IDBR INFECTIOUS DISEASE BOARD REVIEW LIVE/VIRTUAL

AUGUST 19-23 2023

GW | Office of Continuing Education in the Health Professions

28th Annual

COMPREHENSIVE REVIEW *for* INFECTIOUS DISEASE BOARD PREPARATION

VOLUME 1

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

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

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Agenda Day 1: Saturday, August 19, 2023

#	Start		End	Presentation	Faculty
AM Moderator: Henry Masur, MD					
1	8:30 AM EDT	-	9:00 AM EDT	Introduction	John Bennett, MD and Henry Masur, MD
2	9:00 AM	-	9:15 AM	How to Prepare for the Certification and Recertification, Including the LKA	Helen Boucher, MD
QP1	**9:15 AM**	**-**	**9:45 AM**	**Daily Question Preview: Day 1**	**Henry Masur, MD**
3	9:45 AM	-	10:45 AM	Core Concepts: Microbiology: What You Need to Know for the Exam	Robin Patel, MD
FC1	**10:45- AM**	**-**	**11:00 AM**	**Faculty Q&A**	**Drs. Masur (Moderator), Boucher, and Patel**
4	11:00 AM	-	12:00 PM	Core Concepts: Antibacterial Drugs I Gram Positive Organisms	Helen Boucher, MD
	12:00 PM	-	12:45 PM	Lunch Break	
BR1	**12:45 PM**	**-**	**1:45 PM**	**Board Review Day 1**	**Drs. Masur (Moderator), Boucher, Gandhi, Patel, Pavia, and Tamma**
PM Moderator: David Gilbert, MD					
5	1:45 PM	-	2:45 PM	Core Concepts: Antibacterial Drugs II Gram Negative Organisms	Pranita Tamma, MD
6	2:45 PM	-	3:30 PM	Core Concepts: Antifungal Drugs	John Bennett, MD
7	3:30 PM	-	4:15 PM	Respiratory Viral Infections Including Influenza, Immunocompetent, and Immunocompromised Patients	Andrew Pavia, MD
FC2	**4:15 PM**	**-**	**4:30 PM**	**Faculty Q&A**	**Drs. Gilbert (Moderator), Bennett, Kotton, and Tamma**
PM Moderator: John Bennett, MD					
8	4:30 PM	-	5:15 PM	Skin and Soft Tissue Infections	Helen Boucher, MD
9	5:15 PM	-	5:45 PM	Core Concepts: Antiviral Drugs	Andrew Pavia, MD
10	5:45 PM	-	6:30 PM	Photo Opportunity I: Photos and Questions to Test Your Board Preparation	Rajesh Gandhi, MD
FC3	**6:30 PM**	**-**	**7:00 PM**	**End of the Day Faculty Q&A**	**Drs. Boucher, Gandhi, Patel, Pavia, Kotton, and Tamma**

Agenda Day 2: Sunday, August 20, 2023

#	Start		End	Presentation	Faculty
AM Moderator: Andrew Pavia, MD					
QP2	**8:30 AM EDT**	**-**	**9:00 AM EDT**	**Daily Question Preview Day 2**	**Andrew Pavia, MD**
11	9:00 AM	-	10:00 AM	Clinical Immunology and Host Defense	Steven Holland, MD
12	10:00 AM	-	10:30 AM	Gastrointestinal Disease: Etiologic Agents	Herbert Dupont, MD
	10:30 AM	**-**	**10:45 AM**	**Faculty Q&A**	**Drs. Pavia (Moderator), Dupont, Holland, and Kotton**
13	10:45 AM	-	11:15 AM	Gastrointestinal Disease: Clinical Syndromes	Herbert Dupont, MD
14	11:15 AM	-	12:00 PM	CMV, EBV, HHV6 and HHV8 in Immunocompetent and Immunocompromised Patients	Camille Kotton, MD
	12:00 PM	-	12:30 PM	Lunch Break	
BR2	**12:30 PM**	**-**	**1:30 PM**	**Board Review Day 2**	**Drs. Kotton (Moderator), Aronoff, Bennett, Chambers, Dupont, and Tunkel**
PM Moderator: Andrew Pavia, MD					
15	1:30 PM	-	2:00 PM	Nocardia, Actinomycosis , Rhodococcus, and Melioidosis	David Aronoff, MD
16	2:00 PM	-	3:00 PM	Endocarditis of Native and Prosthetic Devices, and Infections of Pacers and Ventricular Assist Devices	Henry Chambers, MD
17	3:00 PM	-	3:45 PM	Zoonoses	David Aronoff, MD
FC4	**3:45 PM**	**-**	**4:00 PM**	**Faculty Q&A**	**Drs. Pavia (Moderator), Aronoff and Chambers**
18	4:00 PM	-	4:45 PM	Staphylococcal Disease	Henry Chambers, MD
19	4:45 PM	-	5:15 PM	Helicobacter and Clostridioides Difficile	David Aronoff, MD
20	5:15 PM	-	6:00 PM	Brain Abscess, Cavernous Sinus Thrombosis, and Subdural and Epidural Empyema	Allan Tunkel, MD
FC5	**6:00 PM**	**-**	**6:30 PM**	**End of the Day Faculty Q&A**	**Drs. Aronoff, Chambers, Pavia, and Tunkel**

Agenda Day 3: Monday, August 21, 2023

#	Start		End	Presentation	Faculty
AM Moderator: Paul Auwaerter, MD					
QP3	**8:30 AM EDT**	**-**	**9:00 AM EDT**	**Daily Question Preview Day 3**	**Paul Auwaerter, MD**
21	9:00 AM	-	9:30 AM	Sexually Transmitted Infections: Genital Ulcers Diseases (GUD)	Khalil Ghanem, MD
22	9:30 AM	-	10:15 AM	Infections of Upper and Lower Urinary Tract	Barbara Trautner, MD
FC6	**10:15 AM**	**-**	**10:45 AM**	**Faculty Q&A**	**Drs. Auwaerter (Moderator), Ghanem, and Trautner**
AM Moderator: Richard Whitley, MD					
23	10:45 AM	-	11:15 AM	Sexually Transmitted Infections: Other Diseases and Syndromes	Khalil Ghanem, MD
24	11:15 AM	-	12:00 PM	Encephalitis including West Nile and Rabies	Allan Tunkel, MD
	12:00 PM	-	12:30 PM	Lunch Break	
BR3	**12:30 PM**	**-**	**1:30 PM**	**Board Review Day 3**	**Drs. Auwaerter (Moderator), Bell, Dhanireddy, Ghanem, Klompas, and Trautner**
PM Moderator: Paul Auwaerter MD					
25	1:30 PM	-	2:15 PM	Ticks, Mites, Lice, and the Diseases They Transmit	Paul Auwaerter MD
26	2:15 PM	-	3:00 PM	Immunizations: Domestic, Travel, and Occupational	Shireesha Dhanireddy, MD
27	3:00 PM	-	3:45 PM	Epididymitis, Orchitis, and Prostatitis	Barbara Trautner, MD
FC7	**3:45 PM**	**-**	**4:00 PM**	**Faculty Q&A**	**Drs. Auwaerter (Moderator), Dhanireddy, Trautner**
28	4:00 PM	-	4:30 PM	Lyme Disease	Paul Auwaerter, MD
29	4:30 PM	-	5:30 PM	Hospital Epidemiology	Michael Klompas, MD
30	5:30 PM	-	6:15 PM	Syndromes in the ICU that ID Physicians Should Know	Taison Bell, MD
31	6:15 PM	-	6:45 PM	Pneumonia	Paul Auwaerter, MD
FC8	**6:45 PM**	**-**	**7:00 PM**	**End of the Day Faculty Q&A**	**Drs. Auwaerter, Bell, Dhanireddy, Ghanem, Klompas, and Trautner**

Agenda Day 4: Tuesday, August 22, 2023

AM Moderator: Roy Gulick, MD					
#	Start		End	Presentation	Faculty
QP4	8:30 AM EDT	-	9:00 AM EDT	Daily Question Preview Day 4	Roy Gulick, MD
32	9:00-AM	-	9:45 AM	Clinical Manifestations of Human Retroviral Diseases and Slow Viruses	Frank Maldarelli, MD
33	9:45 AM	-	10:30 AM	HIV-Associated Opportunistic Infections I	Henry Masur, MD
34	10:30 AM	-	10:45 AM	HIV Diagnosis	Frank Maldarelli, MD
FC9	10:45 AM	-	11:00 AM	Faculty Q&A	Drs. Gulick (Moderator), Maldarelli, and Masur
35	11:00 AM	-	11:45 AM	Antiretroviral Therapy	Roy Gulick, MD
36	11:45 AM	-	12:00 PM	HIV Drug Resistance	Michael Saag, MD
37	12:00 PM	-	12:45 PM	Antiretroviral Therapy for Special Populations	Roy Gulick, MD
	12:45 PM	-	1:15 PM	Lunch Break	
BR4	1:15 PM	-	2:15 PM	Board Review Day 4	Drs. Gulick (Moderator), Bennett, Bloch, Dorman, Maldarelli, and Saag
PM Moderator: Roy Gulick, MD					
38	2:15 PM	-	3:00 PM	Syndromes that Masquerade as Infections	Karen Bloch, MD
39	3:00 PM	-	3:45 PM	Tuberculosis in Immunocompetent and Immunosuppressed Hosts	Susan Dorman, MD
40	3:45 PM	-	4:30 PM	Non-AIDS-Defining Complications of HIV/AIDS	Michael Saag, MD
FC10	4:30 PM	-	4:45 PM	Faculty Q&A	Drs. Gulick (Moderator), Bloch, Dorman, Maldarelli, and Saag
41	4:45 PM	-	5:30 PM	HIV-Associated Opportunistic Infections II	Henry Masur, MD
42	5:30 PM	-	5:45 PM	Pharyngitis Syndromes Including Group A Strep Pharyngitis	Karen Bloch, MD
43	5:45 PM	-	6:30 PM	Photo Opportunities: Images You Should Know for the Exam	John Bennett, MD
FC11	6:30 PM	-	7:00 PM	End of the Day Faculty Q&A	Drs. Bennett, Bloch, Dorman, Gulick, Maldarelli, and Saag

Agenda Day 5: Wednesday, August 23, 2023

AM Moderator: Kieren Marr, MD					
#	**Start**		**End**	**Presentation**	**Faculty**
44	8:00 AM	-	9:00 AM	Infections in the Neutropenic Cancer Patient and Hematopoietic Stem Cell Recipients	Kieren Marr, MD
45	9:00 AM	-	10:00 AM	Solid Organ Transplantation	Barbara Alexander, MD
FC12	**10:00 AM**	**-**	**10:15 AM**	**Faculty Q&A**	**Drs. Marr (Moderator) and Alexander**
46	10:15 AM	-	11:00 AM	Nontuberculous Mycobacteria in Normal and Abnormal Hosts	Kevin Winthrop, MD
47	11:00 AM	-	12:00 PM	Lots of Protozoa	Edward Mitre, MD
	12:00 PM	-	12:30 PM	Lunch Break	
PM Moderator: John Bennett, MD					
BR5	**12:30 PM**	**-**	**1:15 PM**	**Board Review Day 5**	**Drs. Alexander (Moderator), Marr, Mitre, Nelson, Rose, Winthrop, and Whitley**
48	1:15 PM	-	2:00 PM	Bone and Joint Infections	Sandra Nelson, MD
49	2:00 PM	-	2:30 PM	HSV and VZV in Immuno-competent and Immunocompromised Hosts	Richard Whitley, MD
50	2:30 PM	-	3:15 PM	Worms and More Worms	Edward Mitre, MD
FC13	**3:15 PM**	**-**	**3:30 PM**	**Faculty Q&A**	**Drs. Bennett (Moderator) Mitre, Nelson, and Winthrop**
51	3:30 PM	-	4:15 PM	Fungal Diseases in Normal and Abnormal Hosts	John Bennett, MD
52	4:15 PM	-	4:30 PM	Penicillin Allergies	Sandra Nelson, MD
53	4:30 PM	-	5:15 PM	Kitchen Sink: Syndromes Not Covered Elsewhere	Stacey Rose, MD

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	Acute Hepatitis	David Thomas MD
OL - 4	40 Mins	HIV-Associated Opportunistic Infections III	Henry Masur, MD
OL - 5	40 Mins	HIV-Associated Opportunistic Infections IV	Henry Masur, MD
OL - 6	33 Mins	Other Antibacterial Drugs (Macrolides, TMP, SMX, etc)	Pranita Tamma, MD
OL - 7	45 Mins	Viral and Bacterial Meningitis	Allan Tunkel, MD
OL - 8	60 Mins	Chronic Hepatitis	David Thomas MD
OL – 9	30 Mins	Even More Worms	Edward Mitre, MD
OL – 10	25 Mins	Statistics	Khalil Ghanem, 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	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 W. Michael Scheld, 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
Photo Opportunities	100

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Course Overview

About the Course

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

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

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

Educational Objectives

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

PROGRAM FACILITATORS

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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 2023**."
4. To start using the app, please log in with the email and password emailed to you prior to your arrival.

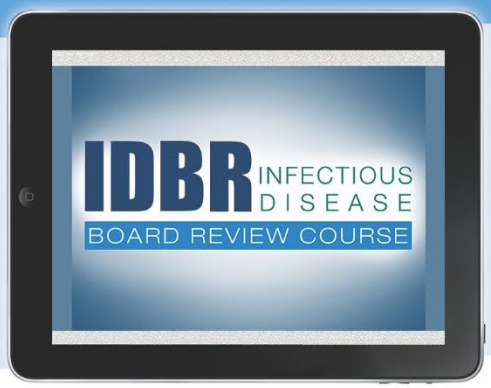
To Access the App via PC:

1. Go to: https://tinyurl.com/IDBR2023.
2. To start using the app, please log in with the email and password emailed to you prior to your arrival.

Please Note:

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

Using the eventScribe® App



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"2023 IDBR"

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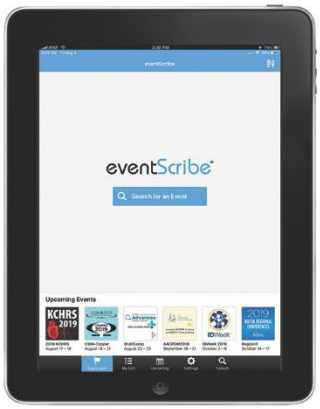

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Event Code **IDBR2023**

3. Take notes on presentation slides

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

No mobile device? No Problem.

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

https://www.tinyurl.com/IDBR2023

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 - 74 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, 2023** in order **for the MOC points to count toward any MOC requirements that are due by the end of 2023.**

CEHP will continue to submit participant completion data for the course until **August 20, 2024**. **No ABIM MOC credit will be awarded for this activity after August 20, 2024**.

OVERVIEW AND INSTRUCTIONS FOR CLAIMING CME CREDIT AND MOC POINTS

LIVE MATERIALS

<table>
<tr><th colspan="2">Live Lectures</th></tr>
<tr><td colspan="2">Participants can receive CME credits and MOC points by listening to the live lectures, participating in the daily ARS questions, and completing the course evaluation.
In addition, the archived recordings of these lectures will be available on or before September 8th and will be organized chronologically by day. You have the option to view them online with the slides with streaming audio, or you can download the MP3 audio file onto your personal computer or mobile device.</td></tr>
<tr><td>CME Hours:

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

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

ONLINE MATERIALS

Credit

The George Washington University School of Medicine and Health Sciences designates this enduring material for a maximum of 74 *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 74 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 74 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, 2023** in order **for the MOC points to count toward any MOC requirements that are due by the end of 2023.**

CEHP will continue to submit participant completion data for the course until **August 20, 2024. No ABIM MOC credit will be awarded for this activity after August 20, 2024**.

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: 55**	**MOC Points: 55**
• There are four (4) sets of 100 board prep questions. • There are one (1) set of 100 photo opportunity questions. • You will see the correct answer and rationale after submitting each question. • You can only go in the forward direction when answering questions. • You cannot go backwards, but you can retake each set of questions as many times as you like.		
Online Primers and Study Guides	**CME Hours: 12**	**MOC Points: 12**
• There are eight (8) study guides and primers that present core material for you to review. • This PDF reviews information that summarizes important topics in photos, tables and short summaries.		

GUIDE TO ONLINE MATERIALS ACCESS

Initial Notification

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

Current Access

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/idbr23/homepage

Important Links

Please note that you must be logged in to access.

- **Main Course Link**: https://cme.smhs.gwu.edu/idbr23/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:** https://cme.smhs.gwu.edu/user/login?destination=my/orders

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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:

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- Herbert L. Dupont, MD
- Rajesh Gandhi, MD
- Khalil G. Ghanem, MD
- David Gilbert, MD
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- Frank Maldarelli, MD
- Edward Mitre, MD
- Sandra Nelson, MD
- Stacey R. Rose, MD, FACP
- Michael Saag, MD
- Pranita Tamma, MD
- Allan R. Tunkel, MD, PhD, MACP

PLANNERS

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

Both planners also resolved financial disclosures

STAFF

- Leticia Hall
- Naomi Loughlin
- Sheena P. King
- Kelly Byrne
- 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, Wellstat • Research: Pfizer
Barbara D. Alexander, MD, MHS	• Consulting: Scynexis, Astellas, Merck, HealthTrackRx, ThermoFisher • Research Grant (Institution): Leadiant • 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 • Consultant: Elsevier
Henry F. Chambers, MD	• Equity: Moderna, Merck • Data Monitoring Committee: Merck • Medicalexpert, product liability: Lilly • Medical expert, patent dispute: Nexus Pharmaceuticals
Michael Klompas, MD	• Grant Funding: Centers for Disease Control and Prevention, Agency for Healthcare Research and Quality, Mass Department of Public Health • Royalties: UpToDate
Camille Kotton, MD	• Consulting: Hookipa (CMV Vaccine trial), Merck (CMV), Takeda (CMV), Natera • Scientific Advisory Board: Roche Diagnostics, ResTORBio, Evrys • Research Funding: Beigene • Speaker: Oxford Immunotec
Kieren A. Marr, MD	• Consulting: Cidara Therapeutics • Employment: Sfunga Therapeutics • Ownership Interests: Pearl Diagnostics, Sfunga Therapeutics

Robin Patel, MD	• Contracted Research: ContraFect, TenNor Therapeutics Limited, BioFire • Consulting: PhAST, Torus Biosystems, Day Zero Diagnostics, Mammoth Biosciences, HealthTrackRx, Netflix, Abbott Laboratories, Oxford Nanopore Technologies, and CARB-X • Patent: Bordetella pertussis/parapertussis PCR; a device/method for sonication; an anti-biofilm substance • Mayo Clinic and Dr. Patel have a relationship with Adaptive Phage Therapeutics and Pathogenomix
Andrew T. Pavia, MD	• Commercial Interests: Antimicrobial Therapy Inc, WebMD, Merck and Company • Consulting: GlaxoSmithKline
David L. Thomas, MD, MPH	• Data and Safety Monitoring Board: Merck • Advisory Board: Merck, Excision Bio
Barbara W. Trautner, MD	• Consulting: Genentech (Covid-related research) • Research Funding: Genentech
Richard J. Whitley, MD	• Member of the Board of Directors and the Health Policy Advisory Board: Gilead Sciences • Chairperson: NIAID Covid-19 Vaccine DSMB, Merck Letermovir DMC and GSK IDMC (Zoster) • Scientific Advisory Board: Treovir, LLC, Altesa Biosciences • Member of the Board of Directors: Evrys Bio, Virios Therapeutics
Kevin L. Winthrop, MD	• Research: Insmed • Consulting: Insmed, Spero, Red Hills, Paratek, AN2

Agenda Day 1: Saturday, August 19, 2023

#	Start		End	Presentation	Faculty
AM Moderator: Henry Masur, MD					
1	8:30 AM EDT	-	9:00 AM EDT	Introduction	John Bennett, MD and Henry Masur, MD
2	9:00 AM	-	9:15 AM	How to Prepare for the Certification and Recertification, Including the LKA	Helen Boucher, MD
QP1	**9:15 AM**	**-**	**9:45 AM**	**Daily Question Preview: Day 1**	**Henry Masur, MD**
3	9:45 AM	-	10:45 AM	Core Concepts: Microbiology: What You Need to Know for the Exam	Robin Patel, MD
FC1	**10:45- AM**	**-**	**11:00 AM**	**Faculty Q&A**	**Drs. Masur (Moderator), Boucher, and Patel**
4	11:00 AM	-	12:00 PM	Core Concepts: Antibacterial Drugs I Gram Positive Organisms	Helen Boucher, MD
	12:00 PM	-	12:45 PM	Lunch Break	
BR1	**12:45 PM**	**-**	**1:45 PM**	**Board Review Day 1**	**Drs. Masur (Moderator), Boucher, Gandhi, Patel, Pavia, and Tamma**
PM Moderator: David Gilbert, MD					
5	1:45 PM	-	2:45 PM	Core Concepts: Antibacterial Drugs II Gram Negative Organisms	Pranita Tamma, MD
6	2:45 PM	-	3:30 PM	Core Concepts: Antifungal Drugs	John Bennett, MD
7	3:30 PM	-	4:15 PM	Respiratory Viral Infections Including Influenza, Immunocompetent, and Immunocompromised Patients	Andrew Pavia, MD
FC2	**4:15 PM**	**-**	**4:30 PM**	**Faculty Q&A**	**Drs. Gilbert (Moderator), Bennett, Kotton, and Tamma**
PM Moderator: John Bennett, MD					
8	4:30 PM	-	5:15 PM	Skin and Soft Tissue Infections	Helen Boucher, MD
9	5:15 PM	-	5:45 PM	Core Concepts: Antiviral Drugs	Andrew Pavia, MD
10	5:45 PM	-	6:30 PM	Photo Opportunity I: Photos and Questions to Test Your Board Preparation	Rajesh Gandhi, MD
FC3	**6:30 PM**	**-**	**7:00 PM**	**End of the Day Faculty Q&A**	**Drs. Boucher, Gandhi, Patel, Pavia, Kotton, and Tamma**

01

Introduction

Drs. Bennett and Masur

01 – Introduction

Speaker: John Bennett, MD and Henry Masur, MD

IDBR INFECTIOUS DISEASE BOARD REVIEW LIVE/VIRTUAL AUGUST 19-23 2023

Introduction

Henry Masur, MD
Jack Bennett, MD

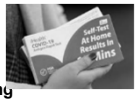
7/28/2023

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!!!

Covid Precautions

- **Self Administered covid tests on day 0 and day 3**
  - Registration includes one *I Health* kit with two tests: more available if needed
  - you tube instructions: https://www.youtube.com/watch?v=_juFqYI25I
  - 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**
- **Masks encouraged in lecture room when not eating/drinking**
- **Sodas and coffee allowed in conference room**
- **Eating: encouraged to occur outside conference room**



Video, Audio, Online Materials

- **All Materials Are Available On Website until December 2024**
  - Syllabus
    - Current lectures will be replaced on e-version with the slides "as presented"
      - (in case there are minor changes or answers included that were absent from syllabus)
  - Corrections, answers to daily questions and other material will be added daily to the website during course and later as appropriate ("Online Materials" tab)

Components of the Hybrid Course

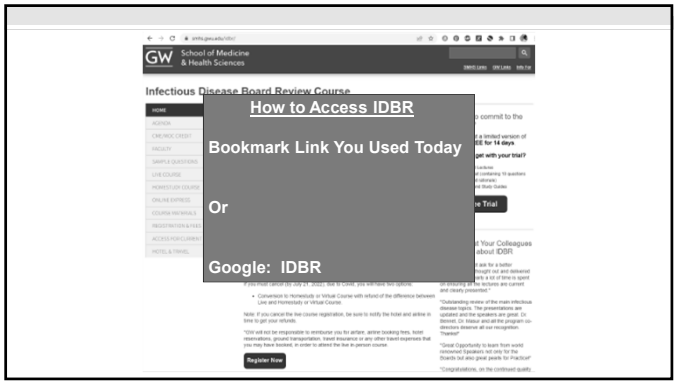
• **Preview Questions**	**Live**
• **Lectures**	**Live**
• **Faculty interaction sessions**	**Live**
• **"Lunch" Board Review Sessions**	**Live**
• **Scoring for all your ARS responses** – Polling/Real Time – Comparison to group metrics	**Live**

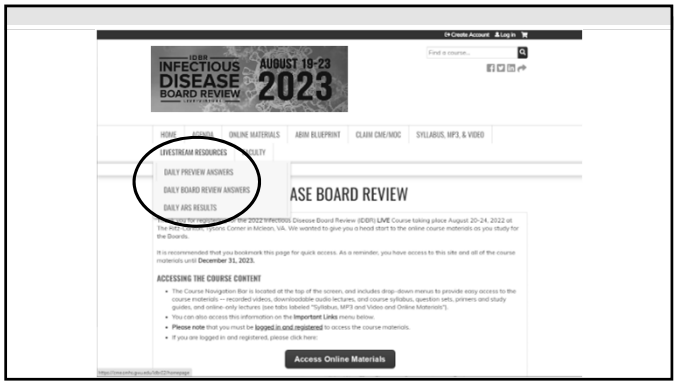
Components of the Hybrid Course

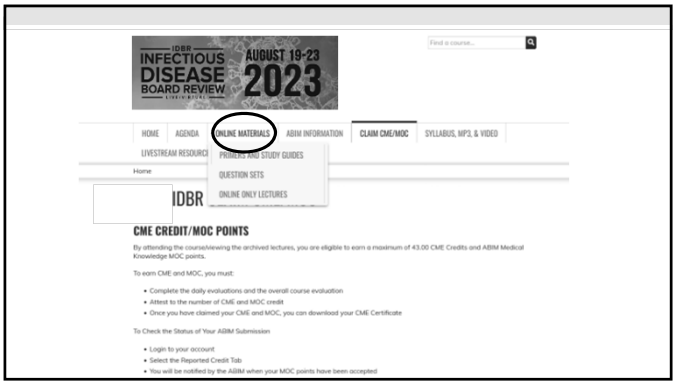
- **Virtual Audience Is *Permanently Muted* on Course Site**
  - **For questions use Q and A function**
  - **For social comments to your friends use Chat Box**
- **Live Audience Can Go to Microphone to Ask Questions**
  - **Can also use Q and A function**

01 – Introduction

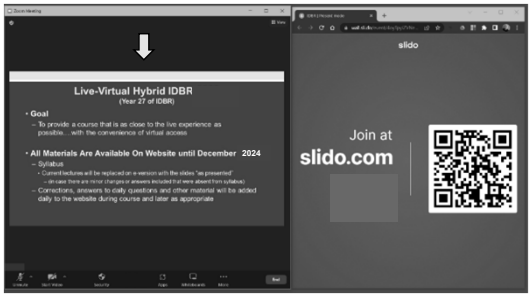
Speaker: John Bennett, MD and Henry Masur, MD







You Need One Window for Zoom and Second Window For Slido

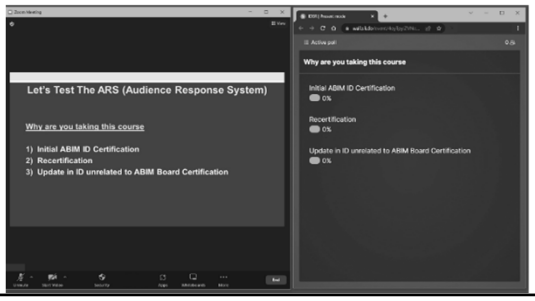


01 – Introduction

Speaker: John Bennett, MD and Henry Masur, MD

Look Up Results Each Day By SLIDO Log In

Zoom / Slido Polling



IDBR APP

- **Download the IDBR App from Apple store or Google Play store**
  - Download Eventscribe
  - Search for course by entering "**2023IDBR**"
  - Log in with the email and password that was emailed to you
  - Problems: email info@idboardreview.com or call (202) 994-4285
- **You can use this app during the course, or until 12/2024, on your cell phone or tablet to look at the syllabus**

Which Will You Be?

