Should Know

Speaker: Taison Bell, MD

DRESS (drug-induced hypersensitivity syndrome)

Rash Characteristics	Morbilliform involving >50% BSA, inflamed, facial edema, infrequent mucosal involvement
Onset	Usually 1-3 (up to 6) weeks after drug exposure
Other Features	Fever, LAD, other organ involvement in 80% (liver, kidney, pancreas, heart, lung), expansion of CD4/8 T cells → Herpesviridae reactivation (HHV6)
Lab Findings	Eosinophilia, lymphocytosis/lymphopenia, atypical lymphocytes
Classic Meds	Aromatic AEDs (highest with lamotrigine), Vancomycin, Raltegravir, Dapsone and other Sulfas, anti-TB RIPE
DDx	SLE, mycoplasma, viral hepatitis, mononucleosis
Treatment	Withhold offending agent, supportive care Steroids, CsA, IVIg are controversial. Mortality is high

Exanthematous drug eruptions

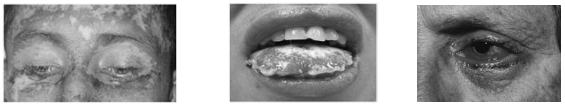
- T-cell-mediated, delayed type IV hypersensitivity reaction
- Diffuse maculopapular rash (morbilliform)
- Highest incidence with aromatic antiseizure medications: carbamazepine, phenytoin, and lamotrigine (1:100)

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

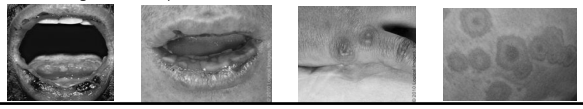
Stevens Johnson and Toxic Epidermonecrolysis



- "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 usually asymptomatic
  - Febrile prodrome in some cases
- Often associated with oral, ocular, and genital mucosal lesions
- Less severe than DRESS or SJS or TEN
- Causes: Infection > Drugs
  - 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

32 – Syndromes in the ICU that ID Physicians Should Know

Speaker: Taison Bell, MD

Question 3

- You are called to the PACU to see a 29-year-old previously healthy male with a fever of 41.6℃ who is 4 hours post-op from an arthroscopy for a rotator cuff injury.
- He initially 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

Malignant Hyperthermia

- Syndrome - Rare (~700 cases/year) but 5-10% mortality
  - Early signs: Steep rise in CO2, tachycarida, tachypnea, muscle rigidity/contraction (masseter spasm)
  - Late signs: Hyperthermia, acidosis, hyperkalemia, cardiac arrythmias
- Genetic defect in the RYR1 or (less commonly) CACNAS1S gene
  - Ca++ transport in skeletal muscle
  - Autosomal dominant
    - (excessive calcium accumulation)
- Triggers
  - Usually < 1 hour after trigger (up to 10 hours)
  - Classic: Volatile anesthetics (halothane, sevoflurane, desflurane), succinylcholine

Neuroleptic Malignant Syndrome (NMS)

- Frequent trigger = haloperidol
  - Any "neuroleptic" (antipsychotic)
  - Lead pipe rigidity
  - Antiemetics such as metoclopramide
  - Withdrawal of antiparkinson drugs (L dopa)
- Onset variable: 1-3 days/within first 2 weeks
  - Time of drug initiation
  - When dose changed
- Management
  - Dantrolene
    - (direct muscle relaxant for up to 10 days)
  - Dopamine agonists (bromocriptine and others)

Serotonin Syndrome

Clinical Characteristics of Serotonin Syndrome	
Pathogenesis	Excess Serotoninergic Activity • Therapeutic drugs, drug interactions, self poisoning
Triggers	• Linezolid = MAO Inhibitor • SSRI inhibitors (Bupropion) • Antiemetics (Granisetron) • Tricyclic antidepressants (amitriptyline)
Clinical Manifestations	• Acute onset (within 24 hrs of new drug/drug change) • Hyper-reflexive>bradyreflexia • Nausea, vomiting, diarrhea, tremors followed by shivering
Treatment	• Withdraw offending medication • Consider benzodiazepines and cyproheptadine