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
- **Use the ARS System to Answer Questions**
  - To stay awake, be engaged and competitive!
  - Answer the questions and see how you compare to your peers

IDBR Program for Certification/Recertification Preparation

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

- **Live/Virtual course for 5.0 days**
  - **Live Board Review Questions**
  - **Rationales and daily scores published online by pin # at end of each day**
- **Online Board Review Type Questions**
  - **400 Online questions with rationales**
- **Online Primers (Tables or Charts or Photos)**
  - **Clinical Microbiology**
  - **Resistance: Antibacterial, Antifungal, Antiviral, HIV**
  - **Skin Ulcers**
  - **Rickettsia**
- **Online Recordings of Live 2023 Lectures (posted ASAP- within a few days to 2 wks after course)**
  - **Listen to audio by MP3 (download and transfer to any device)**
  - **Watch slides while listening to synchronized audio**
- **Online Only Lectures**
  - **Talks we wished we had time for during these 5.0 virtual days**
  - **Equally important as live lectures**

01 – Introduction

Speaker: John Bennett, MD and Henry Masur, MD

Accessing The Course

- **Problems accessing lectures or chat room?**
  - **Telephone help line: (202) 994-4285**
  - **Email help hotline: info@idboardreview.com**
  - **Naomi Loughlin**
    - **nbl7396@gwu.edu**
    - **(202) 994-4509 (office)**
- **Faculty welcome your questions**
  - **Send email to info@idboardreview.com or use Q&A feature**

CME and MOC
Total Possible: 117 CME and 117 MOC

- **CME**
  - **You must fill out lecture evaluations (via IDBR website)**
  - **You must request CME (via IDBR website)**
  - No pre-test or post-test
  - Total possible hours - 117
    - Lectures - 43
    - Enduring Material - 74 (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)

IDBR Directors and Co-Directors



Richard Whitley
University of Alabama


Andy Pavia
University of Utah


Kieren Marr
Johns Hopkins


Trip Gulick
Weill Cornell


Paul Auwaerter
Johns Hopkins


David Gilbert
University of Oregon

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CE Coordinator


Naomi Loughlin
IDBR Program Coordinator


Dorothy Martinez
Live Course Manager


Kelly Byrne
IDBR Lead Manager


Mike D'Anthony
Recording


Mark LaBue
AV Director

Advice from Jack Bennett MD

Let's Test the ARS (Audience Response System)

<u>Why are you taking this course</u>

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 on line materials have you looked at prior to the course

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

Let's Begin!

The End

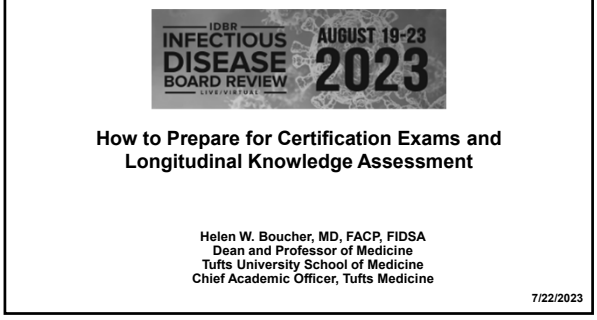
02

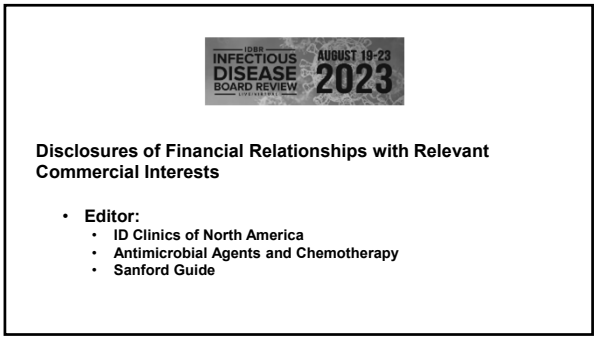
How to Prepare for the Certification, Recertification, or Check-in Exam

Dr. Helen Boucher

02 – How to Prepare for Certification Exams and Longitudinal Knowledge Assessment

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

Times are Changing at ABIM! Infectious Diseases Certification

- Initial Certification Exam – no change
- Maintenance of Certification Options:
  - Every 10 year MOC exam
  - 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/

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02 – How to Prepare for Certification Exams and Longitudinal Knowledge Assessment

Speaker: Helen Boucher, MD

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

Enrollment for the LKA **opens 12/1/22 and closes 6/30/23.**

QUARTER	OPENS	CLOSES
1	1/1/23	3/31/23 at 11:59 p.m. ET
2	4/1/23	6/30/23 at 11:59 p.m. ET
3	7/1/23	9/30/23 at 11:59 p.m. ET
4	10/1/23	12/31/23 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

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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**

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**

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02 – How to Prepare for Certification Exams and Longitudinal Knowledge Assessment

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

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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

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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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02 – How to Prepare for Certification Exams and Longitudinal Knowledge Assessment

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*

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Exam Content

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

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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

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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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02 – How to Prepare for Certification Exams and Longitudinal Knowledge Assessment

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**

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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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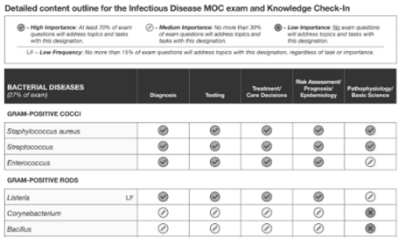
Pass rates 1st-time Takers-Initial certification

Year	# of Examinees	Pass Rate
2008		86%
2009		93%
2010	359	91%
2011	348	96%
2012	342	95%
2013	364	87%
2014	361	86%
2015	347	94%
2016	348	98%
2017	339	97%
2018	338	98%
2019	362	98%
2020	364	94%
2021	372	92%
2022	379	94%

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

29

How is MOC Content Different?



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

30

02 – How to Prepare for Certification Exams and Longitudinal Knowledge Assessment

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%

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

31

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.)

32

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

Dr. Helen Boucher
XXXXXXXXXXXXXX
XXXXXXXXXXXXXX
XXXXXXXXXXXXXX

35

Appendix

36

02 – How to Prepare for Certification Exams and Longitudinal Knowledge Assessment

Speaker: Helen Boucher, MD

Exam Content

- More specific details of content can be found on ABIM website.

For example……

37

Bacterial Diseases (27%)*

	Approximate % of total exam
• Gram-positive cocci	4.5%
• Gram-positive rods	<2%
• Gram-negative cocci/bacilli	2%
• Gram-negative rods	2.5%
• Anaerobes	2.5%
• Actinomycetes	<2%
• Mycobacteria	5% etc.

* percentages describe content of typical exam and are approximate

38

Bacterial Diseases (27%) - details

	Approximate % of total exam
• Gram-positive rods	<2%

Which may include:

Listeria
Corynebacterium
Bacillus
Erysipelothrix

39

Bacterial Diseases (27%) - details

	% of total exam
• Syndromes with bacterial pathogens	3%

Which may include:

– Head and neck, Respiratory, Gastrointestinal, Ophthalmologic, Genitourinary, Dermatologic (including skin and soft tissue infections), Musculoskeletal, Neurologic, Cardiovascular

40

HIV Infection (15%)

	Approximate % of exam
• **Epidemiology**	**<2%**
• **Pathogenesis**	**<2%**
• **Laboratory testing**	**<2%**
• **HIV treatment regimens**	**4.5%**
• **Opportunistic conditions**	**5%**
• **Malignancies**	**<2%**
• **Immune reconstitution (IRIS)**	**<2%**
• **Other complications of HIV**	**2%**
• **Related issues**	**<2%**

41

HIV Infection (15%) - details

	Approximate % of exam
• **Other complications of HIV**	**2%**

Which may include:

Thrombocytopenic disorders
Hypercoagulability, Castelman's disease
HIV infection of specific organs
Endocrine manifestations

- **Related issues** **<2%**

Which may include:

Substance abuse, Organ transplantation, Primary care, Non-HIV-related complications more common in HIV

42

02 – How to Prepare for Certification Exams and Longitudinal Knowledge Assessment

Speaker: Helen Boucher, MD

Viral Diseases (7%)

	Approximate % of exam
• DNA Viruses	4%
• RNA Viruses	2.5%
• Prions	<2%

43

General Medicine, Critical Care and Surgery (18%)

Approximate % of exam

- **General Internal Medicine: 7.5%**
  Malignancies, Hemophagocytic Syndrome, Collagen vascular and autoimmune disorders, Dermatologic disorders, , Bites, stings and toxins, Non-infectious central nervous system disease, Drug fever, Ethical and legal decision making.
- **Critical Care Medicine: 8%**
  SIRS and sepsis, Ventilator-assoc. pneumonias, Non-infectious pneumonias (ARDS), Hyperthermia and hypothermia, Near drowning and Scedosporium (Pseudallescheria) infection

44

Infection Prevention and Control (5%) More details on website, e.g.

Approximate % of exam

- **Applied epidemiology and biostatistics <2%**
  Outbreak investigation, Healthcare quality improvement, Informatics
- **Prevention of HAIs in special patients <2%**
  Obstetrics, Spinal cord injury, Neoplastic diseases, Organ transplant, Stem cell transplant.

45

Fungi (5%)

	Approximate % of total exam
• Yeasts, Endemic mycoses, Molds	<2% each
• Superficial / subcutaneous mycoses Mycetoma, Chromoblastomycosis, Malassezia, Dermatophytes	<2%
• Therapy	<2%
• Pneumocystis	<2%
• Therapy	<2%
• Diagnostic testing*	<2%
• Syndromes	<2%

*histopathology, culture, nonculture methods

46

Other

- **Pharm and OPAT 2.5%**
- **Note:**
  <2% of 240 = about 5 questions

47

QP1

Daily Question Preview 1

Dr. Henry Masur (Moderator)

QP1 – Daily Question Preview: Day 1

Moderator: Henry Masur, MD

IDBR INFECTIOUS DISEASE BOARD REVIEW LIVE/VIRTUAL AUGUST 19-23 2023

Daily Question Preview: Day 1

Moderator: Henry Masur, MD, FIDSA, MACP

8/2/2023

PREVIEW QUESTION INFECTIOUS DISEASE BOARD REVIEW 2023

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 INFECTIOUS DISEASE BOARD REVIEW 2023

1.2 **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**

1 of 2

PREVIEW QUESTION INFECTIOUS DISEASE BOARD REVIEW 2023

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

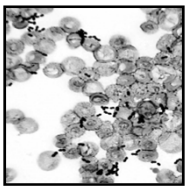
	Cefazolin	Cefotaxime	Ceftazidime	Piperacillin/ tazobactam	Imipenem	Aztreonam
A)	R	S	S	S	S	S
B)	R	R	R	S	S	R
C)	R	R	R	R	S	R
D)	R	R	R	R	R	R

1 of 2

PREVIEW QUESTION INFECTIOUS DISEASE BOARD REVIEW 2023

1.4

- **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.**



1 of 3

PREVIEW QUESTION INFECTIOUS DISEASE BOARD REVIEW 2023

1.4 **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

2 of 3

QP1 – Daily Question Preview: Day 1

Moderator: Henry Masur, MD

PREVIEW QUESTION INFECTIOUS DISEASE BOARD REVIEW 2023

1.5 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 INFECTIOUS DISEASE BOARD REVIEW 2023

1.6 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.

1 of 3

PREVIEW QUESTION INFECTIOUS DISEASE BOARD REVIEW 2023

1.6 Which of the following would be most appropriate?

A) Voriconazole

B) Anidulafungin

C) Fluconazole

D) Liposomal amphotericin B

E) Itraconazole

2 of 3

PREVIEW QUESTION INFECTIOUS DISEASE BOARD REVIEW 2023

1.7 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.

1 of 3

PREVIEW QUESTION INFECTIOUS DISEASE BOARD REVIEW 2023

1.7 The most probable cause was:

A) porphyria cutanea tarda

B) graft versus host disease

C) drug interaction

D) voriconazole

E) Bactrim allergy

2 of 3

PREVIEW QUESTION INFECTIOUS DISEASE BOARD REVIEW 2023

1.8

- 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.

1 of 3

QP1 – Daily Question Preview: Day 1

Moderator: Henry Masur, MD

PREVIEW QUESTION INFECTIOUS DISEASE BOARD REVIEW 2023

1.8 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

2 of 3

PREVIEW QUESTION INFECTIOUS DISEASE BOARD REVIEW 2023

1.9

- 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 2023

1.9 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 2023

1.10

- 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

1 of 3

PREVIEW QUESTION INFECTIOUS DISEASE BOARD REVIEW 2023

1.10 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

2 of 3

PREVIEW QUESTION INFECTIOUS DISEASE BOARD REVIEW 2023

1.11 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 INFECTIOUS DISEASE BOARD REVIEW 2023

1.11 **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 INFECTIOUS DISEASE BOARD REVIEW 2023

1.12 **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***

*Talan, D. CID 2003; 37: 1481

1 of 3

PREVIEW QUESTION INFECTIOUS DISEASE BOARD REVIEW 2023

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

A) *Viridans streptococci*

B) *Eikenella corrodens*

C) *Peptostreptococcus*

D) *Fusobacterium species*

2 of 3

PREVIEW QUESTION INFECTIOUS DISEASE BOARD REVIEW 2023

1.13 **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.**

1 of 4

PREVIEW QUESTION INFECTIOUS DISEASE BOARD REVIEW 2023

1.13 **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**

2 of 4

PREVIEW QUESTION INFECTIOUS DISEASE BOARD REVIEW 2023

1.13 **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*

3 of 4

QP1 – Daily Question Preview: Day 1

Moderator: Henry Masur, MD

PREVIEW QUESTION INFECTIOUS DISEASE BOARD REVIEW 2023

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

A) Ceftolozane-tazobactam

B) Ceftazidime-avibactam

C) Meropenem-vaborbactam

D) Imipenem-cilastatin-relebactam

1 of 2

PREVIEW QUESTION INFECTIOUS DISEASE BOARD REVIEW 2023

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

A) Ceftolozane-tazobactam

B) Ceftazidime-avibactam

C) Meropenem-vaborbactam

D) Imipenem-cilastatin-relebactam

1 of 2

03

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

Microbiology Questions That Could be on the Exam

Dr. Robin Patel

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

Speaker: Robin Patel, MD

IDBR INFECTIOUS DISEASE BOARD REVIEW LIVE/VIRTUAL AUGUST 19-23 2023

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

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

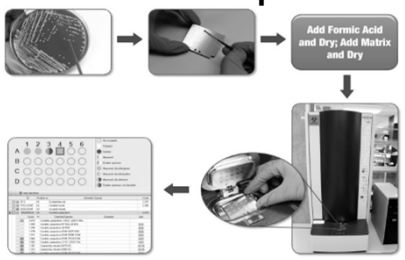
6/19/2023

INFECTIOUS DISEASE BOARD REVIEW AUGUST 19-23 2023

Disclosures of Financial Relationships with Relevant Commercial Interests

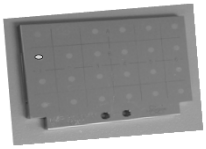
- **Contracted Research: ContraFect, TenNor Therapeutics Limited, and BioFire**
- **Consultant: PhAST, Torus Biosystems, Day Zero Diagnostics, Mammoth Biosciences, HealthTrackRx, Netflix, Abbott Laboratories, Oxford Nanopore Technologies, and CARB-X**
- **Mayo Clinic and Dr. Patel have a relationship with Adaptive Phage Therapeutics and Pathogenomix**
  Patents: Bordetella pertussis/parapertussis PCR; device/method for sonication; anti-biofilm substance

MALDI ToF Mass Spectrometry

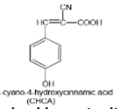


MAYO CLINIC

MALDI ToF Mass Spectrometry



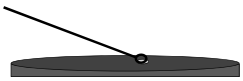
1. **Add colony**
2. **Add matrix (1-2 µl)**



α-cyano-4-hydroxycinnamic acid (CHCA)

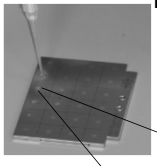
Dissolved in acetonitrile (50%) & 2.5% trifluoroacetic acid

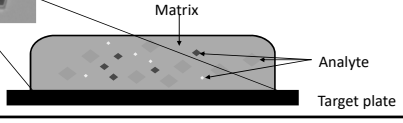
3. **Dry – room air 5 min**



MAYO CLINIC

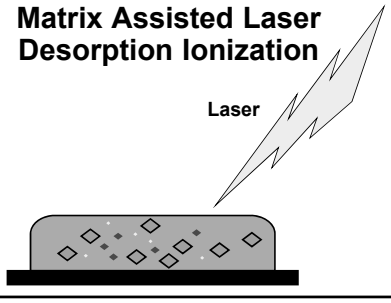
Matrix Assisted Laser Desorption Ionization





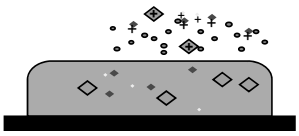
MAYO CLINIC

Matrix Assisted Laser Desorption Ionization



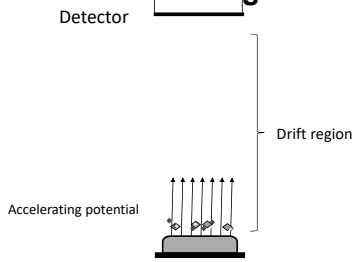
MAYO CLINIC

Matrix Assisted Laser Desorption Ionization



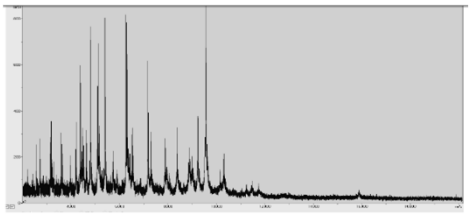
MAYO CLINIC

Time of Flight



MAYO CLINIC

Mass Spectrum Generated Compared with Library (Database)



QUESTION #1

INFECTIOUS DISEASE BOARD REVIEW 2023 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 (+/-)
- *Burkholdheria pseudomallei* (+/-)
- *Campylobacter* species
- *Francisella tularensis* (+/-)
- *Helicobacter pylori*
- *Legionella* species
- *Mycoplasma* species (+/-)
- *Ureaplasma* species

QUESTION #2

INFECTIOUS DISEASE BOARD REVIEW 2023 PREVIEW QUESTION

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

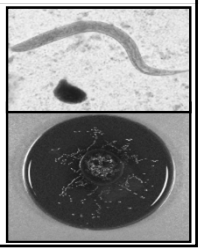
Which of the following, if present in a clinical specimen, poses a hazard for laboratory personnel?

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)**



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

Speaker: Robin Patel, MD

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	Luminex GPP	BioFire GIP
Number of targets	8	14	22
Campylobacter species	✓	✓	✓
Salmonella species	✓	✓	✓
Shigella species/Enteroinvasive *E. coli*	✓	✓	✓
Vibrio species	✓	✓	✓
Yersinia enterocolitica	✓	✓	✓
Escherichia coli 0157		✓	✓
Enterotoxigenic *E. coli*		✓	✓
Enteropathogenic *E. coli*			✓
Enteroaggregative *E. coli*			✓
Plesiomonas shigelloides			✓
Shiga toxin-producing *E. coli*	✓	✓	✓
Clostridioides difficile		✓	✓
Norovirus	✓	✓	✓
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
- HHV6 & CMV may not be clinically significant

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 varricola	✓	
Legionella pneumophila	✓	✓
Moraxella catarrhalis	✓	✓
Morganella morganii	✓	
Mycoplasma pneumoniae	✓	✓
Proteus spp.	✓	✓
Pseudomonas aeruginosa	✓	✓
Serratia marcescens	✓	✓
Staphylococcus aureus	✓	✓
Stenotrophomonas maltophilia	✓	
Streptococcus agalactiae		✓
Streptococcus pneumoniae	✓	✓
Streptococcus pyogenes		✓

	Curetis Unyvero	BioFire
Viruses		
Influenza A		✓
Influenza B		✓
Respiratory Syncytial Virus		✓
Human Rhinovirus/Enterovirus		✓
Human Metapneumovirus		✓
Parainfluenza virus		✓
Adenovirus		✓
Coronavirus (non-SARS-CoV)		✓
SARS-CoV-2		✓
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*		✓

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 BCID2	VERIGENE®	GenMark$_{dx}$	
		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 BCID2	VERIGENE®	GenMark$_{dx}$	
		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

MAYO CLINIC

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

	FilmArray BCID2	VERIGENE®		GenMark$_{dx}$	
		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 BCID2	GenMark$_{Dx}$		
		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

- Methicilllin resistance mediated by *mecA* (or rarely *mecC*) gene products
  - Penicillin binding protein (PBP) target altered (PBP2a)
    - Confers resistance to all available β-lactams (except ceftaroline)
    - Even if staphylococci that are methicillin-resistant *appear* susceptible to these other β-lactams, they are not effective
- Oxacillin or cefoxitin tested
- *mecA/C* and MREJ specific for *Staphylococcus aureus*
- For serious infections, susceptibility to oxacillin confirmed using PBP2a testing or nucleic acid amplification test (NAAT) to detect *mecA* (and *mecC*)

MAYO CLINIC

T2Direct Diagnostics
Direct from Blood

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

QUESTION #6

- **A 52 year old woman receives a liver transplant (CMV D^+/R^-) at your medical center.**
- **Seven months later (after she has completed a course of valganciclovir), she develops fever and diarrhea and is found to have a CMV viral load of 20,000 IU/ml.**
- **In addition to treating the patient with intravenous ganciclovir and performing a colonoscopy to assess for CMV colitis, you recommend follow-up CMV viral load testing.**

QUESTION #6

How often should this test be performed?

A. Daily
B. Twice a week
C. Weekly
D. Every two weeks
E. Monthly

OPTIMAL FREQUENCY CMV VIRAL LOAD TESTING

- **Weekly viral load testing sufficient to document antiviral response, antiviral resistance emergence**
  - **$T_{1/2}$ virus ~5-8 days**
  - **May rise 1st few days on therapy**
  - **Obtain baseline viral load day therapy started**
- **Treatment**
  - **Until viral clearance, symptom resolution and 2 week minimum**
- **Changes >3-fold (>0.5 log)**
  - **Biologically important changes in viral replication**
- **Preemptive treatment → weekly viral load testing**

QUESTION #7

You are consulted to advise on the course of action for a 57 year old female liver transplant recipient (transplant for alcoholic steatohepatitis; CMV D^+/R^+) who has a whole blood HHV-6 viral load of $3.6x10^6$ copies/ml at three months post-transplant. The test was performed because of a report of subjective fever of four days' duration. She has no other new symptoms. The patient received one month of acyclovir prophylaxis post-transplant and is currently receiving mycophenolate mofetil, prednisone and trimethoprim-sulfamethoxazole. Her post-transplant course was complicated by one episode of treated rejection on day 30 post transplant. Physical examination is unremarkable and she is afebrile.

QUESTION #7

Which of the following would you recommend?

A. Intravenous ganciclovir
B. Oral valganciclovir
C. Oral acyclovir
D. Intravenous foscarnet
E. No antiviral therapy is indicated

CHROMOSOMALLY INTEGRATED HUMAN HERPESVIRUS-6

- High HHV-6 levels in whole blood
  - (>5.5 $\log_{10}$ copies/ml)
  - Suggest chromosomally integrated HHV-6
- 1:1 ratio of viral to human genomes

Pellett et al. Rev Med Virol. 2012;22:144-55

QUESTION #8

A 65 year old man has multiple blood cultures positive for *Pseudomonas aeruginosa* resistant to amikacin, gentamicin, tobramycin, aztreonam, cefepime, ceftazidime, meropenem, piperacillin-tazobactam, ciprofloxacin, and levofloxacin. You call the clinical microbiology laboratory to request susceptibility testing of an additional antimicrobial.

Which of the following is most appropriate?

A. Dalbavancin
B. Tedizolid
C. Ceftolozane/tazobactam
D. Oritavancin

QUESTION #9

You are asked to see a 43 year old woman to advise on management of a positive blood culture.