What to Look for on the Exam

	Malignant Hyperthermia	NMS	Serotonin Syndrome
Trigger	Succinylcholine or inhaled halogenated anesthesia	Withdrawal of L Dopa in Parkinsons or Neuroleptic Drugs	SSRIs, Antiemetics, Linezolid, Lithium, Street Drugs
Onset	Rapid onset in perioperative period	Subacute over 1-3 days	6-24 hours of starting a drug or increasing dose
Exam	Masseter spasm, Lead pipe rigidity	Mental status change with dysautonomia, catatonia, mutism, stupor, coma	Shivering, myoclonus, n/v/d, hyper-reflexia, flush skin
Labs	Severe hypercarbia, rhabdomyolysis	CK rise, myoglobinemia	Nothing classic

Hypothermia: <35℃

- 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

32 – Syndromes in the ICU that ID Physicians Should Know

Speaker: Taison Bell, MD

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

Differential Diagnosis of Shock

Ohm's Law →

MAP = CO x SVR

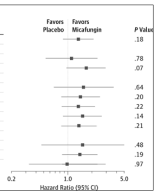
Cardiogenic (flow)
- MI/CHF/Tamponade
- PE
- Tension PTX
- Hypovolemia

Distributive (resistance)
- Sepsis
- Toxic shock syndrome
- Aspiration
- Anaphylaxis
- Neurogenic
- Adrenal insufficiency

Why not empiric antifungal? EMPIRICUS

Muti-center RCT of 260 Adults in ICU
- Non-neutropenic
- Multiorgan failure
- ICU-acquired sepsis
- On MV at least 5d
- At least 4d broad spectrum Abx in prior week
- Multifocal candida colonization

	Micafungin		Placebo			
	Survived at Day 28, No.	Total No.	Survived at Day 28, No.	Total No.	Hazard Ratio (95% CI)	P Value
All patients	87	128	74	123	1.35 (0.87-2.08)	.18
SOFA score						
≤8	51	66	52	68	1.11 (0.53-2.33)	.78
>8	36	62	22	55	1.69 (0.96-2.94)	.07
Admission category						
Surgical	22	34	16	31	1.56 (0.67-3.70)	.64
Medical	65	94	58	92	1.43 (0.83-2.50)	.20
Colonization index ≥0.5[a]	68	101	58	99	1.35 (0.84-2.17)	.22
Corrected colonization index ≥0.4[b]	52	76	45	80	1.52 (0.87-2.63)	.14
Candida score ≥3	64	96	47	85	1.37 (0.83-2.27)	.21
(1→3)-ß-D-glucan, pg/mL[c]						
>250	14	21	14	25	1.52 (0.47-5.00)	.48
>80	58	91	47	84	1.41 (0.85-2.33)	.19
≤80	29	37	27	39	0.98 (0.30-2.94)	.97



JAMA. 2016;316(15):1555-1564

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

32 – Syndromes in the ICU that ID Physicians Should Know

Speaker: Taison Bell, MD

Managing Sepsis

What's the Bottom Line?

- Some recommendations are plausible
  - Fluid resuscitation with 30 cc's/kg crystalloid
  - Vasopressors for MAP goal 65
    - But do not use Dopamine!
- Some are wrong
  - Early goal directed therapy
  - Tight glucose control. Better outcomes <180
- Two are unequivocally true
  - Early effective antibiotics
  - Source control

Other Things

Stress-dose steroids: conflicting data

- CORTICUS/ADRENAL
  - No change in mortality with hydrocortisone
  - **Quicker reversal of shock**
- Annane/APROCCHSS
  - Improved mortality with hydrocort/fludricort
  - **Quicker reversal of shock**

Antiendotoxin and Anticytokine therapy

- No benefit

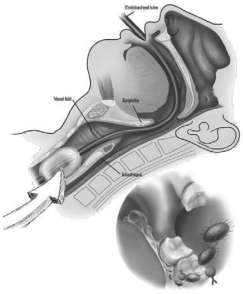
Antithrombosis (Activated Protein C)