- Gram stain of her blood culture bottle shows Gram-negative bacilli.
- A rapid PCR panel performed on the positive blood culture bottle contents detects *Klebsiella pneumoniae* and bla_{KPC}.

QUESTION #9

The bla_{KPC} gene product would be expected to confer resistance to which of the following?

A. Cefepime
B. Plazomicin
C. Colistin
D. Ceftazidime/avibactam

TYPICAL SUSCEPTIBILITY OF A *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: Version 2.0 (idsociety.org)

QUESTION #10

INFECTIOUS DISEASE BOARD REVIEW 2023 PREVIEW QUESTION

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

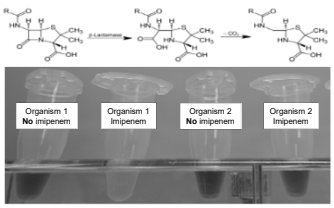
	Cefazolin	Cefotaxime	Ceftazidime	Piperacillin/ tazobactam	Imipenem	Aztreonam
a)	R	S	S	S	S	S
b)	R	R	R	S	S	R
c)	R	R	R	R	S	R
d)	R	R	R	R	R	R

QUESTION #11

Which of the following tests for carbapenemase production?

A. PBP2a test
B. D-test
C. Carba NP test
D. Polymerase chain reaction assay

CARBAPENEMASE PRODUCTION TEST
Carba NP TEST

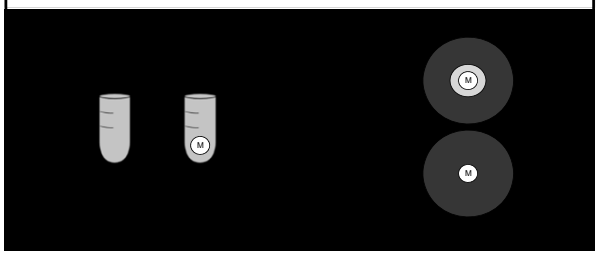


Positive = Carbapenemase Producer

Negative = Carbapenemase Non-Producer

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

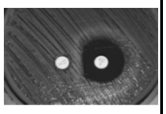
CARBAPENEMASE PRODUCTION TEST MODIFIED CARBAPENEM INACTIVATION



QUESTION #12

The image shows *Staphylococcus aureus* grown with an erythromycin disc (left) and a clindamycin disc (right).

Which of the following is the correct interpretation of these results?



A. Erythromycin susceptibility, inducible clindamycin resistance

B. Erythromycin resistance, constitutive clindamycin resistance

C. Erythromycin resistance, inducible clindamycin resistance

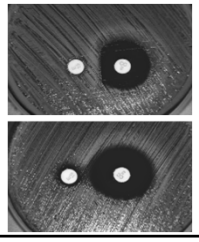
D. Erythromycin susceptibility, constitutive clindamycin resistance

INDUCIBLE CLINDAMYCIN RESISTANCE (D-TEST)

- Macrolide resistance from alteration in ribosomal target → co-resistance to clindamycin; constitutive or inducible
  - Constitutive, erythromycin & clindamycin test resistant
  - Inducible, erythromycin tests resistant but clindamycin tests falsely susceptible
- (Macrolide resistance due to efflux → no effect on clindamycin)

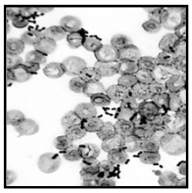
INDUCIBLE CLINDAMYCIN RESISTANCE (D-TEST)

- Erythromycin & clindamycin disks incubated on plate
  - Flattening of zone of inhibited growth between disks = inducible clindamycin resistance (top)
  - If erythromycin does not influence zone around clindamycin disk, clindamycin susceptible (bottom)



QUESTION #13 PREVIEW QUESTION

- **You are asked to see a 95 year old woman who is a resident of a long-term care facility to advise on therapy for bacteremia associated with a urinary tract infection.**
- **She has had two sets of blood cultures collected, both of which signaled positive after 17 hours of incubation.**
- **Gram stain of the bottles is shown.**
- **A rapid PCR panel performed on the positive blood culture bottle detects *Enterococcus* species as well as *vanA/vanB*.**



QUESTION #13 PREVIEW QUESTION

Which of the following is the most likely identity of the blood culture isolate?

A. Enterococcus gallinarum

B. Enterococcus faecium

C. Enterococcus faecalis

D. Enterococcus casseliflavus

E. Enterococcus avium

ENTEROCOCCI
VANCOMYCIN SUSCEPTIBILITY TESTING

- **Vancomycin MICs ≥32 µg/ml**
  - Typically VanA or VanB mediated resistance
  - Typically *E. faecium*
  - Epidemiologically significant
- **Vancomycin MICs, 8-16 µg/ml (intermediate)**
  - VanC
  - *E. gallinarum* or *E. casseliflavus/flavescens*
  - Not epidemiologically significant

QUESTION #14

A 44 year old man who underwent bilateral lung transplantation for pulmonary hypertension develops a sternal wound infection with sternal dehiscence 15 days post-transplant.

Blood cultures are negative. He undergoes sternal debridement with the finding of purulence and negative Gram and KOH stains.

After three days of incubation, pinpoint, clear colonies are visualized on cultures on sheep blood agar, however Gram stain of these colonies is negative.

QUESTION #14

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

a) Cefepime
b) Ceftriaxone
c) Trimethoprim-sulfamethoxazole
d) Azithromycin
e) Doxycycline

Mycoplasma hominis

- Post-cardiothoracic transplant
  - Pleuritis, surgical site infection and/or mediastinitis
- Treatment
  - Inactive
    - Cell wall active antibiotics
    - Trimethoprim/sulfamethoxazole
    - Aminoglycosides
    - Erythromycin and azithromycin
  - Active
    - Tetracyclines (doxycycline preferred)
    - Fluoroquinolones
    - Clindamycin

Sampath, R., et al. EBioMedicine (2017), http://dx.doi.org/10.1016/j.ebiom.2017.04.026

QUESTION #15

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

7/01/16: 26,000 IU/ml (day of diagnosis)
7/11/16: 25,000 IU/ml
7/20/16: 22,000 IU/ml
7/31/16: 27,000 IU/ml

- **The patient is CMV D^+/R^-, received 3 months of valganciclovir prophylaxis, and now has CMV disease after discontinuing valganciclovir.**
- **He has been receiving full dose intravenous ganciclovir since July 1st and his diarrhea is unchanged.**

QUESTION #15

A plasma test for mutations in which of the following genes is most appropriate?

A. UL51
B. UL54
C. UL89
D. UL97
E. Testing is unlikely to be helpful given the patient's viral load

QUESTION #16

Results of testing show a M460V UL97 mutation. This mutation would be expected to confer resistance to:

A. Cidofovir
B. Foscarnet
C. Ganciclovir
D. Ganciclovir and foscarnet
E. Ganciclovir and cidofovir

CYTOMEGALOVIRUS ANTIVIRAL RESISTANCE

- **Risk factors**
  - **Prolonged drug exposure**
  - **D^+R^-, lung transplant recipient**
- **Amplify and sequence directly from plasma**
  - **(viral load ~1,000 IU/ml required)**
- **≥6 weeks antiviral drug exposure**
  - **Should include ≥2 weeks full-dose therapy before testing**
  - **Accelerated schedule: Poor host factors, extreme viral loads**

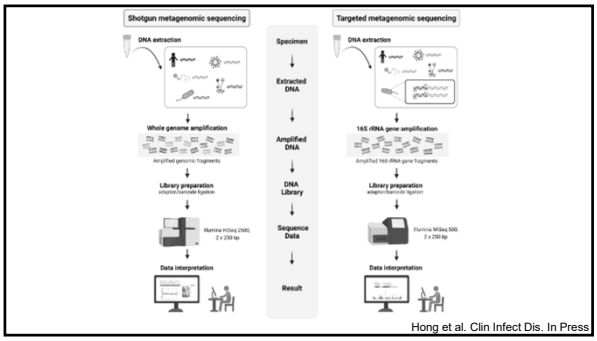
Gene	Drug(s) affected
UL97	Ganciclovir, marabavir
UL54	Ganciclovir and cidofovir (if selected for by these agents); foscarnet (if selected for by foscarnet)
UL56	Letermovir

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

COVID-19 DIAGNOSTICS

- **Healthcare provider or patient collected specimens acceptable**
- **Nasopharyngeal swab, mid-turbinate swab, anterior nasal swab, saliva or combined anterior nasal/oropharyngeal swab acceptable**
- **Suspected lower respiratory infection → upper respiratory sample; if negative, lower respiratory sample**
- **Interpret Ct values with caution**
- **NAAT generally preferred over antigen testing**
  - **Symptomatic individuals suspected of having COVID-19**
  - **Asymptomatic individuals exposed to SARS-CoV-2 infection**
- **Avoid serologic testing for diagnosis in the 2 weeks post symptom onset**
  - **IgG or total antibody tested 3-4 weeks post symptom onset provide evidence of past SARS-CoV-2 infection (clinical or epidemiological purposes)**
  - **Avoid IgA tests**

IDSA Guidelines on the Diagnosis of COVID-19



Hong et al. Clin Infect Dis. In Press

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

	Verigene EP	Luminex GPP	BioFire GIP
Number of targets	8	14	22
Campylobacter species	✓	✓	✓
Salmonella species	✓	✓	✓
Shigella species/Enteroinvasive *E. coli*	✓	✓	✓
Vibrio species	✓	✓	✓
Yersinia enterocolitica	✓	✓	✓
Escherichia coli 0157		✓	✓
Enterotoxigenic *E. coli*		✓	✓
Enteropathogenic *E. coli*			✓
Enteroaggregative *E. coli*			✓
Plesiomonas shigelloides			✓
Shiga toxin-producing *E. coli*	✓	✓	✓
Clostridioides difficile		✓	✓
Norovirus	✓	✓	✓
Rotavirus A	✓	✓	✓
Astrovirus			✓
Adenovirus 40/41		✓	✓
Sapovirus			✓
Cryptosporidium species		✓	✓
Entamoeba histolytica		✓	✓
Giardia lamblia		✓	✓
* *Cyclospora cayetanensis*			✓

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)		✓
SARS-CoV-2		✓
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*		✓

MAYO CLINIC

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

	FilmArray BCID2	VERIGENE®	GenMark$_{Dx}$	
		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 BCID2	VERIGENE®	GenMark$_{Dx}$	
		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

MAYO CLINIC

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

	FilmArray BCID2	VERIGENE®		GenMark$_{Dx}$	
		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 BCID2	GenMark$_{Dx}$		
		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*		✓		✓

*

04

Core Concepts: Antibacterial Drugs I - Gram Positive Organisms

Dr. Helen Boucher

04 – Core Concepts: Antibacterial Drugs I - Gram Positive Organisms

Speaker: Helen Boucher, MD

IDBR INFECTIOUS DISEASE BOARD REVIEW AUGUST 19-23 2023

Antibacterial Drugs I

Helen W. Boucher, MD, FACP, FIDSA
Dean and Professor of Medicine
Tufts University School of Medicine
Chief Academic Officer, Tufts Medicine

7/23/2023

IDBR INFECTIOUS DISEASE BOARD REVIEW AUGUST 19-23 2023

Disclosures of Financial Relationships with Relevant Commercial Interests

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

Overview of Antibacterial Mechanisms

To Orient You: Little is Testable

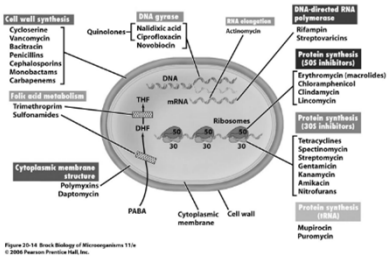


Figure 20-14 Brock Biology of Microorganisms 11/e
© 2006 Pearson Prentice Hall, Inc.

3

Cell Wall Active Agents

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

4

β-lactam Spectrum

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

Gram-positive

Gram-negative

5

β-lactam Antibiotics Share Mechanism of Action

- **Why are there different spectrum of activity for penicillins, cepahalosporins, carbapenems?**
  - **Broad and narrow susceptibility to beta-lactamases**
  - **Different penicillin binding proteins**
  - **Selective efflux pumps**
  - **Ability to reach target site**

6

β-lactam Adverse Effects

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

7

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**

10

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**
  - **Spectrum similar to ceftriaxone**
- **Bactericidal, time dependent killing**

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

12

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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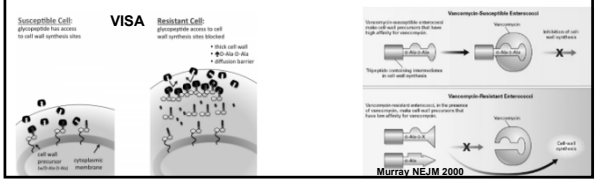
Vancomycin Resistance

- 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



Murray NEJM 2000

Vancomycin for MRSA Bloodstream Infection

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

Dosing Calculator helps!

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

Vancomycin ADRs / Interactions

Adverse Drug Reactions

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

Drug Interactions

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

18

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

20

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

23

Antibiotics Active Intracellularly

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

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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

26

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++

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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

30

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	1mg/kg IV q 12h (over 60 minutes)
	No dose adjustment for renal/hepatic impairment	Dose adjustment with hepatic impairment
Activity	Broad spectrum: Gram-pos including MRSA, VRE; Gram-neg including ESBL, CRE (not all); anaerobes	
Issues	Limited activity vs carbapenem-resistant *K. pneumoniae*	High MIC *Pseudomonas*, *Burkholderia* spp.
Safety	GI, rash, ?heart rate	GI, rash

32

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

34

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

36

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

38

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***

40

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

42

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?

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Tufts

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

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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)

48

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

50

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

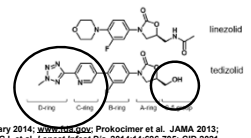
- Other uses
  - Limited data, varying dosing regimens
    - Endocarditis and osteomyelitis
    - Persons who inject drugs
- Case reports of failure with emergence of VISA, presumably associated with low-level drug exposure
  - One patient had VISA detected in urine while on dalbavancin for CLASBI
  - 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.fda.gov; Prokocimer et al. JAMA 2013;
Moran GJ, et al. *Lancet Infect Dis.* 2014;14:696-705; CID 2021

53

Sulfonamides & TMP/SMX

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

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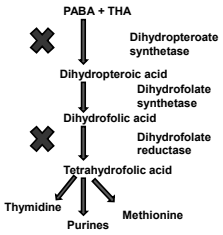
TMP/SMX Mechanism of Action

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



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TMP/SMX Resistance Mechanisms

Sulfamethoxazole

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

Trimethoprim

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

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TMP-SMX Adverse Effects

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

- 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 58

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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BR1

Board Review Session 1

Drs. Masur (Moderator), Boucher, Gandhi, Patel, Pavia, and Tamma

IDBR INFECTIOUS DISEASE BOARD REVIEW LIVE/VIRTUAL AUGUST 19-23 2023

Board Review: Day 1

Moderator: Henry Masur, MD, FIDSA, MACP
Faculty: Drs. Boucher, Gandhi, Patel, Pavia, and Tamma

8/2/2023

BOARD REVIEW DAY 1 INFECTIOUS DISEASE BOARD REVIEW 2023

#1 **A 34-year-old man with HIV disease (CD4=102; vl,<50) presents with complaints of nausea, vomiting, and severe left upper quadrant pain x 1 week.**

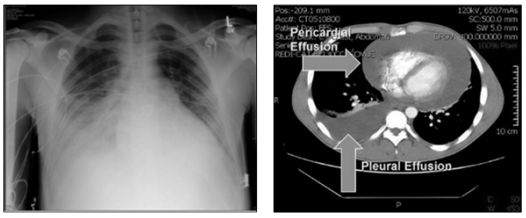
He has no fever and no skin disease suggesting Kaposi's sarcoma.

The patient also has left sided chest pain that worsens with inspiration and is associated with dyspnea on exertion.

1 of 5

BOARD REVIEW DAY 1 INFECTIOUS DISEASE BOARD REVIEW 2023

#1 **A CT scan is shown: there is an effusion involving the pleural space and pericardium but no mass can be seen.**



2 of 5

BOARD REVIEW DAY 1 INFECTIOUS DISEASE BOARD REVIEW 2023

#1 **Evaluation of the fluid shows mononuclear cells but no neutrophils, and all routine microbiologic evaluations have been negative.**

3 of 5

BOARD REVIEW DAY 1 INFECTIOUS DISEASE BOARD REVIEW 2023

#1 **What virus is associated with a malignant process that would characteristically present with pleural effusion, pericardial effusion, and/or ascites in this type of patient?**

A) EBV

B) CMV

C) HHV 6

D) HHV 8

E) HSV

4 of 5

BOARD REVIEW DAY 1 INFECTIOUS DISEASE BOARD REVIEW 2023

#2 **A 36-year-old man with lymphoma was admitted and his 3rd cycle of chemotherapy begun.**

Within 4 days of admission, he developed pneumonia and was treated with vancomycin and piperacillin-tazobactam.

Sputum culture revealed a heavy growth of Staphylococcus aureus, methicillin resistant (MRSA), with a vancomycin MIC of 4 mcg/ml (intermediate resistance).

1 of 5

BOARD REVIEW DAY 1 INFECTIOUS DISEASE BOARD REVIEW 2023

#2 **Blood cultures were negative.**

The isolate was susceptible in vitro to linezolid, daptomycin, tigecycline and rifampin.

Piperacillin-tazobactam was discontinued.

After another 2 days, it was apparent that the patient was not responding clinically.

2 of 5

BOARD REVIEW DAY 1 INFECTIOUS DISEASE BOARD REVIEW 2023

#2 **The vancomycin trough serum concentration was 12 mcg/ml/.**

The Gram stain of a new tracheal aspirate again showed many Gram-positive cocci in clusters.

3 of 5

BOARD REVIEW DAY 1 INFECTIOUS DISEASE BOARD REVIEW 2023

#2 **While awaiting in vitro susceptibility results, which one of the following changes in his treatment regimen would you recommend?**

A) Start Linezolid and stop vancomycin

B) Start Daptomycin and stop vancomycin

C) Start Tigecycline and stop vancomycin

D) Increase dose of Vancomycin to achieve trough levels of 15-20 mcg/ml

E) Continue vancomycin and add rifampin

4 of 5

BOARD REVIEW DAY 1 INFECTIOUS DISEASE BOARD REVIEW 2023

#3 **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 1 INFECTIOUS DISEASE BOARD REVIEW 2023

#3 **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 $bla_{OXA\text{-}48\text{-}like}$.**

A β-lactam/β-lactamase inhibitor is considered for therapy.

2 of 4

BOARD REVIEW DAY 1 INFECTIOUS DISEASE BOARD REVIEW 2023

#3 **Which of the following β-lactamase inhibitors would be most likely to inhibit the detected β-lactamase?**

A) Avibactam

B) Relebactam

C) Vaborbactam

D) Tazobactam

E) Clavulanic acid

3 of 4

BOARD REVIEW DAY 1 INFECTIOUS DISEASE BOARD REVIEW 2023

#4 **A 22-year-old college football player presents with septic shock.**

He has not been near a health care facility for years.

He has a turf burn that became infected during the past week.

Two sets of blood cultures are drawn before antimicrobial therapy is started.

1 of 4

BOARD REVIEW DAY 1 INFECTIOUS DISEASE BOARD REVIEW 2023

#4 **Sixteen hours later both sets are growing Staphylococcus aureus which is found, on the third post admission day, to be oxacillin resistant and vancomycin and linezolid susceptible.**

2 of 4

BOARD REVIEW DAY 1 INFECTIOUS DISEASE BOARD REVIEW 2023

#4 **Which one of the following is likely responsible for the oxacillin resistance?**

A) mecA gene encoding penicillin binding protein 2a

B) β-lactamase production

C) Panton-Valentine leucocidin

D) Altered porins causing decreased permeability

E) Activation of efflux pumps

3 of 4

BOARD REVIEW DAY 1 INFECTIOUS DISEASE BOARD REVIEW 2023

#5 **A 50-year-old female was well until 7 days prior to admission when she noted "bite" on left thigh.**

The lesion enlarged over several days.

Four days prior to admission, she developed fatigue, arthralgias, myalgias, fever, headache.

On the day of admission, she developed generalized rash on extremities, trunk, back.

1 of 5

BOARD REVIEW DAY 1 INFECTIOUS DISEASE BOARD REVIEW 2023

#5 **She lived in New England.**

She had seen a mouse in her basement.

She denied any sexual activity.

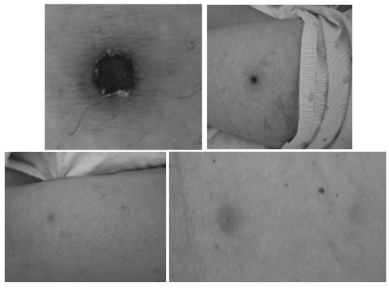
PE: appeared well. 100.5 F. No adenopathy.

There was a lesion present on left thigh (see picture). She had a papular erythematous rash on her extremities, back, chest.

2 of 5

BOARD REVIEW DAY 1 INFECTIOUS DISEASE BOARD REVIEW 2023

#5



3 of 5

BOARD REVIEW DAY 1 INFECTIOUS DISEASE BOARD REVIEW 2023

#5 **What is the most likely diagnosis?**

A) Varicella

B) Monkeypox

C) Cutaneous anthrax

D) Rickettsialpox

E) Lyme

4 of 5

BOARD REVIEW DAY 1 INFECTIOUS DISEASE BOARD REVIEW 2023

#6 **A 72-year-old male living in a rural area of Southern New York State was admitted to the hospital in June with a five-day history of nausea, vomiting, headache, fever, somnolence and confusion.**

On examination he had a temperature of 39°C, oriented only to person, weakness in the right lower extremity, a faint maculopapular rash on his upper chest and back and a right facial droop.

1 of 5

BOARD REVIEW DAY 1 INFECTIOUS DISEASE BOARD REVIEW 2023

#6 **Routine laboratory tests were normal. LP: showed 108 WBC/mm3 with 31% PMN, protein 113 mg/dl, and glucose 67 mg/dl. IgM serology for West Nile Virus on the CSF and serum was negative, as was the PCR for herpes simplex and West Nile virus.**

MRI showed diffuse hyperintensity in the left basal ganglia on T2 and FLAIR imaging. He became progressively obtunded, requiring intubation for airway protection.

2 of 5

BOARD REVIEW DAY 1 INFECTIOUS DISEASE BOARD REVIEW 2023

#6 **According to his wife, he had been in good health and returned two weeks prior to illness from a camping trip with his family in a lake area in New Hampshire.**

She said her husband had been concerned about finding a few ticks on his body while camping but had removed them the day he thought he had acquired them.

3 of 5

BOARD REVIEW DAY 1 INFECTIOUS DISEASE BOARD REVIEW 2023

#6 **Which of the following agents is the most likely cause of this illness?**

A) Tick-borne encephalitis virus

B) Herpes simplex virus

C) Zika virus

D) Powassan virus

E) Enterovirus D68

4 of 5

BOARD REVIEW DAY 1 INFECTIOUS DISEASE BOARD REVIEW 2023

#7 **A 50-year-old woman with AML presents with 3 days of dysuria 32 days post a myeloablative allogeneic stem cell transplant.**

Her course was notable for asymptomatic CMV DNAemia following engraftment for which she has started on foscarnet 7 days prior to presentation.

1 of 4

BOARD REVIEW DAY 1 | INFECTIOUS DISEASE BOARD REVIEW 2023

#7 **Physical exam shows ulcerations on the inner labia but no other skin lesions or rash.**

HSV PCR of the ulcers is negative and urinalysis shows 0-5 RBCs and 3 WBCs/hpf, urine culture is negative, and BK virus PCR of urine is negative.

2 of 4

BOARD REVIEW DAY 1 | INFECTIOUS DISEASE BOARD REVIEW 2023

#7 **The most likely cause of the dysuria is:**

A) CMV
B) BK virus
C) Adenovirus
D) Foscarnet
E) Graft vs Host Disease

3 of 4

BOARD REVIEW DAY 1 | INFECTIOUS DISEASE BOARD REVIEW 2023

#8 **A 66-year-old male retired architect was asked to return to the hospital because the platelets he had donated at the blood bank were found on routine culture to contain Streptococcus bovis (newer taxonomy: Streptococcus gallolyticus, subsp. gallolyticus).**

1 of 5

BOARD REVIEW DAY 1 | INFECTIOUS DISEASE BOARD REVIEW 2023

#8 **Physical examination of the platelet donor was normal, as were chest x-ray, transthoracic cardiac ultrasound, routine blood chemistries for liver and renal function, complete blood count, sedimentation rate and cultures of blood (three sets) and urine.**

2 of 5

BOARD REVIEW DAY 1 | INFECTIOUS DISEASE BOARD REVIEW 2023

#8 **His dental hygiene was good, he was afebrile and he had been asymptomatic at the time of the donation and in the week subsequently.**

He bicycled into the hospital about three miles and back to donate the platelets and to come to clinic as requested.

3 of 5

BOARD REVIEW DAY 1 | INFECTIOUS DISEASE BOARD REVIEW 2023

#8 **You should suggest which of the following:**

A) Dental films
B) Transesophageal echocardiogram
C) CT of the abdomen
D) Renal ultrasound
E) Colonoscopy

4 of 5

BOARD REVIEW DAY 1 INFECTIOUS DISEASE BOARD REVIEW 2023

#9 **A 43-year-old woman in Arizona with history of transfusion-dependent Diamond-Blackfan syndrome, hepatitis C virus infection, and splenectomy presented to the Emergency Department with fever of 3 days' duration.**

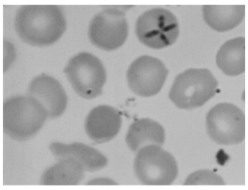
She was admitted for presumptive pneumonia.

1 of 4

BOARD REVIEW DAY 1 INFECTIOUS DISEASE BOARD REVIEW 2023

#9 **The next day, routine examination of a peripheral blood smear showed the finding in the image.**

She had not traveled outside of Arizona.