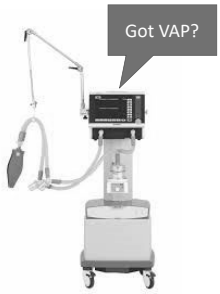
- Taken off the market

Surviving Sepsis Campaign Bundles

3 Hour Bundle	6 Hour Bundle
- Measure lactate level - Draw blood cultures - Administer broad spectrum antibiotics - Administer 30 cc/kg IV crystalloid	- Start vasopressors if MAP <65 despite fluid resuscitation - Reassess volume status if hypotension persists after fluid resuscitation or if initial lactate ≥ mmol/L

Ventilator Associated Pneumonia





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 6

34 year-old woman with opiate use disorder is admitted to the medical ICU for acute respiratory distress syndrome requiring intubation. She has been receiving intravenous daptomycin through a PICC for tricuspid valve endocarditis for the past three weeks. Transthoracic echo is unchanged from prior and chest CT shows bilateral ground glass opacities with scattered areas of consolidation. Blood cultures are negative. Bronchial alveolar lavage shows a predominance of eosinophils with negative cultures.

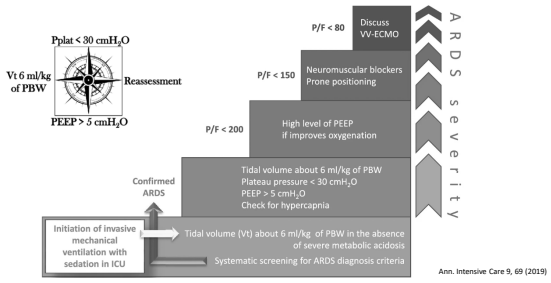
Which of the following is the most likely cause of her respiratory illness?

A. Injection drug use
B. Septic pulmonary emboli
C. Daptomycin
D. Sepsis

Eosinophilic Pneumonia

- Rare disorder characterized by eosinophil infiltration of the pulmonary parenchyma
- Often associated with peripheral eosinophilia
- Many drugs linked: daptomycin, nitrofurantoin, amiodarone, ACE-i's, etc.
- Daptomycin-induced EP: precise mechanism unknown but believed to be related to daptomycin binding to pulmonary surfactant leading to epithelial injury

ARDS Management



Ann. Intensive Care 9, 69 (2019)

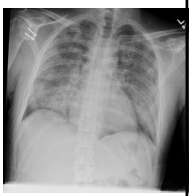
Question 7

A 22-year-old male presents to the ED with a three-week history of cough, shortness of breath, and low-grade fever. His past medical history is unremarkable. There are no sick contacts or recent travel. He went to an urgent care center one week ago and was prescribed levofloxacin but has not improved. ROS is notable for frequent use of e-cigarettes with THC-containing products. Physical examination reveals mild tachycardia, tachypnea, and decreased breath sounds bilaterally. His oxygen saturation is 88% on room air. A chest X-ray shows bilateral diffuse opacities. Laboratory studies reveal an elevated white blood cell count and elevated inflammatory markers.

What is the most likely diagnosis?

A. Community acquired pneumonia
B. Acute respiratory distress syndrome (ARDS)
C. E-cigarette or vaping product use–associated lung injury (EVALI)
D. Tuberculosis
E. Pulmonary embolism

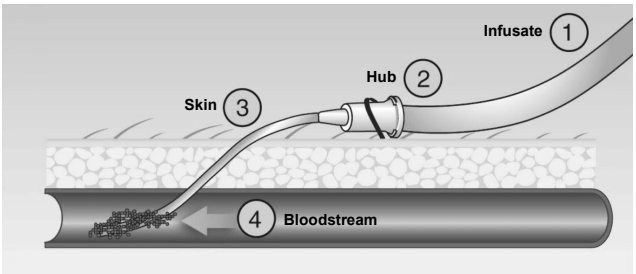
E-cigarette or vaping product use associated lung injury (EVALI)