2 of 4

BOARD REVIEW DAY 1 INFECTIOUS DISEASE BOARD REVIEW 2023

#9 **How did she most likely acquire this infection?**

A) Blood transfusion

B) Tick bite

C) Mosquito bite

D) Pet canary

E) Foodborne

3 of 4

BOARD REVIEW DAY 1 INFECTIOUS DISEASE BOARD REVIEW 2023

#10 **A 60-year-old woman with lymphoma, receiving chemotherapy and rituximab, is admitted to the hospital with fever and shortness of breath for 5-6 days.**

On exam, temperature is 101F, BP 120/70, pulse 82, BMI 30, crackles at both lung bases, O_2 saturation 89%, rising to 95% on 3 L supplemental O_2.

Labs: positive SARS CoV-2 PCR on nasal swab, WBC 18,000/mcl.

1 of 3

BOARD REVIEW DAY 1 INFECTIOUS DISEASE BOARD REVIEW 2023

#10 **Which treatment would you recommend for her COVID-19?**

A) Remdesivir

B) Nirmatrelvir/ritonavir (Paxlovid)

C) Molnupiravir

D) Remdesivir + dexamethasone 6 mg daily

E) Remdesivir + dexamethasone 20 mg daily

2 of 3

BOARD REVIEW DAY 1 INFECTIOUS DISEASE BOARD REVIEW 2023

#11 **A 72-year-old retired firefighter who has a history of chronic obstructive lung disease is seen in the emergency department because of 96 hours of cough, chills, sore throat, and body aches.**

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

1 of 4

BOARD REVIEW DAY 1 INFECTIOUS DISEASE BOARD REVIEW 2023

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

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

He is hypoxemic and admitted to the intensive care unit.

2 of 4

BOARD REVIEW DAY 1 INFECTIOUS DISEASE BOARD REVIEW 2023

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

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

B) Zanamivir

C) Zanamivir and Oseltamivir

D) Oseltamivir

E) Rimantadine

3 of 4

BOARD REVIEW DAY 1 INFECTIOUS DISEASE BOARD REVIEW 2023

#12 **The 16S ribosomal RNA (rRNA) gene is a conserved gene among which of the following?**

A) Viruses

B) Bacteria

C) Protozoa

D) Fungi

E) Helminths

1 of 2

BOARD REVIEW DAY 1 INFECTIOUS DISEASE BOARD REVIEW 2023

#13 **A 49-year-old man working as a missionary in rural Guatemala suffered a comminuted compound fracture of his tibia in an auto accident.**

Open reduction and external fixation was followed by infection.

On transfer to his home in Tucson, methicillin resistant Staphylococcus (MRSA) was isolated from pus in his wound and around the pin insertion sites.

1 of 5

BOARD REVIEW DAY 1 INFECTIOUS DISEASE BOARD REVIEW 2023

#13 **Azotemia attributed to vancomycin prompted a change to daptomycin and rifampin.**

On the 22nd day of that regimen he developed fever, cough and dyspnea.

2 of 5

BOARD REVIEW DAY 1 INFECTIOUS DISEASE BOARD REVIEW 2023

#13 **Peripheral white blood cell count, 5,800/mm^3 a week ago, is 26,400 with 87% neutrophils, 12% lymphocytes, and 3% eosinophils.**

Chest radiograph shows interval development of patchy bilateral airspace consolidations. Mixed oral flora are seen on sputum Gram stain.

Bronchoalveolar lavage found 9.3% macrophages, 7.1% neutrophils, 14.6% lymphocytes, and 69% eosinophils.

3 of 5

BOARD REVIEW DAY 1 INFECTIOUS DISEASE BOARD REVIEW 2023

#13 **What is the most likely explanation for this clinical picture?**

A) Hyperinfection strongyloidiasis

B) Coccidioidomycosis

C) Rifampin hypersensitivity

D) Daptomycin hypersensitivity

E) Rifampin-daptomycin interaction

4 of 5

BOARD REVIEW DAY 1 INFECTIOUS DISEASE BOARD REVIEW 2023

#14 **A 37-year-old woman from St. Louis is referred to you by her rheumatologist for treatment of possible Lyme arthritis of six month's duration.**

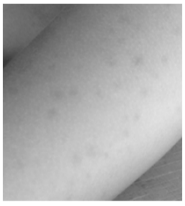
Her symptoms began shortly after a week's vacation in Jamaica.

Towards the end of her stay she developed fever, malaise, muscle aches, headache and then a nonpruritic rash over her trunk and extremities.

1 of 4

BOARD REVIEW DAY 1 INFECTIOUS DISEASE BOARD REVIEW 2023

#14 **She took a picture of the rash with her cell phone (see figure).**



As her rash and fever faded away, she developed joint pains in her hands, feet, ankles and wrists. This has persisted to the present.

2 of 4

BOARD REVIEW DAY 1 INFECTIOUS DISEASE BOARD REVIEW 2023

#14 **The most likely useful diagnostic test is a serology for:**

A) O'nyong-nyong virus

B) STARI

C) Measles virus

D) Chikungunya virus

E) Borrelia burgdorferi

3 of 4

BOARD REVIEW DAY 1 INFECTIOUS DISEASE BOARD REVIEW 2023

#15 **An asymptomatic 18-year-old female is being evaluated because her aunt, whom she lives with, has recently been diagnosed with active pulmonary tuberculosis on the basis of a positive smear and confirmatory nucleic acid amplification test (NAAT) .**

The 18-year-old is healthy with no underlying medical conditions.

1 of 4

BOARD REVIEW DAY 1 INFECTIOUS DISEASE BOARD REVIEW 2023

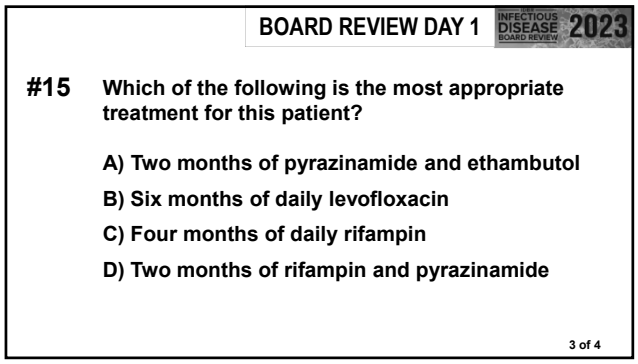
#15 **Her aunt's isolate is isoniazid resistant but susceptible to all other agents.**

The patient's initial IGRA was negative; the IGRA at 8 weeks is positive.

She has normal vital signs and a normal physical examination.

Her chest X-ray is also normal.

2 of 4



05

Core Concepts: Antibacterial Drugs II: Gram Negative Organisms

Dr. Pranita Tamma

05 – Core Concepts: Antibacterial Drugs II - Gram Negative Organisms

Speaker: Pranita Tamma, MD

Antibacterial Drugs II
Gram-Negative Organisms

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

7/25/2023

Disclosures of Financial Relationships with Relevant Commercial Interests

- **None**

Objectives

- Review antibiotic treatment options for:
  - Extended-spectrum beta-lactamase producing Enterobacterales **(ESBL-E)** infections
  - Enterobacterales infections considered at moderate to high risk for clinically significant AmpC **(AmpC-E)** production
  - *Pseudomonas aeruginosa* infections with difficult-to-treat resistance **(DTR-*P. aeruginosa*)**
  - Carbapenem-resistant Enterobacterales **(CRE)** infections
  - Carbapenem-resistant *Acinetobacter baumannii* **(CRAB)** infections

ESBL-E Infections

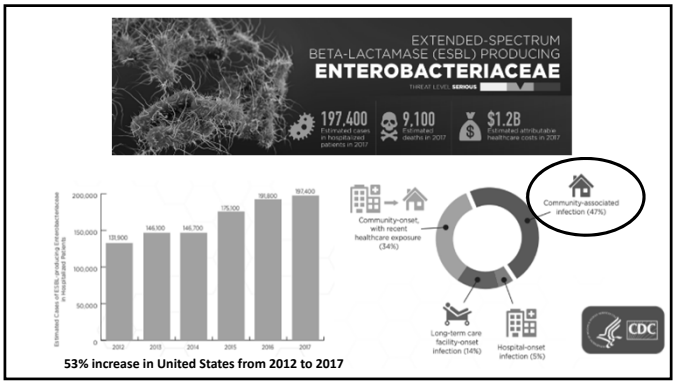
Clinical Case

- 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

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

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

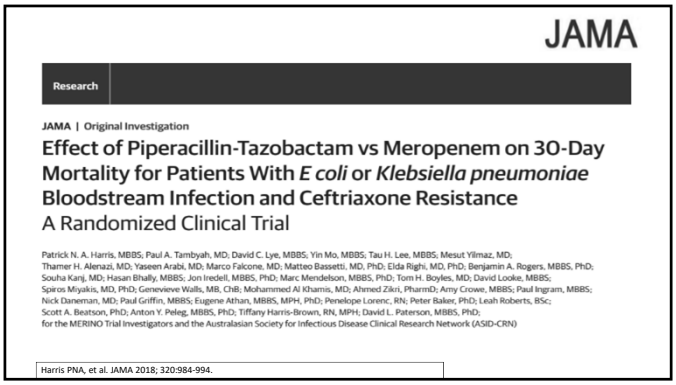
1. Cefepime
2. Trimethoprim-sulfamethoxazole
3. Meropenem
4. Piperacillin-tazobactam



53% increase in United States from 2012 to 2017

A Primer on ESBL-E

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


JAMA

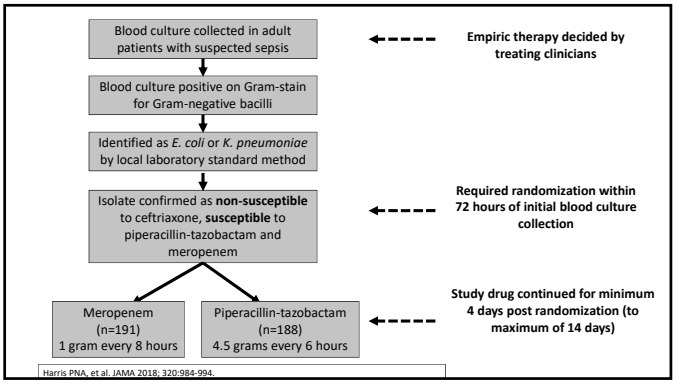
Research

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)

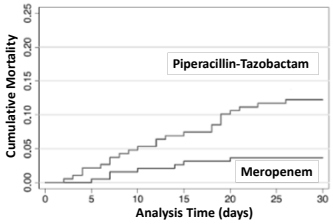
Harris PNA, et al. JAMA 2018; 320:984-994.



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

Results

- 30-day mortality
  - Piperacillin-tazobactam 12% vs. meropenem 4%
  - aOR 3.41 (95% CI 1.38-8.38)
- Study terminated early
  - Unlikely to demonstrate non-inferiority



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

Clinical Infectious Diseases
IDSA GUIDELINES

Infectious Diseases Society of America 2022 Guidance on the Treatment of Extended-Spectrum β-lactamase Producing Enterobacterales (ESBL-E), Carbapenem-Resistant Enterobacterales (CRE), and *Pseudomonas aeruginosa* with Difficult-to-Treat Resistance (DTR-*P. aeruginosa*)

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. 2022;75:187-212.

Cefepime for ESBL-E Infections

- ESBLs commonly hydrolyze cefepime
- Poorer outcomes with cefepime for the treatment of ESBL-E infections

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.

Clinical Infectious Diseases
IDSA GUIDELINES

Infectious Diseases Society of America 2022 Guidance on the Treatment of Extended-Spectrum β-lactamase Producing Enterobacterales (ESBL-E), Carbapenem-Resistant Enterobacterales (CRE), and *Pseudomonas aeruginosa* with Difficult-to-Treat Resistance (DTR-*P. aeruginosa*)

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. For patients who are critically ill and/or experiencing hypoalbuminemia, meropenem or imipenem-cilastatin are the preferred carbapenems. 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. 2022;75:187-212.

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

- TMP-SMX not hydrolyzed by ESBL enzymes
- Reasonable treatment option for ESBL-E infections (if susceptible)

ESBL-E: Testable Points

- Hydrolyze 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 also reasonable if non-severe infection

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*

Overview of AmpC Enzymes

- Assist with bacterial cell wall recycling
- Capable of hydrolyzing certain antibiotics
  - Most notorious = ceftriaxone
- *Enterobacter cloacae*, *Citrobacter freundii*, *Klebsiella aerogenes* recovered in clinical isolates = avoid ceftriaxone

Clinical Infectious Diseases
IDSA GUIDELINE

Infectious Diseases Society of America Guidance on the Treatment of AmpC β-Lactamase–Producing Enterobacterales, Carbapenem-Resistant *Acinetobacter baumannii*, and *Stenotrophomonas maltophilia* Infections

Question 2.3: What is the role of cefepime for the treatment of infections caused by Enterobacterales at moderate to high 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 to high risk of significant AmpC production (i.e., *E. cloacae* complex, *K. aerogenes*, and *C. freundii*).

Tamma PD, et al. Clin Infect Dis. 2022;74(12):2089-2114.

DTR-*P. aeruginosa* Infections

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

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

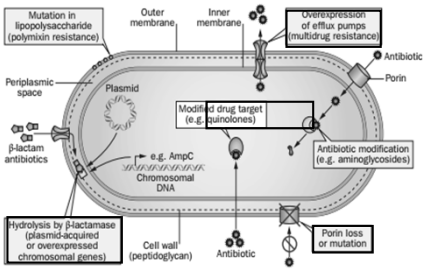
***Pseudomonas aeruginosa* with "difficult-to-treat resistance" = resistance to all traditional beta-lactam and fluoroquinolone agents**

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 are the Polymyxins No Longer Suggested as Preferred Therapy?

- Poor penetration into lungs
- Difficult to achieve adequate colistin plasma concentrations
- Colistin reasonable for uncomplicated cystitis
- Clinical failure and resistance emergence with monotherapy

Adverse Events Associated with Polymyxins

- **Nephrotoxicity**
  - ~40-60% with colistin; ~20-30% with polymyxin B
  - Usually reversible
- **Neurotoxicity**
  - <5% of patients; mostly polymyxin B
  - Paresthesias, seizures, neuromuscular blockade
  - Usually reversible

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%
- ~50% of *P. aeruginosa* isolates develop resistance after ceftolozane-tazobactam or ceftazidime-avibactam treatment
- 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 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

2023 PREVIEW QUESTION

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
- 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

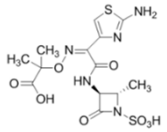
Sabour S, et al. Antimicrob Agents Chemother 2021; 65(e0110521). van Duin D, et al. Lancet Infect Dis 2020; 20:731-741.

NDM-Producing Enterobacterales

- Class B β-lactamases
- Rare in the United States (10% of carbapenemase-producing Enterobacterales)
  - Main risk factor: previous medical care in India, Pakistan
- **Treatment options**
  - Preferred: Cefiderocol or ceftazidime-avibactam PLUS aztreonam

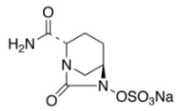
Sabour S, et al. Antimicrob Agents Chemother 2021; 65(e0110521). van Duin D, et al. Lancet Infect Dis 2020; 20:731-741.

Aztreonam



NDMs, VIMs, IMPs

Avibactam



ESBLs, AmpCs, KPCs, OXA-48-like

OXA-48-Like-Producing Enterobacterales

- Class D β-lactamases
- Rare in the United States (4% of carbapenemase-producing Enterobacterales); increasingly common in Europe
- **Treatment options**
  - Preferred: Ceftazidime-avibactam
  - Alternative: Cefiderocol

Sabour S, et al. Antimicrob Agents Chemother 2021; 65(e0110521). van Duin D, et al. Lancet Infect Dis 2020; 20:731-741.

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
  - OXA-48-like producers: ceftazidime-avibactam

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

Overview of CRAB

- Distinguish if likely colonization or infection
- Generally cause ventilator-associated pneumonia, wound infections (combat-related)
- Always produce Class D carbapenemases
- Combination therapy generally administered:
  - Ampicillin-sulbactam
  - Cefiderocol
  - Minocycline/tigecycline
  - Polymyxins

Sulbactam

- Competitive, irreversible β-lactamase inhibitor
- In high doses, saturates PBP1 and PBP3 of *A. baumannii* isolates
- High-dose ampicillin-sulbactam (total daily dose of 6-9 grams of sulbactam) recommended
  - 2:1 formulation (e.g., 3 grams of ampicillin-sulbactam = 2 grams of ampicillin + 1 gram of sulbactam)
- Ampicillin-sulbactam and amoxicillin-clavulanate NOT interchangeable
- New drug (2023): sulbactam-durlobactam

CRAB: Testable Points

- Identification of CRAB does not always mean treatment is indicated
- Combination therapy preferred
- Sulbactam-based regimens remain the cornerstone of treatment

06

Core Concepts: Antifungal Drugs

Dr. John Bennett

06 – Core Concepts: Antifungal Drugs

Speaker: John Bennett, MD

IDBR INFECTIOUS DISEASE BOARD REVIEW LIVE/VIRTUAL AUGUST 19-23 2023

Core Concepts: Antifungal Drugs

John E. Bennett, MD
Bethesda, Maryland

7/23/2023

IDBR INFECTIOUS DISEASE BOARD REVIEW LIVE/VIRTUAL AUGUST 19-23 2023

Disclosures of Financial Relationships with Relevant Commercial Interests

- **None**

Disclosures of Off-Label Use

- **Will be cited as discussed**

Plan of the talk

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

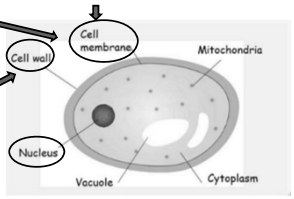
Antifungal drugs

Amphotericin makes cell membrane leak

Azoles stops sterol synthesis for the cell membrane

Echinocandins block cell wall synthesis (glucan fibers)

Flucytosine blocks DNA synthesis in nucleus



ANTIFUNGAL RESISTANCE altered target ezymes

AZOLE RESISTANCE IN CANDIDA AND ASPERGILLUS

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

ECHINOCANDIN RESISTANCE IN CANDIDA

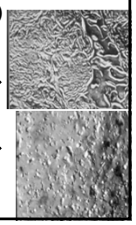
Fungus modifies the drug targets, glucan synthase, (genes fks1, fks2) so echinocandins no longer block synthesis of beta-D- glucan, which is necessary for cell wall synthesis. Cross resistance between echinocandins is usual.

Antifungal resistant species

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

Amphotericin B

- Azotemia (less with saline loading), hypokalemia, renal tubular acidosis, anemia (erythropoietin loss)
- Conventional (deoxycholate) colloid
  Lipid complex: (ABLC) less toxic . flakes ⇒
- Liposomal (AmBisome) tiny particles ⇒



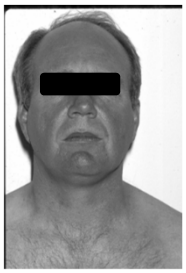
Azole antifungals

All azoles teratogenic. CYP 3A4 drug interactions.
Fluconazole: Candida, Cryptococcus. IV, PO.
Not Aspergillus, Mucor. Good concentration CSF, urine.
HSCT prophylaxis. Cocci.
Itraconazole: Histoplasma, Blastomyces, ringworm
Voriconazole: Aspergillus, molds not Mucor. Candida.
Check blood levels.
Posaconazole: Aspergillus, Mucor follow-up.
HSCT prophylaxis
Isavuconazole : Aspergillus. Mucor?? Low drug interactions

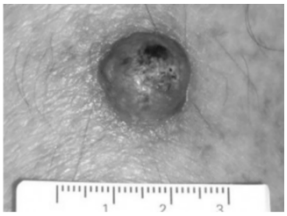
Voriconazole: the fundamentals

- Candida, Aspergillus , Scedosporium apiospermum, etc.
- Children are rapid metabolizers. Japanese 20% slow (2C19)
- Good CSF levels, none in urine.
- IV (sulfobutylcyclodextran=16x vori dose) accumulates in azotemia but not obviously toxic. Use oral in azotemia.
- Many drug interactions, Increases other drug levels: cyclosporine, tacrolimus, serolimus, steroids (budesonide, fluticasone), etc
- Side effects: hallucinations, hepatitis, photosensitivity, visual changes, peripheral neuropathy
- Many months of Rx: skin cancer, periostitis

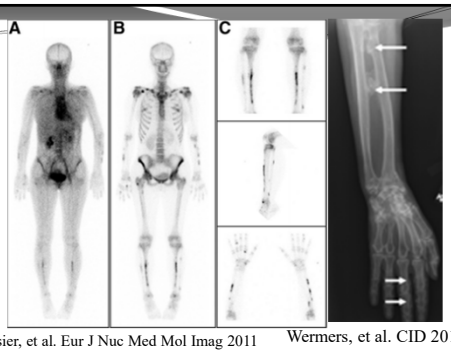
Photosensitivity from voriconazole



Skin cancer after months of sun



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



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

Wermers, et al. CID 2011

Isavuconazonium/Isavuconazole

- Noninferior to vori in invasive aspergillosis.
- Use for mucor controversial
- Inferior to caspofungin for candidemia
- No good data on prophylaxis
- Pharma: like vori but long half life (5.4 days), no drug in CSF or urine. Fewer drug interactions than vori or posa. Teratogenic.
- Isavuconazonium 372mg=isavuconazole 200 mg
- Load with 200 mg q8h X6 then 200 mg qd, IV or PO
- No dose change for renal or moderate liver failure.

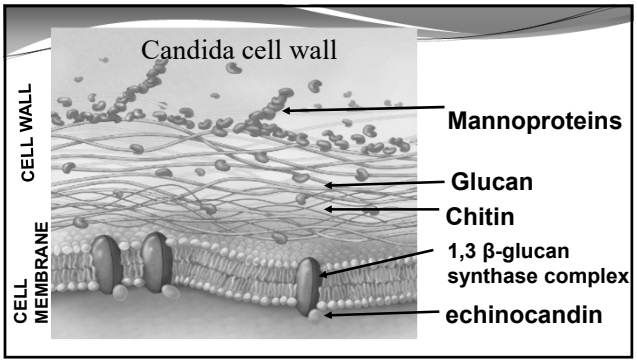
Posaconazole

- Approved for prophylaxis in GVHD or prolonged neutropenia, oral thrush. Aspergillosis good data, not approved.
- Extended release three 100 mg tablets twice first day then daily. IV same dose, has cyclodextran. 7-10 days for steady state. Check trough levels (usually 2-5 mcg/ml)
- Has been used in mucormycosis once patient has responded to amphotericin B
- Interactions with CYP3A4 increase some drug levels
- Well tolerated. Hypertension, hypokalemia

FLUCONAZOLE

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

Echinocandins



Caspofungin, Micafungin, Anidulafungin

- All Candida (including C. auris and C. parapsilosis) are susceptible but resistance can arise during long therapy. Mold activity: Aspergillus. Prophylaxis during neutropenia: Candida, Aspergillus?, Pneumocystis???
- Cryptococcus, Trichosporon resistant
- IV once daily. Plasma half life: 10-15 hr.
- No drug in urine. Azotemia: same dose
- Protein binding high: poor penetration into CSF and vitreous humor of eye
- Drug interactions: none important

Rezafungin: new echinocandin

- Anidulafungin derivative. Once a week IV
- Candidemia or invasive candidiasis in adults with limited options. 400 mg week one then 200 mg/wk.
- Weekly cost? ($6,000 then $3,000/wk?) May include savings from early hospital discharge
- Daily generic mica, caspo coast $500/wk fluconazole $3/wk
- No data on candidemia in neutropenia, SBE, arthritis, osteo, meningitis
- Prophylaxis trial underway: ??Candida, Aspergillus, PJP??

Flucytosine

- Bioavailability 100%, good levels in CSF, eye, urine
- Accumulates in azotemia: bone marrow depression, hepatitis, colitis. Measure blood levels/dose adjust.
- Drug resistance arises during monotherapy.
- Used with ampho in cryptococcal meningitis

Now for a few questions

Question #1

INFECTIOUS DISEASE BOARD REVIEW AUGUST 16-27 2023 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. A. Candida parapsilosis
b. B. Cryptococcus gattii
c. C. Candida auris
d. D. Candida krusei
e. E. Candida glabrata

Question #2

A 72 yr man with diabetes mellitus, renal failure and a central venous catheter developed fever and hypotension. Blood cultures grew Candida lusitaniae. On day 5 of liposomal amphotericin B 5 mg/kg he remained febrile and his creatinine rose from 4.5 to 6.0 mg/dl.

Question #2 Continued

In addition to changing his IV catheter, which of the following would be most appropriate?:

A. Itraconazole
B. Micafungin
C. Amphotericin B lipid complex
D. IV Voriconazole
E. Isavuconazole

Question #3

Echinocandin class of antifungals has which mechanism of action:

A. inhibits synthesis of membrane sterols
B. damages cytoplasmic membrane
C. interferes with synthesis of fungal cell wall glucans
D. inhibits fungal DNA synthesis
E. interfere with synthesis of fungal cell wall chitin

PREVIEW QUESTION

Question #4

A 37 yr female with diabetes mellitus is admitted for ketoacidosis, fever and sinus pain. Biopsy of a necrotic area of the middle turbinate shows wide, branching nonseptate hyphae. Serum creatinine is 2.5 mg/dl.

PREVIEW QUESTION

Question #4 Continued

Which of the following would be most appropriate?

A. Voriconazole
B. Anidulafungin
C. Fluconazole
D. Liposomal amphotericin B
E. Itraconazole

Question #5

You are asked to advise your hem-onc colleagues as to what prophylactic antifungal agent might be useful in preventing aspergillosis in their patients with prolonged neutropenia or acute graft-vs-host disease .

Question #5 Continued

According to the IDSA guidelines and literature you recommend:

A. itraconazole solution
B. posaconazole
C. micafungin
D. voriconazole
E. caspofungin

PREVIEW QUESTION

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.

PREVIEW QUESTION

Question #6 Continued

The most probable cause was:

A. porphyria cutanea tarda
B. graft versus host disease
C. drug interaction
D. voriconazole
E. Bactrim allergy

Question #7

A 66 yr old male with neutropenia following chemotherapy for lung cancer, serum creatinine 5 mg/dl, and congestive heart failure is found to have a Scedosporium apiospermum lung abscess.

Question #7 Continued

Which of the following would be preferred?

A. Anidulafungin
B. Itraconazole
C. Micafungin
D. Oral voriconazole
E. Liposomal amphotericin B

Question #8

- 65 yr wm admitted with cryptococcal meningitis, seizures, diabetes mellitus and granulomatosis with polyangiitis. Given conventional amphotericin B, flucytosine, phenytoin, glipizide, prednisone and cyclophosphamide.
- By the end of the first week of treatment, his creatinine had risen from 1.6 to 3 mg/dl.
- By the end of the second week his WBC had fallen to 1.2K, platelets 60K and diarrhea began.

Question #8 Continued

The cause of his WBC falling to 1.2K, platelets 60K and copious diarrhea is most likely which of these drugs?

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

Take home messages

- Ampho: not *Scedosporium (Pseudallescheria boydii), Candida lusitaniae, Asperillus terreus*
- Only ampho for mucormycosis
- Fluconazole: not *Candida krusei , Candida auris,*
- +/- *Candida glabrata*
- Echinocandins: not Trichosporon or crypto
- Know mechanisms of action: glucan, sterol, cell membrane, DNA synthesis
- Flucytosine WBC & plt fall, diarrhea, hepatitis

Take home, continued

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

New oral antifungals approved for vulvovaginal candidiasis

- Ibrexafungerp glucan synthase inhibitor
  - Acute infection: two 150 mg tabs (300 mg) 12 hours apart on same day. Cost $ 475
  - Recurrent infection 300g bid q month for six months $2,992.50

Otesaconazole

recurrent infections in women not breastfeeding or capable of childbearing. Start with one week of fluconazole or otesaconazole then otesaconazole once a week for 11 weeks. $2,966. Drug persists about 2 years

Investigational antifungals in clinical trials

- **Olorofim**. Novel drug for Aspergillus, cocci, some molds includes 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

The End

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7

Respiratory Viral Infections Including Influenza, Immunocompetent, and Immunocompromised Patients

Dr. Andrew Pavia

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

Speaker: Andrew T. Pavia, MD

IDBR INFECTIOUS DISEASE BOARD REVIEW LIVE/VIRTUAL AUGUST 19-23 2023

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

6/19/2023

IDBR INFECTIOUS DISEASE BOARD REVIEW LIVE/VIRTUAL AUGUST 19-23 2023

Disclosures of Financial Relationships with Relevant Commercial Interests

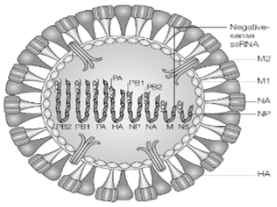
- **Commercial Interests: Antimicrobial Therapy Inc, WebMD, Merck**

What you need to know for the boards

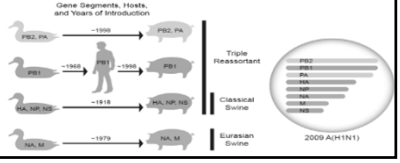
- Minimal virology
- Epidemiology including avian influenza
- Diagnosis
- Complications
- Treatment
- Vaccines

Influenza virus

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



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

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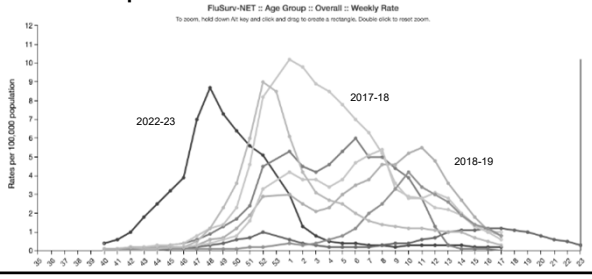
Winter but variable timing and intensity; hospitalization rates from FluSurv-NET



Groups at Risk for Complications of Influenza

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

Influenza Transmission

- Incubation period: 1-4 days (average: 2 days)
- Serial interval: estimated 3-4 days among household contacts
- 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

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

What makes a human influenza strain

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

Influenza A viruses infecting humans

- H1N1*: Emerged in 1918. Re-emerged in 1977
- H2N2: 1956-1977 but replaced by H3N2
- H3N2*: Emerged in 1968 (Hong Kong flu)
- H3N2v*: Assorted swine associated variants
- H5N1*: Emerged 2003 in Hong Kong. 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; ongoing
- 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

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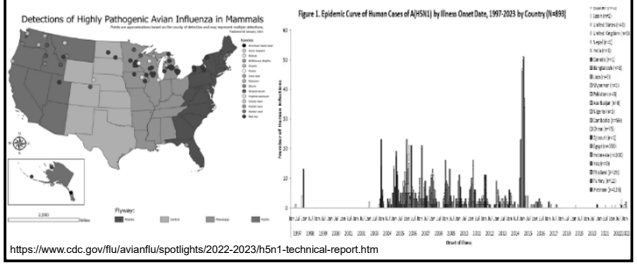
HPAI H5N1 influenza

- 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
- Large outbreaks and massive culling among commercial and backyard poultry around the world
- ~ 57 million birds culled in US in since 2020
- Recent outbreaks in mammals are concerning

Photo: Mads Claus Rasmussen

Human and other mammalian cases of H5N1 (Not testable)



https://www.cdc.gov/flu/avianflu/spotlights/2022-2023/h5n1-technical-report.htm

Question #1

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 Continued

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

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

Mild complications of influenza

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

Severe complications of influenza

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

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Influenza associated hemorrhagic pneumonitis

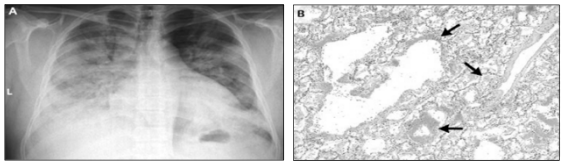

Photo: Perez-Padilla. *NEJM* 009; 361 (7): 680

Non-respiratory complications of influenza

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

PREVIEW QUESTION

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.

PREVIEW QUESTION

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

Diagnosis of influenza

- Performance of all tests depends on prevalence of virus in community and specimen quality
- Clinical diagnosis: up to 80% PPV during peak
- Rapid influenza detection tests have low-moderate sensitivity 10-70% (less for H1N1); reasonably specific
- Positive 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 useless for clinical diagnosis

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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

PREVIEW QUESTION

Question #3

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

PREVIEW QUESTION

Question #3 continued

Which of the following is correct?

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

ACIP and IDSA Guidelines for Antiviral Use 2022

- 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

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

ACIP Guidelines for Antiviral Use 2022 (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

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

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

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Baloxavir

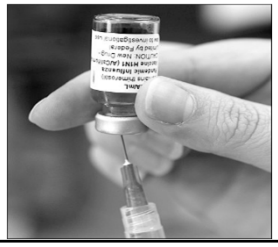
- Cap-dependent polymerase inhibitor
- Non inferior to oseltamivir in two phase 3 studies
- Superior for influenza B in patients with risk factors
- Shorter duration of shedding
- Resistance mutations emerge on treatment in 10-20%
- ? Testable

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

Antiviral Prophylaxis

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

Vaccines



ACIP Recommendations for Influenza vaccination 2023-2024

- Routine influenza vaccination is recommended for all persons aged 6 months and older.
- All vacines now quadrivalent (QIIV = Quadrivalent inactivated influenza vaccine) H1N1, H3N2, B Yamagata, B Victoria
- Enhanced vaccines recommended for those >65
  - High dose inactivated, adjuvanted, recombinant

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

Vaccine pearls (con't.)

- Enhanced vaccines recommended for those >65
  - High dose inactivated, adjuvanted, recombinant
- 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

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

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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.

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

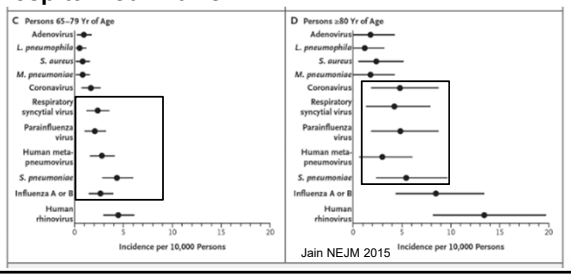
Other important respiratory viruses Adenovirus, RSV, hMPV, parainfluenza, coronaviruses, hantaviruses (and more)

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

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

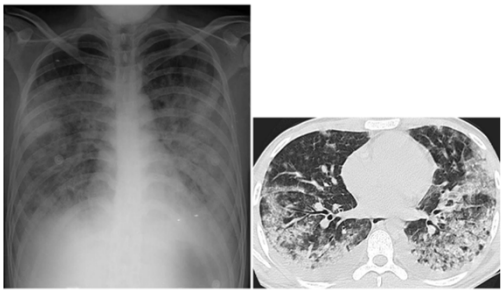
07 - Respiratory Viral Infections Including Influenza, Immunocompetent, and Immunocompromised Patients

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



Korean J Radiol 17(6), Nov/Dec 2016

2023 PREVIEW QUESTION

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

2023 PREVIEW QUESTION

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

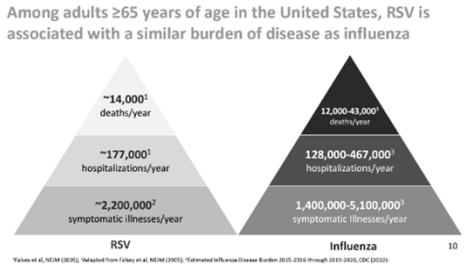
RSV

- 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

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

Speaker: Andrew T. Pavia, MD



Havers F, ACIP meeting June 23, 2022

RSV

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

RSV Prevention!

- Two licensed vaccines for those > 60
  - Both >80% effective at preventing severe RSV
  - Target pre-fusion F protein
    - GSK adjuvanted single dose
    - Pfizer un-adjuvanted two dose
- Pfizer licensed for pregnant women to protect infant
- New long acting monoclonal Ab nirsevimab approved 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

Adenovirus

- DS DNA; 7 species, >50 serotypes
- Associated with URI, pharyngitis, conjunctivitis, pneumonia, hemorrhagic cystitis; hepatitis, disseminated disease in compromised hosts
- Adenovirus 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

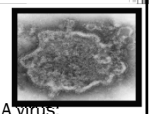
07 - Respiratory Viral Infections Including Influenza, Immunocompetent, and Immunocompromised Patients

Speaker: Andrew T. Pavia, MD

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

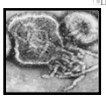
Human Metapneumovirus



- "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

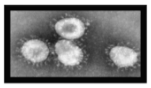
Falsey J Ped Inf Dis 2008
Walter Inf Dis Clin North America 2017

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

Respiratory viruses in older adults

- 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 are important

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

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

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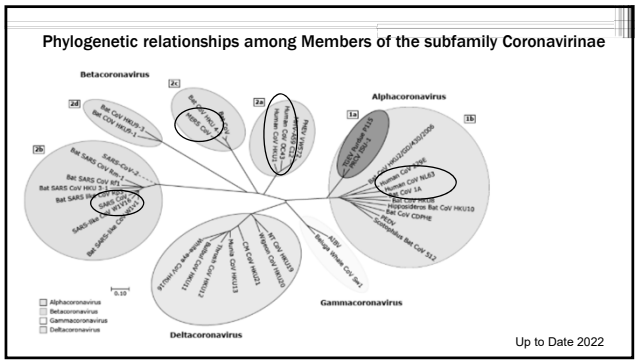
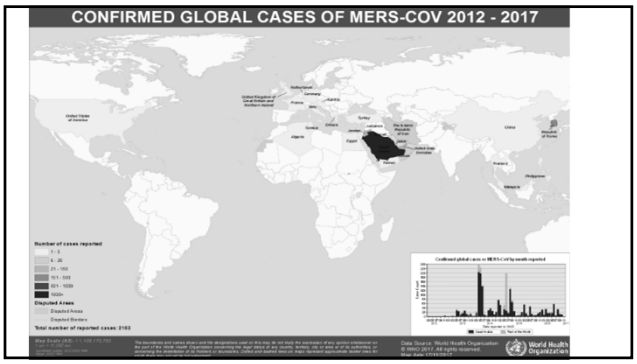




Question #7

- 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)

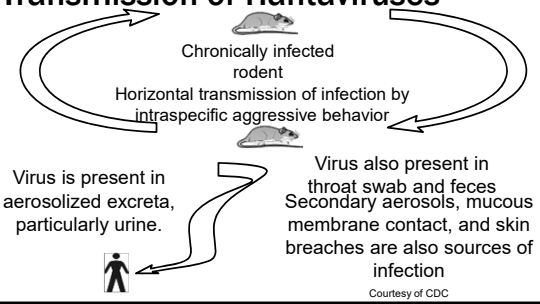
Hantavirus Pulmonary Syndrome HPS

- 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

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

Speaker: Andrew T. Pavia, MD

Transmission of Hantaviruses



Courtesy of CDC

Stages of Hantavirus Pulmonary Syndrome (HPS)

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

HPS-Cardiopulmonary Phase

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

HPS-Cardiopulmonary Phase

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

Good Luck on the Exam!
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Skin and Soft Tissue Infections

Dr. Helen Boucher

08 – Skin and Soft Tissue Infections

Speaker: Helen Boucher, MD

IDBR INFECTIOUS DISEASE BOARD REVIEW LIVE/VIRTUAL AUGUST 19-23 2023

Skin and Soft Tissue Infection

Helen W. Boucher, MD, FACP, FIDSA
Dean and Professor of Medicine
Tufts University School of Medicine
Chief Academic Officer, Tufts Medicine

6/28/2023

IDBR INFECTIOUS DISEASE BOARD REVIEW LIVE/VIRTUAL AUGUST 19-23 2023

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

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 Continued

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***

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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

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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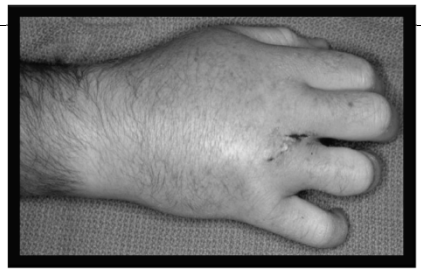
Rat bite fever

- **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

PREVIEW QUESTION

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

BHW1

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**

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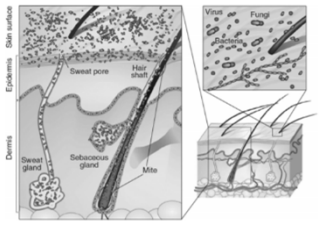
The Skin: Local Invasion by Structure



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

18

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

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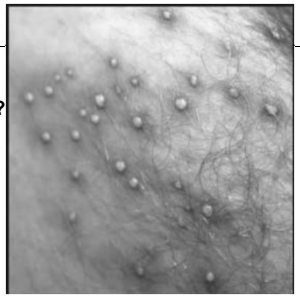
What is this?



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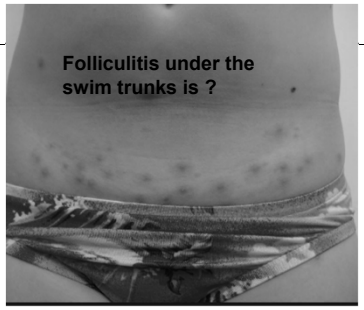
Superficial Folliculitis

- 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 ?



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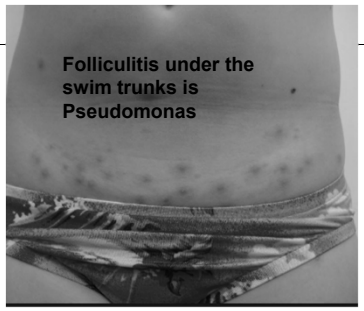
Folliculitis under the swim trunks is Pseudomonas



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**

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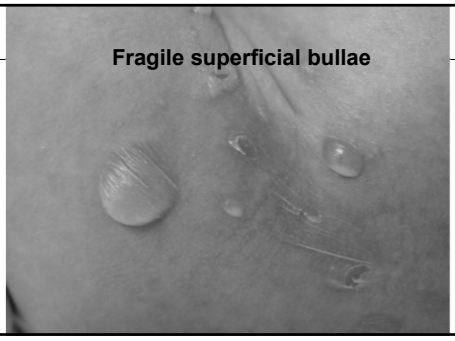
Fragile superficial bullae



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Fragile Bullae in Epidermis

Diagnosis?

- **Bullous impetigo**

Etiology?

- ***S. aureus***

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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**

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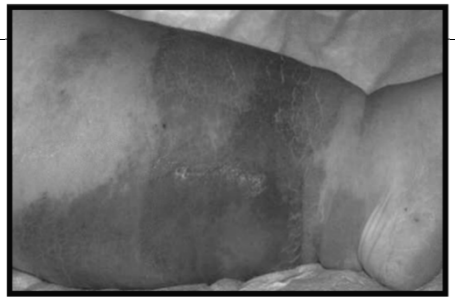
Complications of *S.pyogenes, S. dysgalactiae (Groups C&G)* impetigo

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

29



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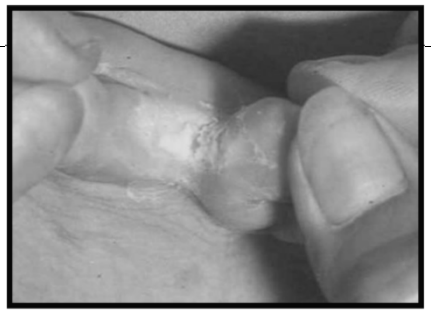


31

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

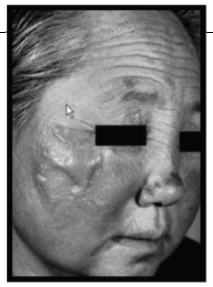
Diagnosis?

- **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



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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

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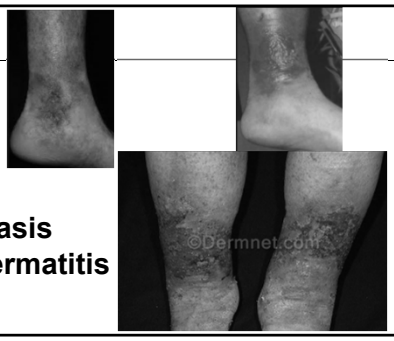
Stasis Dermatitis



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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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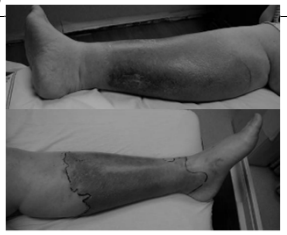
Cellulitis



- 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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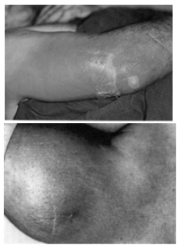
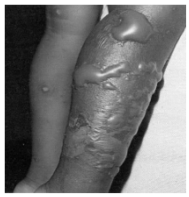
Severe Cellulitis





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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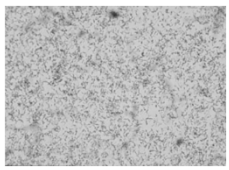
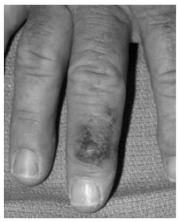
Erysipelothrix rhusiopathiae Infection



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



Resolving cellulitis caused by *Erysipelothrix rhusiopathiae*

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Question #6

PREVIEW QUESTION

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

PREVIEW QUESTION

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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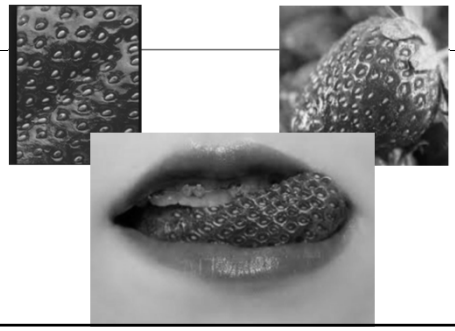

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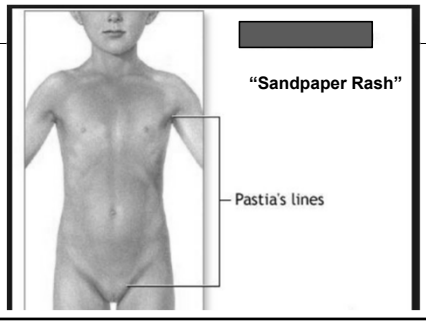

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The most likely diagnosis ?

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

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The most likely diagnosis ?

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

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Question 7:

- 18 year old male 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?

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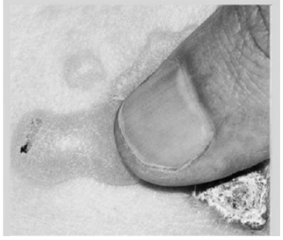
Nikolsky sign



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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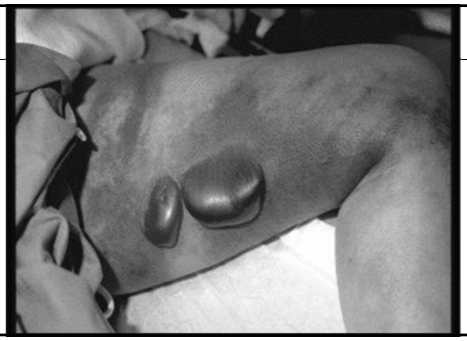

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Erysipelas with loss of pain, hemorrhagic bullae, rapid progression..

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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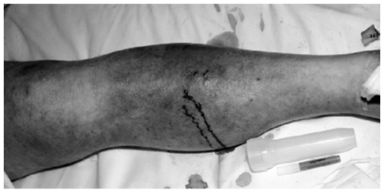
Necrotizing Fasciitis: at the bedside



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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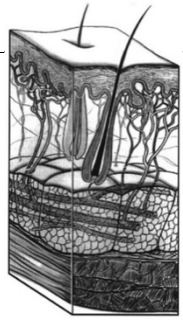

Anatomy	Syndrome
Epidermis Skin	Erysipelas Impetigo Folliculitis
Dermis	Ecthyma Furunculosis Carbunculosis
	All of this is Cellulitis
Superficial fascia Subcutaneous tissue Subcutaneous fat, Nerves, arteries, veins	Necrotizing fasciitis
Deep fascia	
Muscle	Myonecrosis (clostridial and non-clostridial)

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Question #8

A 50-year-old male african american fisherman with known 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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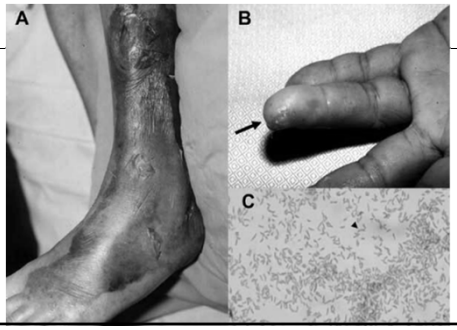

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Vibrio vulnificus

- 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)

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Organisms Whose Growth is Stimulated by Excess Iron

- ***Vibrio vulnificus*** ***V***
- ***Escherichia coli*** ***E***
- ***Listeria monocytogenes*** ***L***
- ***Aeromonas hydrophilia*** ***A***
- ***Rhizopus species (Mucor)*** ***R***
- ***Yersinia enterocolitica*** ***Y***

Definition: "The sails of a ship"

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Thank You!

- **David Gilbert**
- **Our patients and their families**

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Questions, Comments?