- Primarily associated with e-cigarettes and vaping products, particularly THC-containing compounds
- Clinical presentation is very similar to community acquired pneumonia
- Exact cause not fully understood but believed to be related to direct lung injury → inflammatory response
- Treatment: supportive care, cessation of e-cigarette use

MMWR. 2019;68(46):1076

CLABSI



32 – Syndromes in the ICU that ID Physicians Should Know

Speaker: Taison Bell, MD

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)

Remove the 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

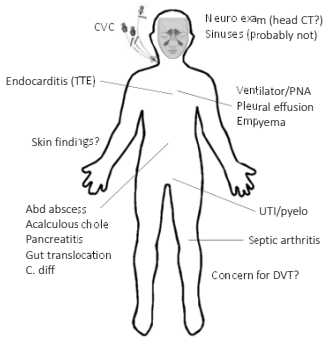
- Not likely testable on the boards
- They have a role, but not well defined

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

Approach

- Run med list
- Consider AI
- Pyrexic syndromes



Thank You

- Good luck!
- Please give feedback
- Contact
  - taison.bell@virginia.edu
  - Twitter/X: @TaisonBell (but not on it as much these days)

33

Pneumonia

Dr. Paul Auwaerter

33 – Pneumonia

Speaker: Paul Auwaerter, MD

IDBR INFECTIOUS DISEASE BOARD REVIEW AUGUST 17-21, 2024

Pneumonia

Paul G. Auwaerter, MD
Sherrilyn and Ken Fisher Professor of Medicine
Clinical Director, Division of Infectious Diseases
Johns Hopkins University School of Medicine

7/1/2024

IDBR INFECTIOUS DISEASE BOARD REVIEW AUGUST 17-21, 2024

- **Disclosures of Financial Relationships with Relevant Commercial Interests**
  - **Consultant: Gilead, Shionogi**
  - **Research Grant: Pfizer**
  - **Ownership Interest: Johnson & Johnson**

Community-acquired Pneumonia: Meta-analysis Traditional culture + PCR for "atypicals" + viruses

Pathogen	Total (%)*
None	4380 (61.3)
Pathogen detected	3279 (48.7)
Etiology Bacterial	
• *S. pneumoniae*	33%
• *H. influenzae*	8.6%
• *S. aureus*	4.9%
• *M. catarrhalis*	2.4%
• Gram negatives	6.0%
• Mycobacteria	1.8%
• Other bacteria	1.94%

- 12 modern studies
  - 2005-2019
  - Inpatient n = 4399
  - In- & outpatient = 2752
  - Outpatient = 0
- Hospital mortality: 12-15%

Shoar and Musher, Pneumonia (2020) 12:11

*Etiologic agents percentages

Community-acquired Pneumonia: Meta-analysis Traditional culture + PCR for "atypicals" + viruses

Pathogen	Total (%)*
Etiology Viral & "Atypicals" And co-infections	
• *Mycoplasma pneumoniae*	8.9%
• *Legionella pneumoniae*	6.2%
• *C. pneumoniae*	2.9%
• *Pneumocystis*	0.2%
• *Influenza*	9.2%
• *Rhinovirus*	11.5%
• Parainfluenza or RSV	9.3%
• Bacterial + viral coinfection	5.9%

- 12 modern studies
  - 2005-2019
  - Inpatient n = 4399
  - In- & outpatient = 2752
  - Outpatient = 0

Shoar and Musher, Pneumonia (2020) 12:11

*Etiologic agents percentages

Case 1

- 35 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

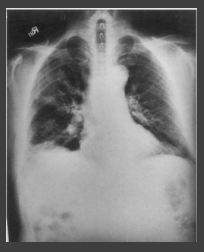
Which antibiotic will lead to the most rapid improvement?