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- Helen.boucher@tufts.edu
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Dr. Helen Boucher
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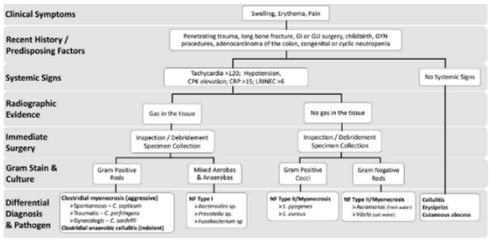
Algorithm for Diagnosis of Necrotizing Infections



* Stevens, et al., Infect Dis Clin N Am 35 (2021) 135–155

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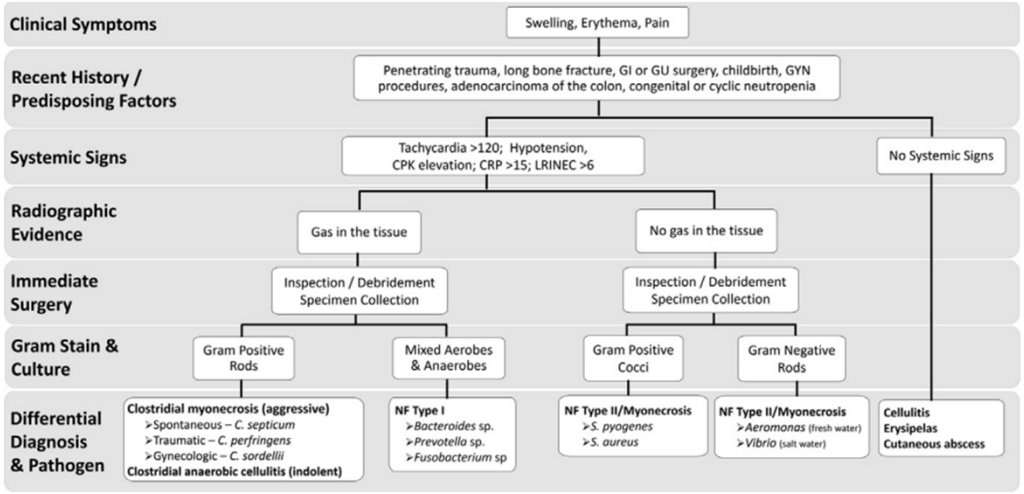
Algorithm for Diagnosis of Necrotizing Infections



Stevens, et al., Infect Dis Clin N Am 35 (2021) 135–155

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9

Core Concepts: Antiviral Drugs

Dr. Andrew Pavia

09 - Core Concepts: Antiviral Drugs

Speaker: Andrew T. Pavia, MD

IDBR INFECTIOUS DISEASE BOARD REVIEW LIVE/VIRTUAL AUGUST 19-23 2023

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

6/19/2023

IDBR INFECTIOUS DISEASE BOARD REVIEW AUGUST 19-23 2023

Disclosures of Financial Relationships with Relevant Commercial Interests

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

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
- It is possible that remdesivir, Paxlovid, or molnupiravir will be on the exam by mechanism

Herpes Viruses

Herpes Viruses

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

Herpes Virus Resistance Testing

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

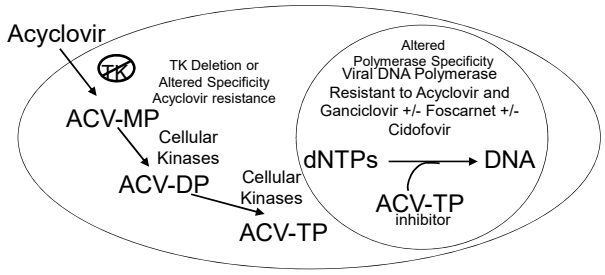
Acyclovir and Valacyclovir

- Acyclic guanosine nucleoside analogs, act as chain terminators
- Therapeutic uses:
  - HSV-1, HSV-2, VZV but NOT CMV or EBV
- Resistance occurs almost exclusively in immunosuppressed hosts (especially HSCT recipients and advanced HIV)
  - More common with HSV than VZV
  - When acyclovir resistant HSV or VZV disease is successfully treated, if recurrent disease occurs, the recurrent isolate is characteristically wild type, i.e. acyclovir sensitive
  - Secondary resistance (due to drug pressure) is more common than primary (the acquired virus is resistant)
  - Acyclovir resistance also confers resistance to valacyclovir (and famciclovir which is not available in US)

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

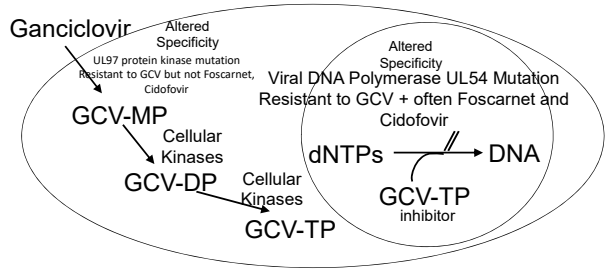
Acyclovir Mechanism of Action Mechanism of Resistance Within Virus



Ganciclovir and Valganciclovir

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

Mechanism of Action of Ganciclovir Mechanism of Resistance Within Virus



Foscarnet

- Activity
  - Binds to DNA polymerase
  - Active against HSV, VZV, CMV, 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

Maribavir

- Mechanism of action
  - Inhibits protein kinase UL97
- Activity
  - CMV including most GCV-, foscarnet-, and cidofovir-resistant strains, EBV
- Resistance
  - Mutations in UL 97 (upstream of GCV resistance sites)
- Complex drug interactions

Hepatitis B

Therapy for Hepatitis B

- Lamivudine
  - Active against both HIV and HBV
  - Resistance:
    - most common: YMDD motif in viral DNA polymerase, (similar to M184V in HIV)
    - most often in patients chronically treated with lamivudine monotherapy
- Tenofovir (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

Influenza

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 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)
- Molnupiravir
  - Mechanism
    - Acts as nucleoside analog
    - Causes "catastrophic errors" in replication
- Nirmaltrevir/ritonavir (Paxlovid)
  - Inhibits Mpro (main protease) required to cleave viral polyproteins
  - Several mutations identified in Mpro that confer resistance but at fitness cost
  - Clinical importance remains under investigation

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

10

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

Dr. Rajesh Gandhi

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

Speaker: Rajesh Gandhi, MD

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

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

6/29/2023

Disclosures of Financial Relationships with Relevant Commercial Interests

- None

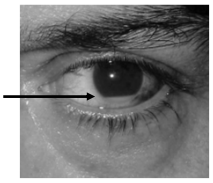
INFECTIOUS DISEASE IMAGES
eMicrobes Digital Library
A Joint Project of the Massachusetts General Hospital Infectious Diseases Division and Microbiology Lab

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

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

What is the diagnosis?

A. Staphylococcal keratitis
B. Herpes simplex keratitis
C. Bacterial endogenous endophthalmitis
D. Pulmonary tuberculosis with chorioretinitis
E. Cytomegalovirus retinitis



Contributed by: Heather Calderon, M.D. Published in NEJM 348:834

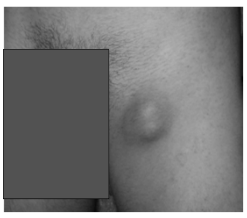
Case 2

- 19 yo M presented with 2 wks of painful swelling in his left groin. He reported fevers to 101 with night sweats, fatigue and malaise.
- Denied urinary complaints, penile discharge or ulcers, change in bowel habits, abdominal pain or trauma to his legs.
- Lived in Northeast US. No travel. Two female sexual partners, one of whom recently immigrated from Mexico. Lived with mother and grandmother, who had a cat and dog. Worked in food services. Denied seeing mice or rats

What is the diagnosis?

T: 98.6 F. Tender lymph node inferior to inguinal ligament. WBC: 9.6; Urinalysis: negative

A. Lymphogranuloma venereum (LGV)
B. Chancroid buboe
C. Bubonic plague
D. Cat-scratch disease (CSD)
E. Incarcerated hernia



Contributed by Stephen Walsh, M.D.

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

Speaker: Rajesh Gandhi, MD

Inguinal adenopathy

- Ddx: HSV, syphilis, LGV, chancroid, CSD, lymphoma, tularemia, *S. aureus,* malignancy
- LGV often involves both femoral and inguinal nodes, producing characteristic "groove" sign

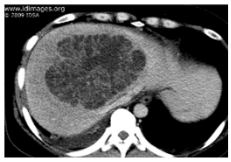
Ballard and Freinkel, Tropical Pathology, 1995.

Cat Scratch Disease Lymphadenitis

- Generally due to infection by *Bartonella henselae*
- Primary papule develops at site of inoculation, may last 1-2 wks, followed by regional adenopathy which can last for 2-4 months.
- About 1/6 develop LN suppuration
- Spontaneous resolution generally occurs.
- Diagnosis: Serology; PCR, rarely by culture
- Most cases self-limited, but azithromycin may hasten resolution of adenopathy

Case 3

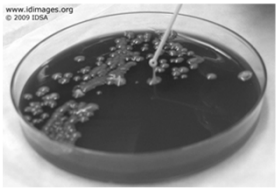
- A woman from China in her 40s developed fever, epigastric pain, and nausea. One week later, she was brought to ED with confusion and fever.
- T 101°F. Right upper quadrant abdominal tenderness
- Abdomen CT: 10 cm hypoattenuated liver lesion



What is the diagnosis?

A. *Entamoeba histolytica*
B. *E. coli*
C. *Streptococcus milleri*
D. *Actinomyces*
E. *Klebsiella pneumoniae*

Culture from liver aspirate



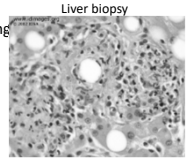
Contributed by Diana I. Mercado MD, Dong H. Lee MD, Todd I. Braun, MD

Case 4

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

Lung exam: fine crackles over the left upper lung

Liver biopsy



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

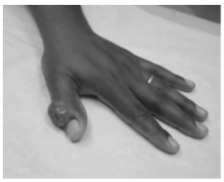
Case 5

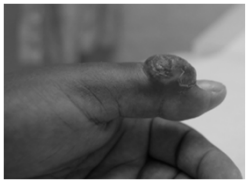
- 35 yo man of Ethiopian descent cut his left thumb with a knife while slaughtering a lamb as part of Easter festivities. He washed the wound with water and applied lemon juice and alcohol. One week later, he developed swelling and tenderness and a fluctuant lesion at the site.
- Two weeks after the injury, he underwent incision and drainage; cultures grew *Staph. aureus* (oxacillin sensitive). Treated with cephalexin but did not improve.

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

Speaker: Rajesh Gandhi, MD

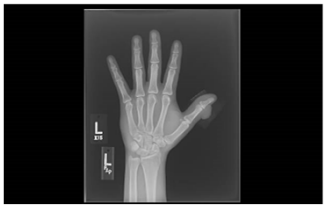
Afebrile. 2 x 2 x 2 cm firm lesion on his thumb, without discoloration, purulent discharge, fluctuance, or bleeding





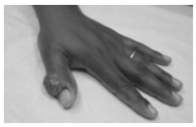
Creatinine and LFTs normal. Glucose 158. WBC 4.2 (normal differential).

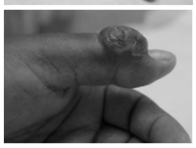
X-ray: fungating soft tissue lesion on dorsal aspect of distal thumb; no underlying bone or joint abnormality



What is the diagnosis?

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

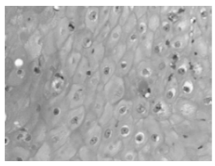




Contributors: Drs. Isaac Bogoch, Rajesh Gandhi

Follow-up

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



Appearance consistent with ecythma contagiousum

Orf (contagious ecthyma)

- Zoonotic infection caused by a dermatropic parapox virus (ds DNA) of goats and sheep
- Transmitted by contact with infected animal or fomites
  - Animal handlers; children after visiting petting zoos, livestock fairs
  - Clusters reported after Eid, other festivities involving lamb sacrifice (Passover, Easter)

Orf (continued)

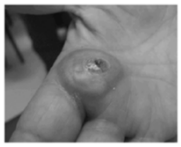
- 3-7 d incubation period.
- Macule or papule → nodule with red center, white halo and peripheral erythema → ulcerative lesion → regenerative papilloma.
- Most resolve in 4-8 wk
- Human-to-human transmission has not been reported
- Protective immunity incomplete; persons can be infected multiple times

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

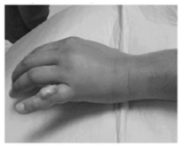
Speaker: Rajesh Gandhi, MD

MMWR (April 13, 2012) highlighted 4 cases of orf associated with household meat processing or animal slaughter

- Bulla caused by orf virus infection after puncture by a bone of a recently slaughtered goat—PA, 2009



- Nodule caused by orf virus infection after contact with a lamb being sacrificed for a holiday — MA, 2010



Case 6

- A woman in her forties presented with 6 days of fatigue, decreased appetite, fevers and chills. She also had severe headache and myalgias.
- **PMH:** None.
- **SH:** Patient was single and not sexually active. She denied cigarette, alcohol or illicit drug use. The patient had recently hiked in New Hampshire. She denied a history of tick bites. She had a dog but no other animal exposures.

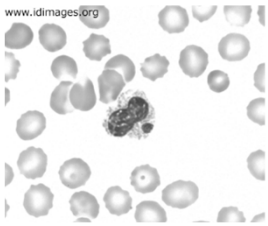
Contributed by Anne Kasmar, M.D.

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

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

21

Neutrophil with additional finding



Differential Diagnosis

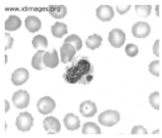
A. Meningococcemia

B. Anaplasmosis

C. Histoplasmosis

D. Babesiosis

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



Differential diagnosis

- **Meningococcemia:** patient did not have meningeal signs or rash to suggest acute meningococcemia; did not have arthritis/tenosynovitis/rash to suggest chronic meningococcemia
- **Histoplasmosis:** patient not immunosuppressed, which predisposes to disseminated histo; CXR not abnormal (infiltrates often present in histo)
- **Babesia:** ring-forms in red cells, not white cells
- **Rocky Mountain Spotted Fever:** would not explain morulae in WBC. RMSF (and human monocytotropic ehrlichiosis) more common in southeast, southcentral US

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

Speaker: Rajesh Gandhi, MD

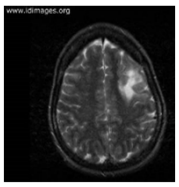
Case 7

- 30 yo woman with HIV (CD4 cell count 20, not on therapy) presented with gradual onset of word-finding difficulties, expressive aphasia and right upper extremity weakness over 4 weeks.
- **Social history:** She lived in New England. No recent travel or known insect bites. Not sexually active.
- **PE:** On exam, she was afebrile. She had oral thrush. She had difficulty naming objects and right-sided weakness.
- **Studies:** WBC count of 2.2 (44% P, 45% L)

Contributed by Wendy Yeh, M.D.

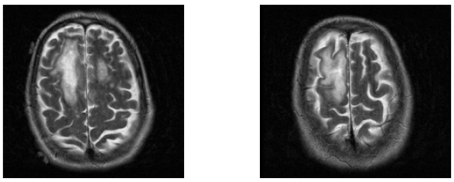
Her clinical syndrome is most likely caused by:

A. An arbovirus
B. A polyomavirus
C. A herpes virus
D. A spirochete
E. A dematiaceous fungus



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

PML



Contributed by Vince Marconi, M.D.

Differential diagnosis

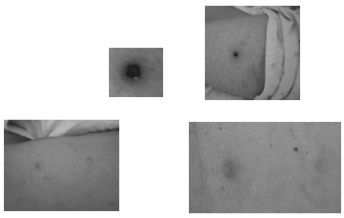
- **Arbovirus, such as West Nile Virus:** Unlikely because of no confusion, headache, meningeal signs, paralysis.
- **Herpes virus, such as HSV:** temporal lobe.
- **Spirochetal infection, such as syphilis:** central nervous system gumma or stroke-like syndrome (meningovascular disease).
- **Dematiaceous fungus:** no risk factors (e.g. adjacent paranasal sinus infection, penetrating trauma); lack of enhancement of brain lesion on head imaging.

Case 8

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

Does this patient most likely have:

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



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

Speaker: Rajesh Gandhi, MD

Case 9

- Previously healthy man in his seventies presented with 2 weeks of fever, headaches, myalgias and 5 days of nonproductive cough, dyspnea, and fevers as high as 102 ºF.

Epidemiologic history

- Lives in Southern California in mountain wilderness.
- Leaves his vehicle outside with the windows down; frequently cleans dashboard and upholstery.
- No domestic pets, but surrounded by rodents, deer, sheep, raccoons, other wildlife.
- Prior to onset of symptoms, he had visited a local zoo; no direct animal contact
- No other travel history outside the country; no known sick contacts.

Case 9 (cont.)

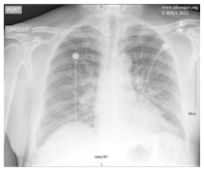
Physical Examination

- Mild respiratory distress
- BP 141/80. Pulse 94. Temp. 97.7 ºF, RR 20, oxygen sat 93% on 6 L oxygen by nasal canula.
- Respiratory exam demonstrated mild rhonchi at the lung bases.
- Examination was otherwise normal.

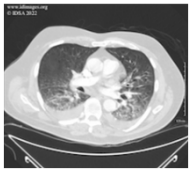
Studies

- WBC 19.3; 10% atypical lymphocytes; no eosinophilia. Hemoglobin 18.4 g/dL. Hematocrit 52.6%. Platelets 102,000
- Basic metabolic panel and liver enzymes normal.
- Chlamydia pneumoniae, Mycoplasma, HIV-1/2, Coxiella serologies were negative.
- *Streptococcus pneumoniae* and *Legionella pneumophila* urine antigen were negative.
- Respiratory viral panel negative.

Studies



Chest X-ray demonstrating ground-glass opacities in the upper and lower lobes consistent with pneumonia.



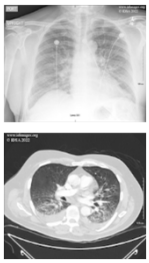
Chest CT: Hazy ground glass densities in the lower lobes bilaterally with bilateral pleural effusions.

Clinical Course Prior to Diagnosis

- Patient was admitted with diagnosis of community-acquired pneumonia.
- He was started on azithromycin and ceftriaxone.
- He was initially requiring minimal supplemental oxygen, however, his respiratory status worsened requiring high flow nasal canula at 20 L with fractional inspired oxygen of 80% saturation (FiO2%) during initial course of hospitalization.

What is the diagnosis?

A. Coccidioidomycosis
B. Legionella pneumonia
C. Hantavirus Cardiopulmonary Syndrome
D. Leptospirosis Pulmonary Hemorrhage Syn.
E. Tularemia



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Agenda Day 2: Sunday, August 20, 2023

AM Moderator: Andrew Pavia, MD					
#	Start		End	Presentation	Faculty
QP2	8:30 AM EDT	-	9:00 AM EDT	Daily Question Preview Day 2	Andrew Pavia, MD
11	9:00 AM	-	10:00 AM	Clinical Immunology and Host Defense	Steven Holland, MD
12	10:00 AM	-	10:30 AM	Gastrointestinal Disease: Etiologic Agents	Herbert Dupont, MD
	10:30 AM	-	10:45 AM	Faculty Q&A	Drs. Pavia (Moderator), Holland, Dupont, and Kotton
13	10:45 AM	-	11:15 AM	Gastrointestinal Disease: Clinical Syndromes	Herbert Dupont, MD
14	11:15 AM	-	12:00 PM	CMV, EBV, HHV6 and HHV8 in Immunocompetent and Immunocompromised Patients	Camille Kotton, MD
	12:00 PM	-	12:30 PM	Lunch Break	
BR2	12:30 PM	-	1:30 PM	Board Review Day 2	Drs. Kotton (Moderator), Aronoff, Bennett, Chambers, Dupont, and Tunkel
PM Moderator: Andrew Pavia, MD					
15	1:30 PM	-	2:00 PM	Nocardia, Actinomycosis , Rhodococcus, and Melioidosis	David Aronoff, MD
16	2:00 PM	-	3:00 PM	Endocarditis of Native and Prosthetic Devices, and Infections of Pacers and Ventricular Assist Devices	Henry Chambers, MD
17	3:00 PM	-	3:45 PM	Zoonoses	David Aronoff, MD
FC4	3:45 PM	-	4:00 PM	Faculty Q&A	Drs. Pavia (Moderator), Aronoff and Chambers
18	4:00 PM	-	4:45 PM	Staphylococcal Disease	Henry Chambers, MD
19	4:45 PM	-	5:15 PM	Helicobacter and Clostridioides Difficile	David Aronoff, MD
20	5:15 PM	-	6:00 PM	Brain Abscess, Cavernous Sinus Thrombosis, and Subdural and Epidural Empyema	Allan Tunkel, MD
FC5	6:00 PM	-	6:30 PM	End of the Day Faculty Q&A	Drs. Aronoff, Chambers, Pavia, and Tunkel

QP2

Daily Question Preview 2

Dr. Andrew Pavia (Moderator)

QP2 – Daily Question Preview: Day 2

Moderator: Andrew T. Pavia, MD

Daily Question Preview: Day 2

Moderator: Andrew T. Pavia, MD

8/2/2023

PREVIEW QUESTION INFECTIOUS DISEASE BOARD REVIEW 2023

2.1 **Low Dose Pathogens Commonly Cause Diarrhea Outbreaks in Day Care Center**

Which of the following doesn't fit?

A) ***Shigella***

B) ***Cryptosporidium***

C) ***Giardia***

D) ***Campylobacter jejuni***

E) ***Norovirus***

1 of 2

PREVIEW QUESTION INFECTIOUS DISEASE BOARD REVIEW 2023

2.2 **A patient develops numbness of lips, burning and tingling of his extremities, and abdominal pain and vomiting 30 minutes after a meal in Jamaica, progressing to respiratory failure.**

1 of 3

PREVIEW QUESTION INFECTIOUS DISEASE BOARD REVIEW 2023

2.2 **What is the likely diagnosis?**

A) Scombroid

B) Paralytic shellfish poisoning

C) Ciguatera

D) Neurotoxic shellfish poisoning

E) Monosodium glutamate toxicity

2 of 3

PREVIEW QUESTION INFECTIOUS DISEASE BOARD REVIEW 2023

2.3 **A 35-year-old woman develops diarrhea, cramps and is passing bloody stools with fever while snorkeling with her family in Cozumel, Mexico.**

1 of 3

PREVIEW QUESTION INFECTIOUS DISEASE BOARD REVIEW 2023

2.3 **What is the preferred treatment for this patient With dysenteric traveler's diarrhea?**

A) Azithromycin 1,000 mg

B) Ciprofloxacin 500 mg twice daily X 3 days

C) Levofloxacin 500 mg

D) Rifaximin 200 mg three times/d for 3 days

E) Oral fluids only

2 of 3

QP2 – Daily Question Preview: Day 2

Moderator: Andrew T. Pavia, MD

PREVIEW QUESTION INFECTIOUS DISEASE BOARD REVIEW 2023

2.4 **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 INFECTIOUS DISEASE BOARD REVIEW 2023

2.4 **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 INFECTIOUS DISEASE BOARD REVIEW 2023

2.5 **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.

1 of 5

PREVIEW QUESTION INFECTIOUS DISEASE BOARD REVIEW 2023

2.5 **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).

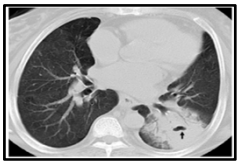
Gram strain of bronchoalveolar lavage fluid reveals beaded gram positive filamentous organisms (image).

2 of 5

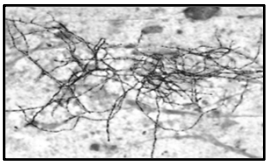
PREVIEW QUESTION INFECTIOUS DISEASE BOARD REVIEW 2023

2.5

Chest CT



BAL



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

3 of 5

PREVIEW QUESTION INFECTIOUS DISEASE BOARD REVIEW 2023

2.5 **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

QP2 – Daily Question Preview: Day 2

Moderator: Andrew T. Pavia, MD

PREVIEW QUESTION INFECTIOUS DISEASE BOARD REVIEW 2023

2.6 **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 INFECTIOUS DISEASE BOARD REVIEW 2023

2.6 **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 INFECTIOUS DISEASE BOARD REVIEW 2023

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

Exam : BP 160/40 P110 , 39.5

- **Rales ½ way up bilaterally**
- **Loud diastolic decrescendo murmur, lower left sternal border**

1 of 4

PREVIEW QUESTION INFECTIOUS DISEASE BOARD REVIEW 2023

2.7 **Labs and studies**

- **WBC 23,000 90% PMNS, HCT 30. Platelets 110.**
- **Creatinine 1.6 mg/dl**
- **TTE 1.5 cm oscillating mass, on bicuspid AV with severe aortic regurgitation**

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

2 of 4

PREVIEW QUESTION INFECTIOUS DISEASE BOARD REVIEW 2023

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

A) Nafcillin

B) Vancomycin

C) Vancomycin + nafcillin

D) Vancomycin + gentamicin

E) Vancomycin + gentamicin + rifampin

3 of 4

PREVIEW QUESTION INFECTIOUS DISEASE BOARD REVIEW 2023

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

Exam: T38.9oC, Pulse 110 , BP 145/95 mm Hg.

- **Lungs are clear**
- **3/6 systolic ejection murmur at the right upper sternal boarder.**

1 of 4

QP2 – Daily Question Preview: Day 2

Moderator: Andrew T. Pavia, MD

PREVIEW QUESTION INFECTIOUS DISEASE BOARD REVIEW 2023

2.8 **Lab results**

- **Serum glucose 340 mg/dl**
- **Serum creatinine 1.7 mg/dl, BMP otherwise normal**
- **UA: 3+ protein, 20-50 wbcs/high power field, 4+ glucose.**
- **Two blood cultures and a urine culture are positive for ampicillin-susceptible *Enterococcus faecalis*.**

2 of 4

PREVIEW QUESTION INFECTIOUS DISEASE BOARD REVIEW 2023

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

A) Ampicillin for 2 weeks

B) Penicillin + gentamicin for 4 weeks

C) Ampicillin + gentamicin for 4 weeks

D) Ampicillin + ceftriaxone for 6 weeks

E) Daptomycin for 8 weeks

3 of 4

PREVIEW QUESTION INFECTIOUS DISEASE BOARD REVIEW 2023

2.9 **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 INFECTIOUS DISEASE BOARD REVIEW 2023

2.9 **Exam: T37oC, 5 cm tender red mass in right midinguinal area, fixed to skin. Genitalia normal.**

Aspiration of soft center: 5 cc yellow pus. Gm stain neg. cephalexin 250 mg qid.

One week later: mass unchanged. Culture neg. Syphilis FTA & HIV neg.

2 of 4

PREVIEW QUESTION INFECTIOUS DISEASE BOARD REVIEW 2023

2.9 **Most likely dx:**

A) *Bartonella henselae*

B) *Treponema pallidum*

C) *Haemophilus ducreyi*

D) *Francisella tularensis*

E) *Klebsiella (Calymmatobacterium) granulomatis*

3 of 4

PREVIEW QUESTION INFECTIOUS DISEASE BOARD REVIEW 2023

2.10

- **28 yr old male presents with temp 39oC, diffuse myalgia, headache, malaise. Returned 2 days ago from "Iron Man" race with running, biking, swimming in lake, climbing in Hawaii. Numerous mosquito bites. Exam: Conjunctival suffusion but no other localizing findings.**
- **WBC 14,500 with 80%PMN, no eos or bands. Platelets 210k.**
- **Bili 2.4, ALT 45, AST 52, Alk Phos 120, Cr 1.6. Hct 45%. BC neg. UA: normal**

1 of 3

PREVIEW QUESTION INFECTIOUS DISEASE BOARD REVIEW 2023

2.10 **Most likely diagnosis:**

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

2 of 3

PREVIEW QUESTION INFECTIOUS DISEASE BOARD REVIEW 2023

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

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

1 of 3

PREVIEW QUESTION INFECTIOUS DISEASE BOARD REVIEW 2023

2.11 **Which one of the alternative agents would you recommend?**

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

2 of 3

PREVIEW QUESTION INFECTIOUS DISEASE BOARD REVIEW 2023

2.12 **A patient with complicated MRSA bacteremia on day 9 of therapy with daptomycin q48h develops myalgias with a creatinine kinase of 1250 u/L (upper limit of normal 200).**

The last positive blood culture was on day 3 of therapy.