A. Ceftriaxone

B. Gentamicin

C. Doxycycline

D. Trimethoprim/sulfamethoxazole



33 – Pneumonia
Speaker: Paul Auwaerter, MD

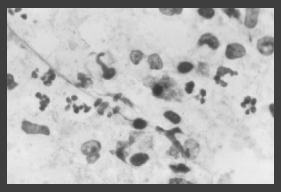
Chlamydia psittaci

- 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

Microbiology

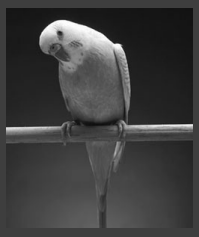
- Two states:
  - Extracellular: infectious, elementary body
    - Bird feces or respiratory secretions → aerosol → human
    - Direct contact
  - Intracellular: replicative



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 burnetti, 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 Microbiol 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	Worse 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 sat 90% on 6L O_2
No lymphadenopathy, no JVD
Lungs: poor air movement, basilar crackles bilaterally
Cor: no murmur
Ext: no edema Skin: no rash

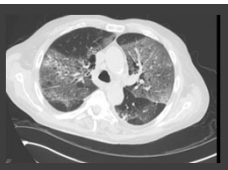
9.5
6.0 — 300K 54%^{N}, 12%^{L}, 24%^{E}

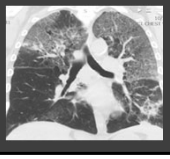
ESR 150 mm/hr NI LFTs
CRP 15 mg/dL (0.0-0.5)

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.

33 – Pneumonia

Speaker: Paul Auwaerter, MD

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

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

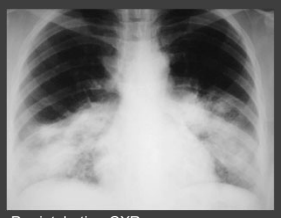
Therapy:
Vancomycin and piperacillin/tazobactam x 3 d

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 pneumophila* 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)

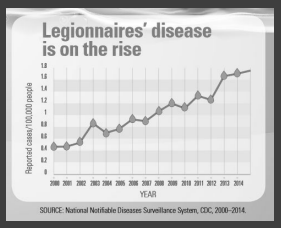
Legionella culture

Culture media: BCYE agar
Small, pearly white colonies

33 – Pneumonia
Speaker: Paul Auwaerter, MD

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



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	FDA approved (2022) in some LRTI multiplex arrays, 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, Legionella Testing and Specimen Collection (accessed 7/10/24)
Avni, J Clin Micro. 2016;54(2):401–11; Muldyermans, Eur J Clin Microbiol Infect Dis 2019 *CDC preferred tests, obtain both in suspected patients

	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

22M landscaper who mows lawns in Ozarks of Arkansas has 5 days of fever, chills and dry cough presenting in early July. He has run over several animal burrows with the mower.

(+) fatigue, myalgia

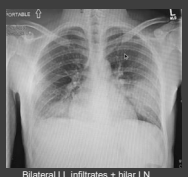
PMH: negative

SH: Occasional MJ

PE: Appears ill, BP 98/70, P 110
T 39.5ºC, PaO_2 = 94%
No lymphadenopathy
Bronchial breath sounds lower fields with crackles bilaterally
No murmur
No hepatosplenomegaly, abdominal tenderness
No rash

Case 4

WBC 18,500 88%N PLT 280K
ALT 267 U/L
CK 3280 U/L


Bilateral LL infiltrates + hilar LN

Consultant. 2020;60(11):27-29.

Select the testing approach most likely to confirm a diagnosis:

A. Respiratory viral panel (RSV, Influenza, SARS-CoV-2)
B. Rickettsia rickettsii acute and convalescent serology
C. Whole blood Ehrlichia chaffeensis PCR
D. Francisella tularensis acute and convalescent serology
E. Blood culture yielding Yersinia pestis