MICs (µg/ml) of the isolate are as follows: vancomycin 2 (S), daptomycin 0.5 (S), dalbavancin 0.25 (S), telavancin 0.5 (S), ceftaroline 1 (S).

1 of 3

PREVIEW QUESTION INFECTIOUS DISEASE BOARD REVIEW 2023

2.12 **Which one of the following would you recommend?**

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

2 of 3

PREVIEW QUESTION INFECTIOUS DISEASE BOARD REVIEW 2023

2.13 **A 25-year-old woman complains of 6 weeks of symptoms consistent with dyspepsia unrelieved by current use of antacids & an OTC PPI.**

1 of 3

PREVIEW QUESTION INFECTIOUS DISEASE BOARD REVIEW 2023

2.13 **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 13C Urea Breath Test

E) D/C PPI for 2 weeks then Hp stool antigen EIA

2 of 3

PREVIEW QUESTION INFECTIOUS DISEASE BOARD REVIEW 2023

2.14 **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

1 of 2

PREVIEW QUESTION INFECTIOUS DISEASE BOARD REVIEW 2023

2.15 **79-year-old female is transferred from a nursing home for failure to thrive as a result of decreased oral intake.**

A nasogastric tube is placed via the left nares for enteral hyperalimentation

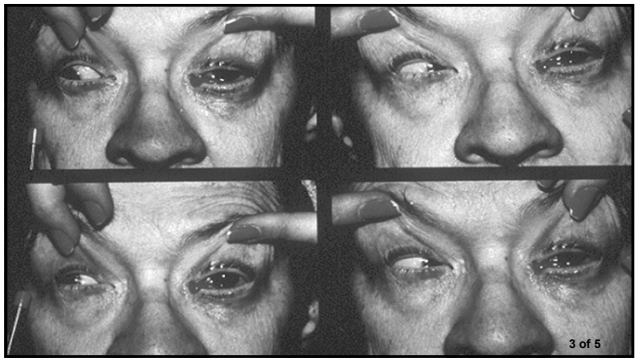
1 of 5

PREVIEW QUESTION INFECTIOUS DISEASE BOARD REVIEW 2023

2.15 **One week into her hospital course, the patient develops fever to 101.5°F, and left periorbital edema and chemosis**

CT scan of the head without contrast reveals opacification of the sphenoid sinus

2 of 5



3 of 5

PREVIEW QUESTION INFECTIOUS DISEASE BOARD REVIEW 2023

2.15 **Which of the following studies should be performed to establish the diagnosis?**

A) CT scan of the head and sinuses with contrast

B) MR imaging with MR venography

C) Cerebral angiography

D) Positron emission tomography of the head

E) Lumbar puncture

4 of 5

11

Clinical Immunology and Host Defense

Dr. Steven Holland

IDBR INFECTIOUS DISEASE BOARD REVIEW LIVE/VIRTUAL AUGUST 19-23 2023

Clinical Immunology and Host Defense

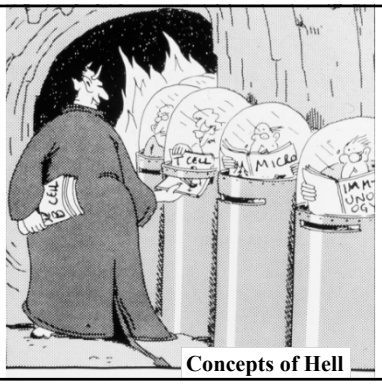
Steven M. Holland, MD
Laboratory of Clinical Immunology and Microbiology
NIAID, NIH

7/2/2023

IDBR INFECTIOUS DISEASE BOARD REVIEW LIVE/VIRTUAL AUGUST 19-23 2023

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

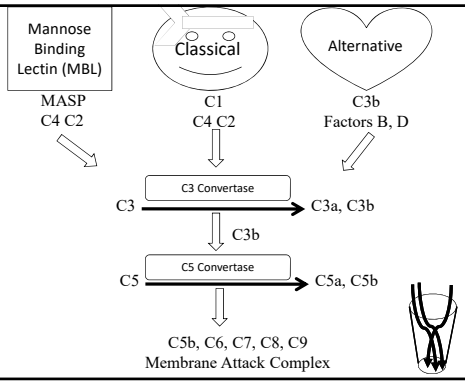
Patients with impaired inflammation:
- may be unable to tell you they are sick (feel fine)
- are often sicker than they look
- often have more extensive disease than is apparent
- may require longer treatment than normals
- may have unusual infections

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), AH50 (Alternative)

Rx- treat infections, prophylaxis if needed, hypervaccination?

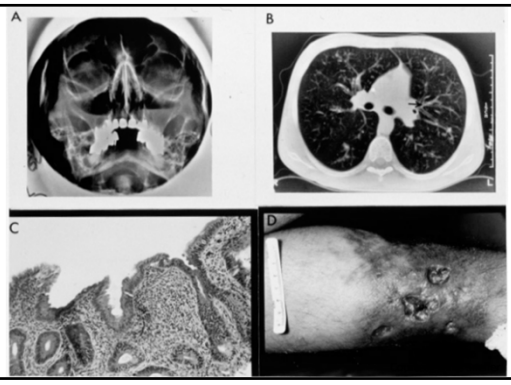
J Clin Immunol 2020 May;40(4):576-591

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.

47 year old woman

Recurrent episodes of bronchitis, recently more exacerbations. Tired.

One episode of documented bacterial pneumonia and sinusitis.

Immunoglobulin levels:

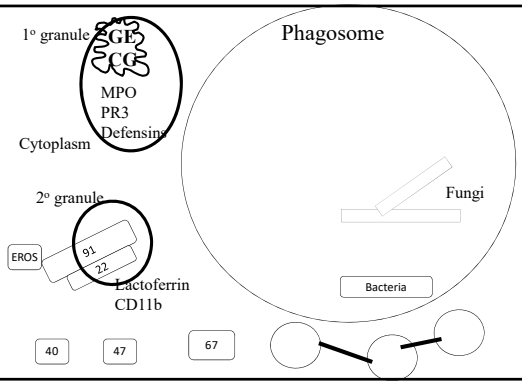
IgG 500 (normal 523-1482)

IgA <10 (normal 51-375)

IgM 165 (normal 37-200)

Next step?

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



52 year old man

referred from his Family Practitioner.

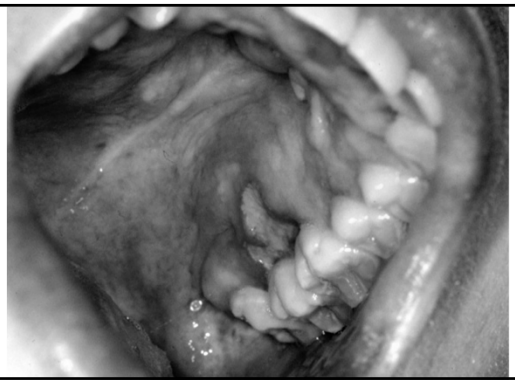
Recurrent digital and oral ulcers occurring every month or so for the last 4 months.

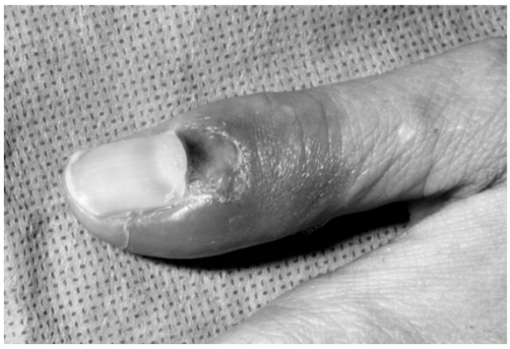
One CBC showed an ANC of 100, but on repeat several days later was normal.

Previous health good.

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

Spleen tip felt.





Cyclic or Acute Neutropenia

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

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

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

Dx- molecular; demonstration of periodicity, family history.

Rx- G-CSF lifts both nadir and baseline

Nat Rev Dis Primers. 2017;3:17032

Acquired Neutropenia in Adults

-Drugs, lupus, etc.

-acquired cyclic neutropenia

(Large Granular Lymphocytosis, LGL)

splenomegaly, often associated with rheumatoid arthritis (Felty Syndrome)

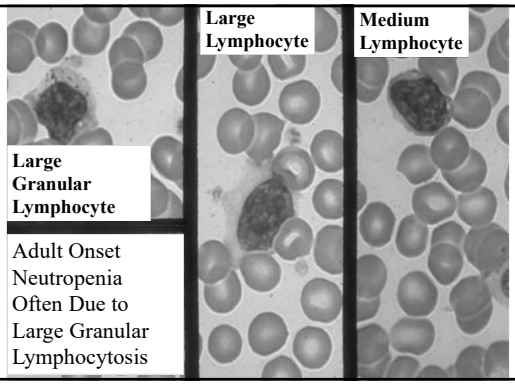
Dx- clonal CD3+/8+/57+ lymphs (LGL)

(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)

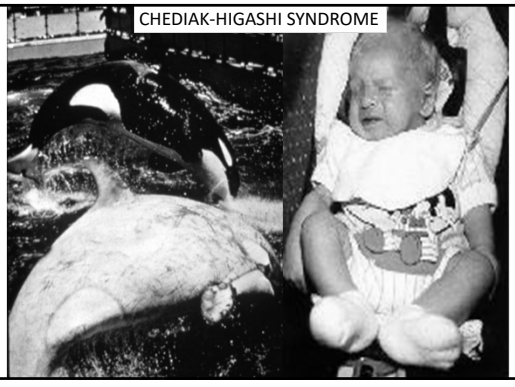
most common neutrophil disorder (1/2000)

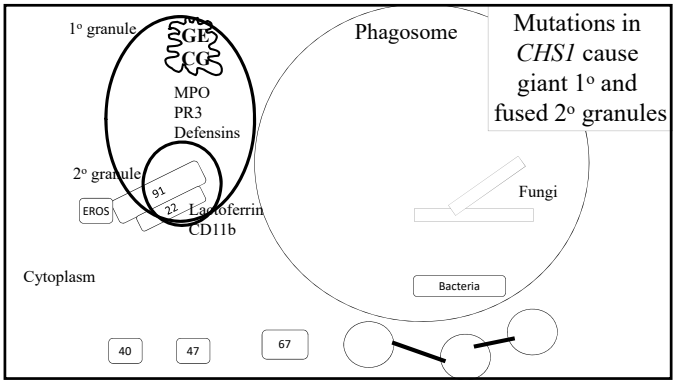
- not a pathologic condition *per se*
- failure of H_2O_2 -----MPO-----> HOCl
- compensated by increased H_2O_2 production
- appears to need another condition to potentiate, such as diabetes mellitus

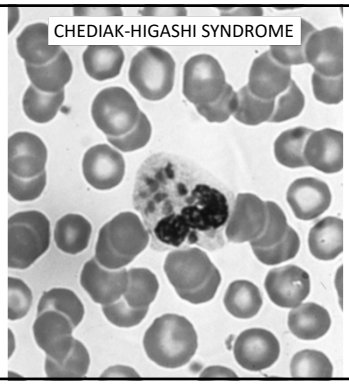
Dx- absence of peroxidase positive granules due to mutations in *MPO* gene

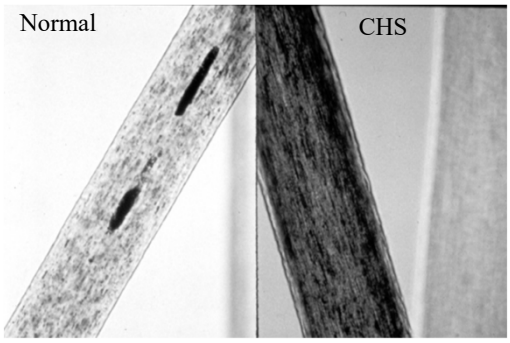
Rx- treat invasive infections (*Candida*), no specific therapy

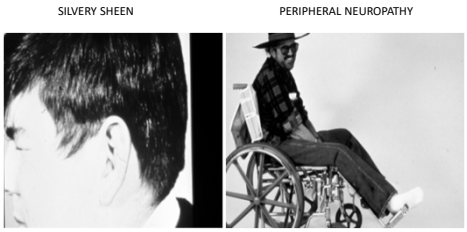
J Leukoc Biol. 2013 Feb;93(2):185-98











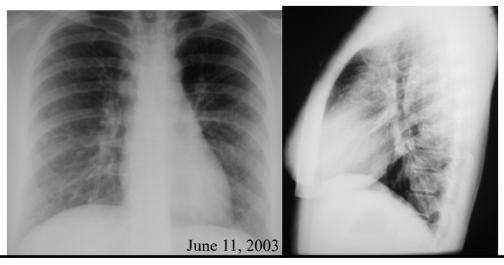
Chediak-Higashi Syndrome (AR)

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

23 yo woman; athletic coach

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



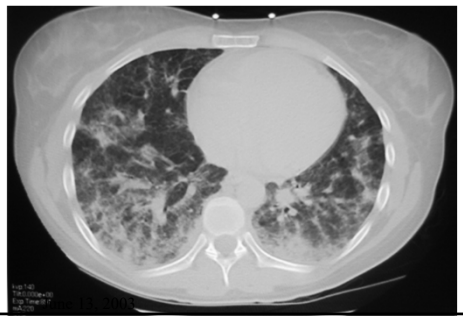
ER presentation

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

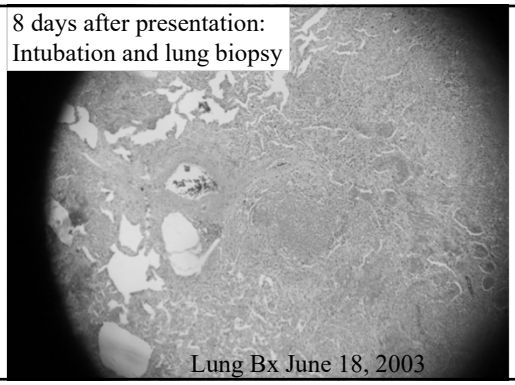
2 days later, hypoxia and fever



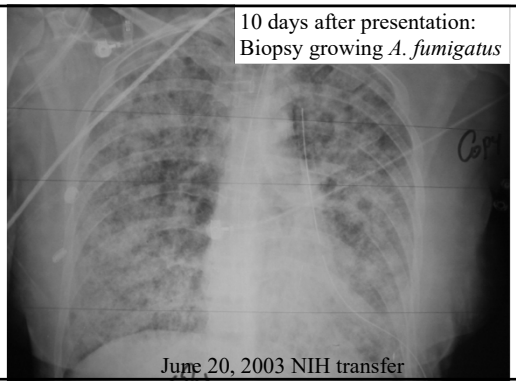
Hospital Course

- 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*



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

a) Allergic bronchopulmonary aspergillosis

b) Cystic fibrosis

c) Lymphocyte dysfunction (SCID)

d) Phagocyte defect

e) Acute HIV

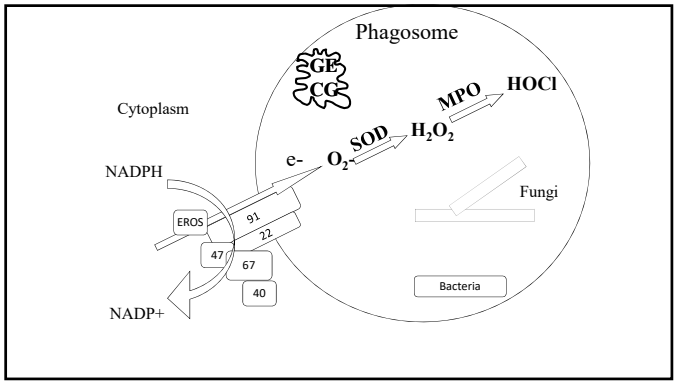
What is so special about phagocytes?

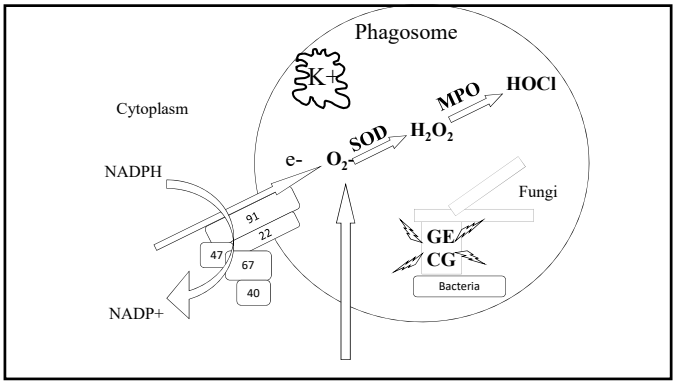
neutrophils, monocytes, macrophages, eosinophils, basophils

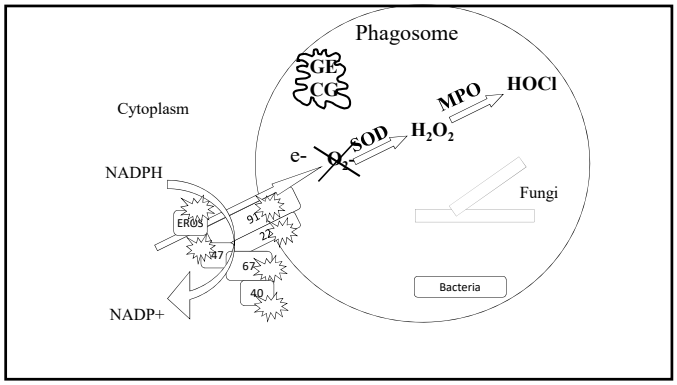
Preformed cytoplasmic granules with stored enzymes

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

Half life of neutrophils in the circulation?
7 hours







Chronic Granulomatous Disease
(X, AR)

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

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

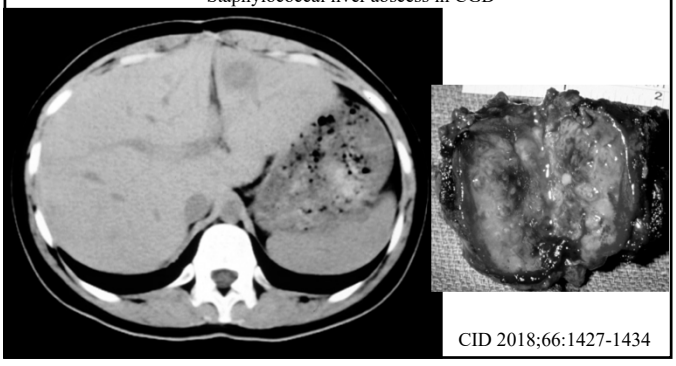
Infections in CGD

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

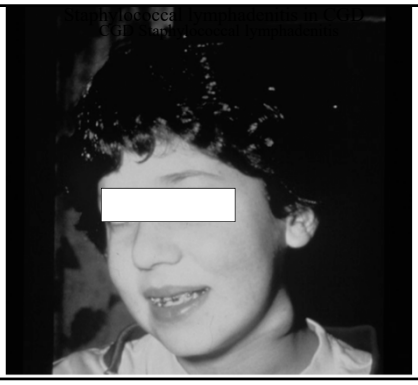
Chromobacterium violaceum *(warm brackish water, soil, e.g., Disney World)*
Francisella philomiragia *(brackish water, Chesapeake Bay, Sounds)*
Burkholderia gladioli *(causes onion rot)*
Granulibacter bethesdensis *(necrotizing LN, hard to grow, likes CYE)*
Paecilomyces spp.

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

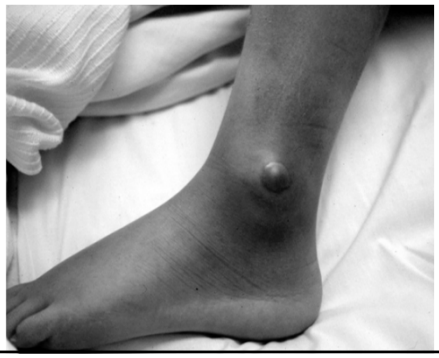
Staphylococcal liver abscess in CGD



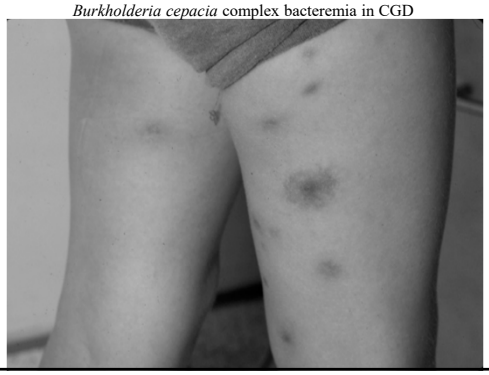
CID 2018;66:1427-1434



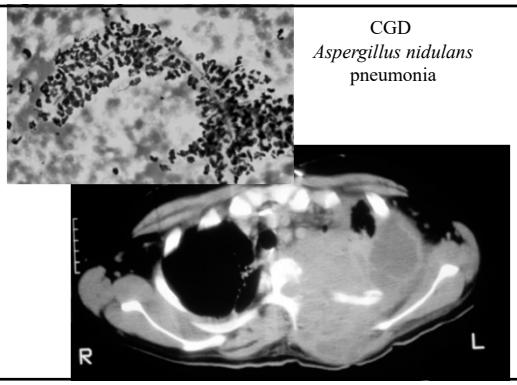
Staph aureus osteomyelitis in CGD



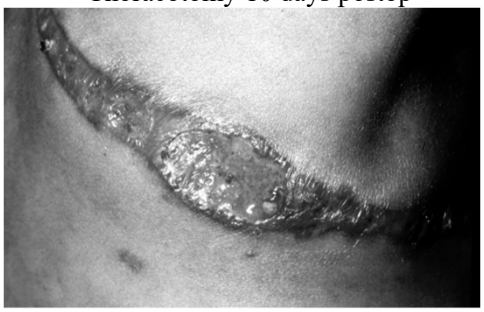
Burkholderia cepacia complex bacteremia in CGD



CGD
Aspergillus nidulans
pneumonia

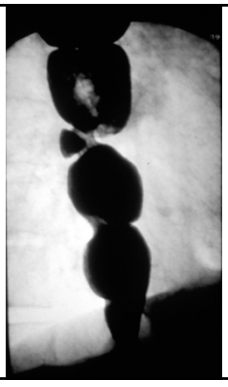


Thoracotomy 10 days postop

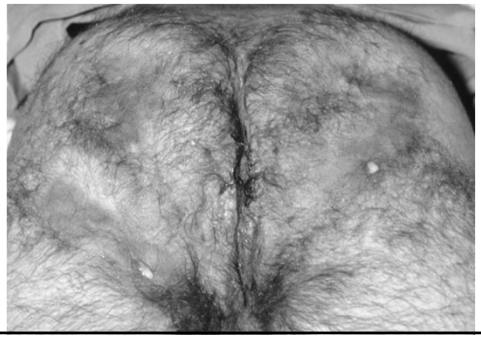


CGD granulomatous wound dehiscence

CGD
granulomatous
esophageal
obstruction



CGD Inflammatory Bowel Disease



Chronic Granulomatous Disease

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

failure to produce neutrophil superoxide and its metabolites

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

BE CAREFUL ABOUT THE LAB!!!!