Francisella tularensis

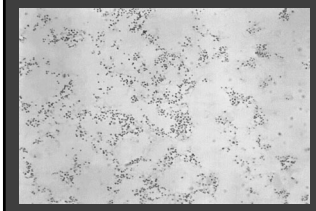

CDC Tularemia reported cases 2011-2020

- Small aerobic Gram negative pleomorphic coccobacillus
- Transmission:
  - US: biting flies (deer flies), ticks
  - Europe: mosquitoes
  - Also: aerosol, contaminated mud/water, infected carcasses, animal bites
- Risk groups:
  - Lab personnel, farmers, landscapers, vets, hunters/trappers, meat handlers
- Bioterrorism agent, Class A
- Inhaled infectious doses: ~10-50 organisms

33 – Pneumonia

Speaker: Paul Auwaerter, MD

Francisella tularensis



Gram stain photomicrograph, CDC

- Small aerobic Gram negative pleomorphic coccobacillus
- Six illness patterns
  - Ulceroglandular (most common ~200 cases/yr)
  - Glandular
  - Oculoglandular
  - Pharyngeal
  - Typhoidal
  - Pneumonic
- Routine cultures often negative or offer incorrect identification
  - Notify lab if suspicious
- Acute/convalescent serology confirms most cases

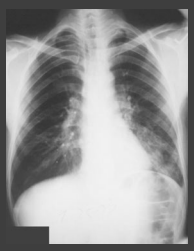
Francisella tularensis

- Differential diagnosis of pneumonic tularemia includes:
  - Plague (*Y. pestis*)
  - Anthrax (*B. anthracis*)
  - Consider bioterrorism
- Treatment
  - Fluoroquinolones
  - Aminoglycosides
    - Streptomycin
    - Gentamicin
  - Tetracyclines (mild-moderate cases)
- Limited data to suggest optimal choices

Nelson CA. CID 2024;78(S1):S15-28

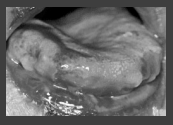
Case 5:

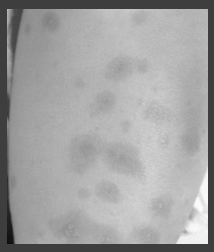
- 18F c/o fever, dry hacking cough, malaise x 3d
- Allergy: erythromycin (N/V)
- Appears well, T38ºC, RR 16, P 80, BP 110/70
  - Oropharynx: normal
  - TMs: normal
  - Chest: some crackles left lower lobe



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)

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	FDA approved, Expensive platforms needed, multiplex	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

- Viruses:
  - Adenovirus
  - Coronaviruses 229E, HKU1, NL63, OC43
  - SARS-CoV-2
  - Human metapneumovirus
  - Rhinovirus/enterovirus
  - Influenza A, A/H1, A/H3, A1-2009, B
  - Parainfluenza 1, 2, 3, 4
  - RSV
- Bacteria
  - *Bordetella parapertussis*
  - *Bordetella pertussis*
  - *Chlamydia pneumoniae*
  - *Mycoplasma pneumonia*

Film Array, NP swab
Multiplex, 22 pathogens
Results in 1 hr

Viruses and some bacteria
Sensitivity: 87, 98-100%
Specificity: 89, 99-100%

Kitano, T. et. al., (2020) J Infect Chemother. 26 (1):82-85

Case 6

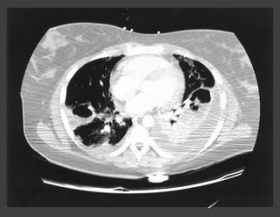
31F fever, cough, myalgia, headache, dyspnea over 1 week ago; February
- No help w/ azithromycin x 3d
- 18 mos daughter, recent bronchitis

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

Era of molecular diagnostics

- Increasing recognition of co-pathogens
  - Multiple viruses
  - Virus + bacteria
- Comprehensive multiplex Lower respiratory panels available, now including *Legionella pneumophila*

- Mixed infections:
  - Johansson CID 2010; 50:202
    - Pathogens detected: 67%
    - Mixed: 12%
  - Jain NEJM 2015;373:415
    - Pathogens detected: 38%
    - Mixed: 3%
- Beware: Positive values from asymptomatic controls
  - Especially viral
  - Prolonged shedding (especially immunocompromised)

33 – Pneumonia

Speaker: Paul Auwaerter, MD