CGD Genetics

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

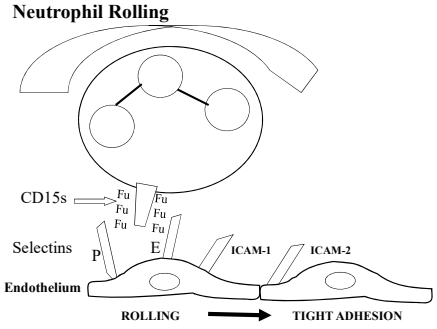
autosomal recessive (30% of cases)
- 1/2000 carry the gene for the most common AR form
  - bad luck happens

CGD Management and Treatment

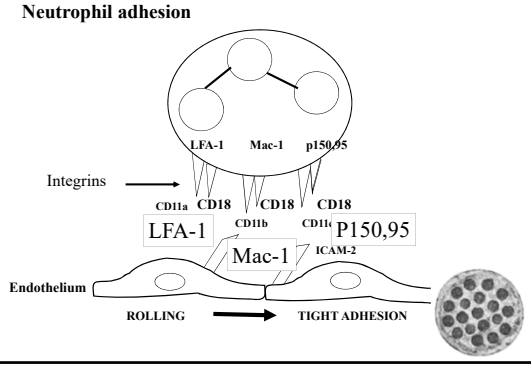
90% overall long-term survival
follow ESR, radiographs
prophylactic antibiotics and antifungals
TMP/SMX, itraconazole
prophylactic interferon gamma
50 µg/m2 subcutaneously three times weekly
aggressive search for and treatment of infections
BMT
(gene therapy)

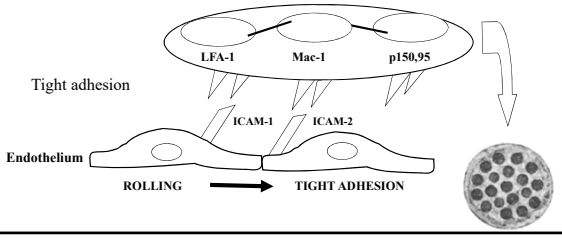
Hematol Oncol Clin North Am. 2013 Feb;27(1):89-99

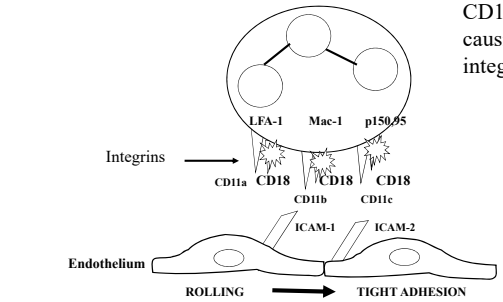
Neutrophil Rolling



Neutrophil adhesion







LAD1 is due to CD18 deficiency, causing loss of integrins

Leukocyte Adhesion Deficiency Type 1 (AR)

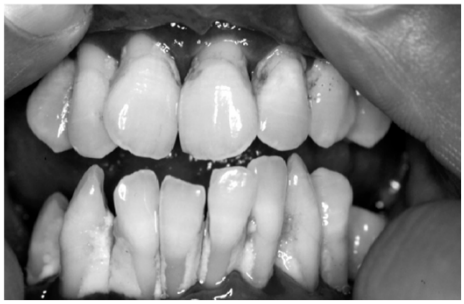
Recurrent necrotizing infections: skin, perineum, lung, gut

Enteric GNR, GPC, NOT fungi or *Candida*

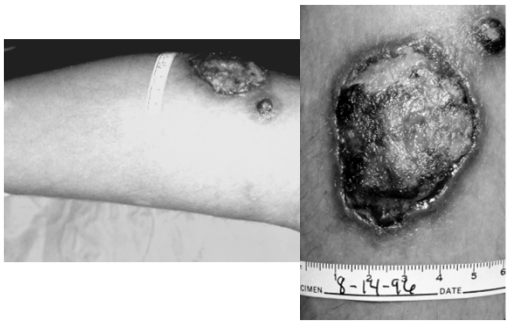
baseline leukocytosis, further WBC increase to infection

rare, consanguinity common

Almost universal tooth loss in LAD1 by adulthood



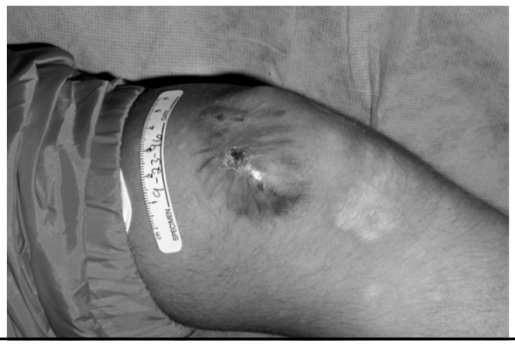
Impaired wound healing in LAD1

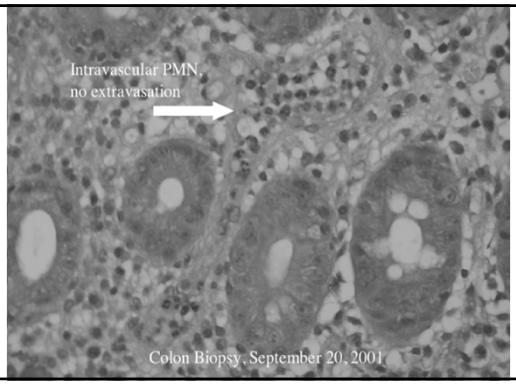


Leukocyte Adhesion Deficiency I

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

Cigarette paper scarring





Leukocyte Adhesion Deficiency 1

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

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

19 year old boy with Pneumonia

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

Ruling against LAD1 would be:

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

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

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

d) Extensive neutrophil infiltration in the left shin ulcer.

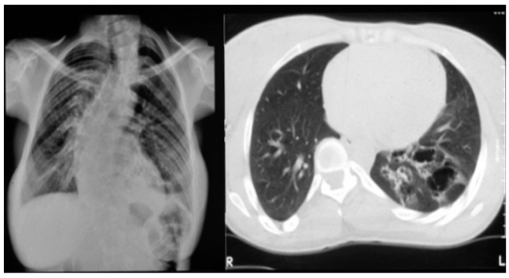
e) Multiple dystrophic scars over the legs from previous ulcers

27 year old woman with boils

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

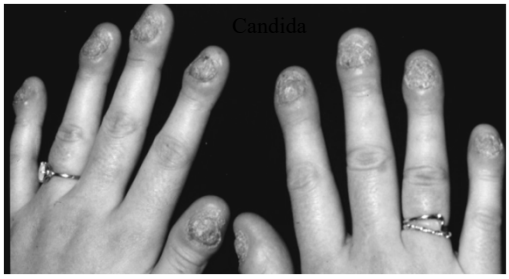
HIE (Job's) Syndrome History and Exam

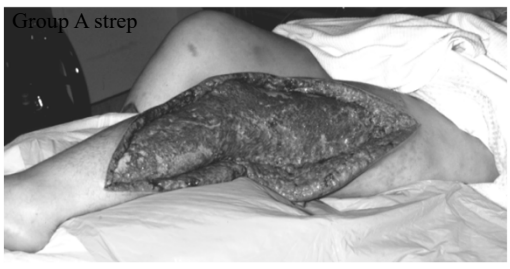
Eczema	100%
Facies	100% (≥16y)
Boils	87%
Pneumonia	87%
Mucocutaneous Candidiasis	83%
Pulmonary Cysts	77%
Scoliosis	76% (≥ 16y)
Delayed dental deciduation	72%
Coronary artery aneurysms	65%
Pathologic fractures	57%



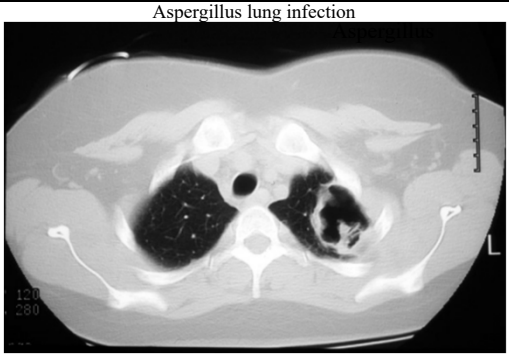
Pulmonary Pathogens in HIE

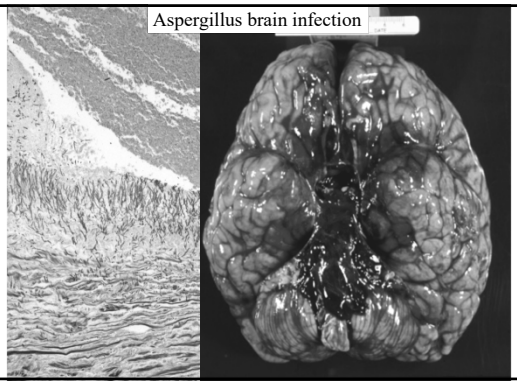
Primary pathogens:
Staphylococcus aureus
Streptococcus pneumoniae
Hemophilus influenzae
Secondary pathogens:
Pseudomonas aeruginosa
Aspergillus fumigatus
Others:
Pneumocystis jiroveci, M. avium complex



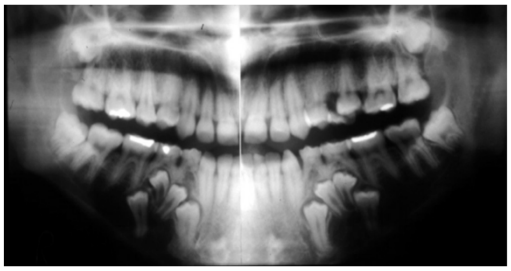


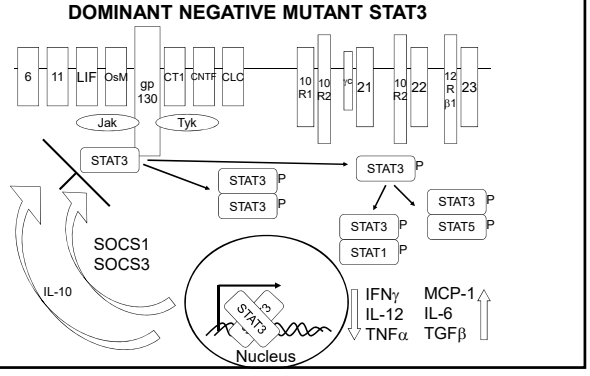
Aspergillus lung infection





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

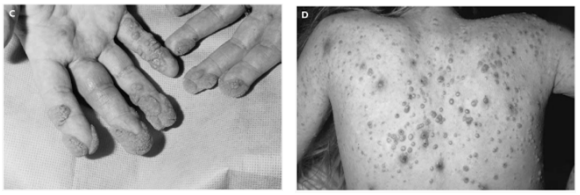
Candida, Cryptococcus, Histoplasma

HPV, HSV, molluscum

Squamous cell carcinomas, lymphoma

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

DOCK8 Deficiency

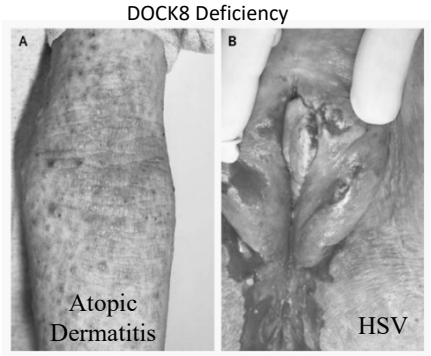


HPV

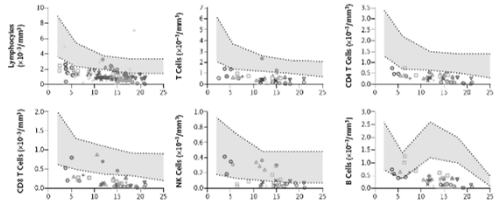
Molluscum contagiosum

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

DOCK8 Deficiency



DOCK8: Lymphopenia is common and somewhat progressive

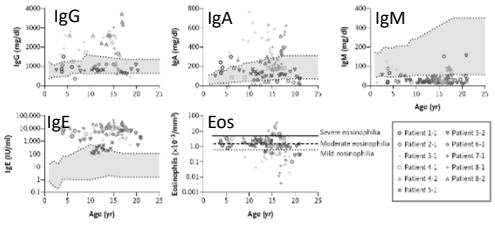


Age in years

*

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

DOCK8: IgE and eosinophils are high, IgM is low



*

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

DOCK8 vs. STAT3 Hyper IgEs

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

15 year old girl with recurrent infections

Infancy: eczema, recurrent pneumonias, skin infections
IgE 14,574 IU/ml
Allergist: use bed covers to avoid dust mites.

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

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

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

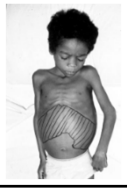
18 year old male with lymph node

Referred from hematologist/oncologist
nodes biopsied for Hodgkin showed granulomata and grew *M. avium.*
PMH recurrent salmonellosis as a child.
Sibling had tuberculosis but is now cured.

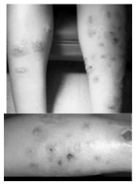
CD4+ number is normal, HIV -

Clinical Spectrum of NTM Infections

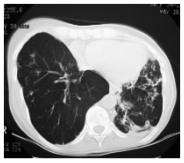
Disseminated
Severe, Young
IFNγ/IL-12 defects
NEMO, STAT1



Skin
Exposure
Inoculation

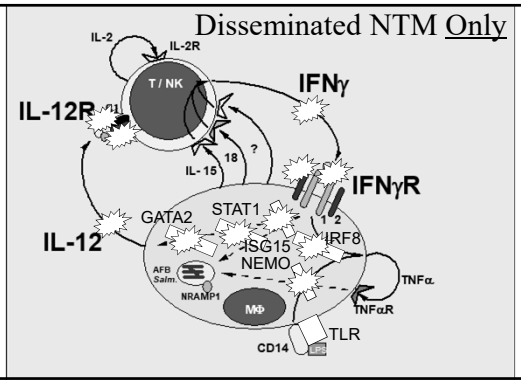


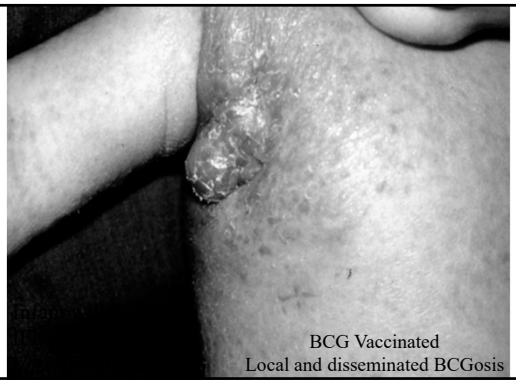
Pulmonary
Chronic, Older
Bronchiectasis
Cystic fibrosis (CF)
Ciliary dyskinesia (PCD)



Lancet Infect Dis. 2015;15:968-80

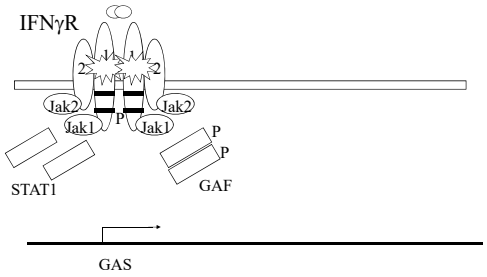
Disseminated NTM <u>Only</u>



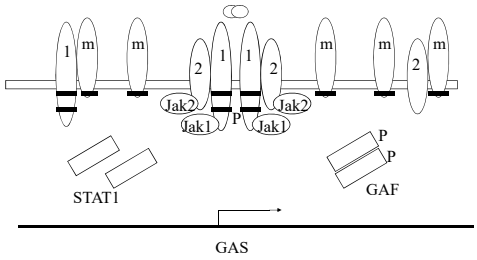


BCG Vaccinated
Local and disseminated BCGosis

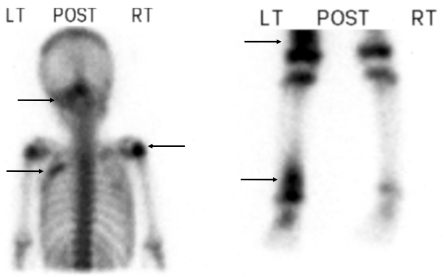
Autosomal Recessive IFNGR1 (both alleles)



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)

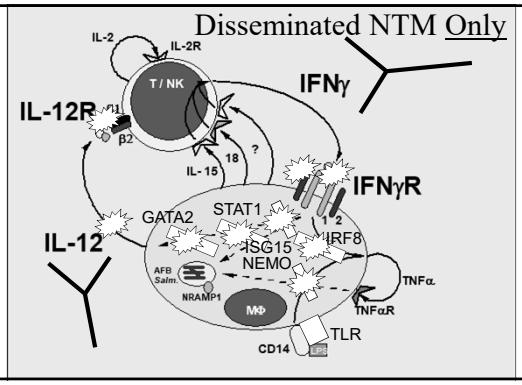
N Engl J Med. 2017;377:1077-1091.

IL-12βR1 Deficiency

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

Dx- genetics, flow cytometry

Rx- antimycobacterials, IFNγ systemically



Anti-IFNγ autoantibody syndrome

Disseminated NTM later in life

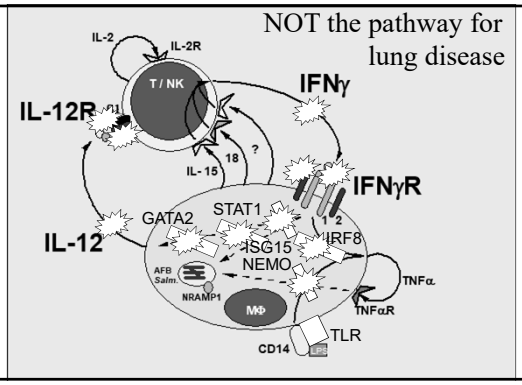
Predominantly female, mostly East Asian

NTM, TB, Talaromyces, Burkholderia, VZV

Dx- autoantibody detection
- Quantiferon is INDETERMINATE

Rx- antimycobacterials, possibly rituximab

NEJM 2012;367:725



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:

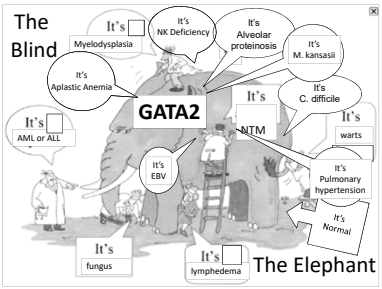
a) Check complements and total IgG
b) Determine anti-IFNγ antibody levels
c) Determine anti-GM-CSF autoantibody levels
d) Determine anti-IFNα autoantibody levels
e) Determine her cellular response to IFNγ

GATA2 Deficiency

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

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

Blood 2014; 123:809-21



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 superoxide
- Genetics

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

It is the SOS

History

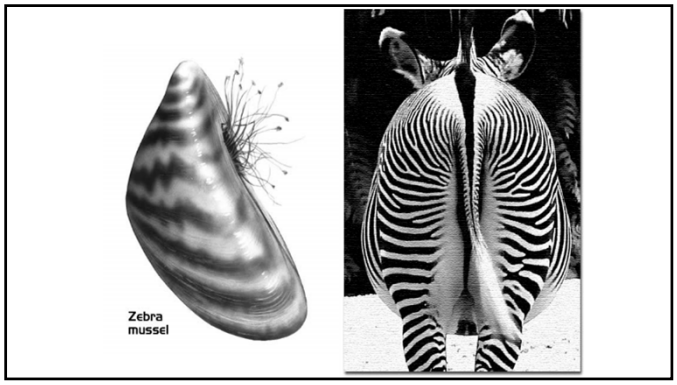
Physical

Imaging

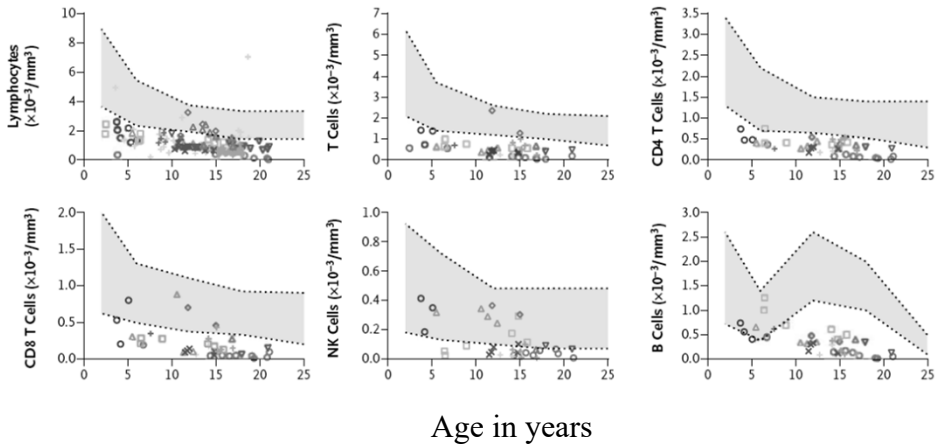
Laboratories
(talk to the lab yourself!!!)

11 - Clinical Immunology and Host Defense

Speaker: Steven Holland, MD



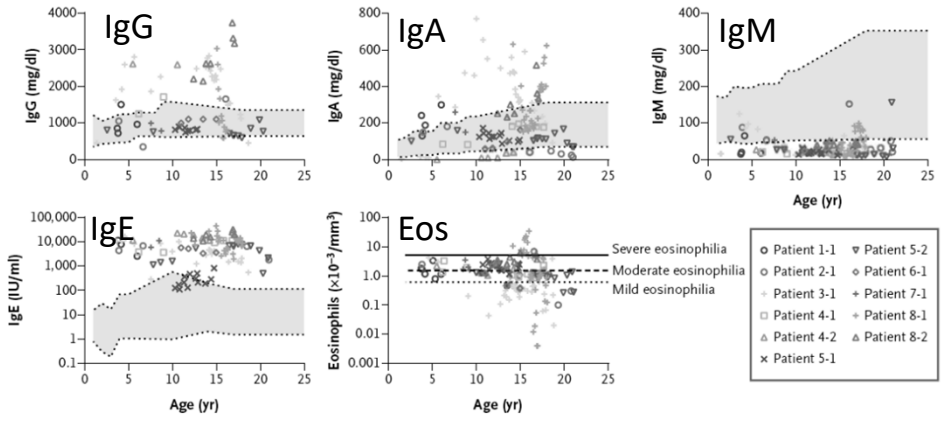
DOCK8: Lymphopenia is common and somewhat progressive



*

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

DOCK8: IgE and eosinophils are high, IgM is low



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

12

Gastrointestinal Disease: Etiologic Agents

Dr. Herbert Dupont

12 – Gastrointestinal Disease: Etiologic Agents

Speaker: Herbert Dupont, MD

IDBR INFECTIOUS DISEASE BOARD REVIEW AUGUST 19-23 2023

Gastrointestinal Disease: Etiologic Agents

Herbert L. DuPont, MD, MACP
Mary W. Kelsey Chair in the Medical Sciences
Professor, Infectious Diseases & Epidemiology
The University of Texas McGovern Medical School & School of Public Health
Clinical Professor, Infectious Diseases
Baylor College of Medicine and MD Anderson Cancer

6/17/2023

IDBR INFECTIOUS DISEASE BOARD REVIEW AUGUST 19-23 2023

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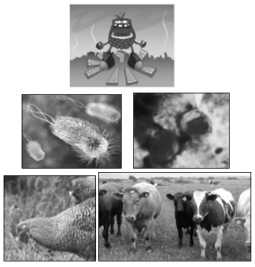
- **None**

OBJECTIVES



- LIST THE MOST COMMUNICABLE AND MOST LETHAL ENTERIC PATHOGENS
- PROVIDE A REVIEW OF THE NEW DEVELOPMENTS FOR ENTERIC PATHOGENS INCLUDING SHIGATOXIN-PRODUCING *E. COLI* AND TRAVELERS' DIARRHEA TREATMENT
- CRITIQUE PCR METHODS TO ESTABLISH ENTERIC INFECTION DIAGNOSIS

ANNUAL DEATHS FROM ENTERIC PATHOGENS IN U.S.

- 83% of deaths occur in adults ≥ 65 years of age; Pediatric deaths from diarrhea 369/year
- *C. difficile* infection (CDI) (29,000) is the most common cause of death (>70% of total)
- Noroviruses (797/year) often in elderly in hospitals or nursing homes
- *Salmonella* (378) and
- *Listeria* (260)

Hall, AJ et al. Clin Infect Dis 2011;55:216-23
CDC http://www.cdc.gov/foodborneburden/2011-foodborne-estimates.html

PATHOGEN COMMUNICABILITY
ALL INFECTIOUS DISEASES SHOW A DOSE THRESHOLD FOR ILLNESS

Pathogen Group	Expected Inoculum Size
Highest rate of transmissibility*: *Shigella*, Noroviruses	10 to 100 organisms
High rate of transmissibility: *Giardia*, *Cryptosporidium*, *Salmonella* (infants only)	80-500 organisms
Lower communicability: Shiga toxin-producing *E. coli*, *Salmonella* (older children/adults), *Campylobacter*	500 to 100,000 organisms
Absence of communicability: enteroinvasive and enterotoxigenic *E. coli* (EIEC, ETEC) and *Vibrio cholerae*	100,000 to > 1,000,000 organisms

*low inoculum requirement, stability in environment, reservoir in children
Immunocompromised/elderly people, infants, those on proton pump inhibitors may be susceptible to lower inoculum sizes

QUESTION #1 — PREVIEW QUESTION

LOW DOSE PATHOGENS COMMONLY CAUSE DIARRHEA OUTBREAKS IN DAY CARE CENTER WHICH OF THE FOLLOWING DOESN'T FIT?

A. *SHIGELLA*
B. *CRYPTOSPORIDIUM*
C. *GIARDIA*
D. *CAMPYLOBACTER JEJUNI*
E. NOROVIRUS

12 – Gastrointestinal Disease: Etiologic Agents

Speaker: Herbert Dupont, MD

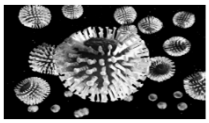
VIRAL GASTROENTERITIS

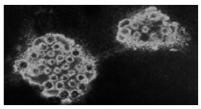
ROTAVIRUS

- KILLER OF 129,000 INFANTS GLOBALLY WITH DECREASES SEEN IN THE 106 COUNTRIES WITH A RV VACCINE (65 COUNTRIES LACK A VACCINE)

NOROVIRUSES (NOW THE MOST COMMON CAUSE OF ENTERIC INFECTION WORLDWIDE)

- 200,000 ANNUAL DEATHS IN THE DEVELOPING WORLD WITH YOUNG CHILDREN AND THE ELDERLY MOST SUSCEPTIBLE
- > 20 MILLION CASES FOODBORNE DISEASE IN U.S. (HALF OF ALL CASES); 26% OF CASES PRESENTING TO ED
- 20% OF U.S. POPULATION NOT SUSCEPTIBLE RELATED TO ANTIGENS THAT DETERMINE BLOOD TYPES
- 10 GENOGROUPS AND 48 GENOTYPES OF WHICH GENOGROUP II, GENOTYPE 4 (GII.4) PREDOMINATES
- SECONDARY ATTACK COMMON (17%)
- MOST COMMON SETTING FOR OUTBREAKS HEALTHCARE FACILITIES, NURSING HOMES, RESTAURANTS AND CATERED EVENTS AND CRUISE SHIPS





SHIGA TOXIN-PRODUCING *E. COLI* INFECTION (~300,000 CASES IN U.S.)

***E. COLI* O157**

SORBITOL-NON-FERMENTING

SORBITOL-MACCONKEY AGAR & O157 SEROTYPING

***E. coli* non-O157**

Sorbitol-positive, test stools, broth or culture plate for *Stx* 1 and 2 by EIA and if positive send *E. coli* to Health Lab

Common groups in U.S. O26, O111, O103, O45, O145 and O121

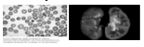
Hemorrhagic colitis

Dysentery

85%

13%

Hemolytic Uremic Syndrome



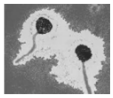
9%

9%

STEC strains are threatening our food supply

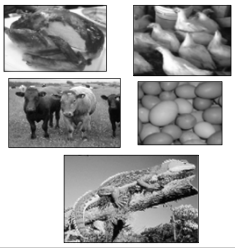
Person-to-person spread seen in day care centers and in families

SHIGA TOXIN PRODUCTION UNDER PHAGE CONTROL



- SOME ANTIBIOTICS MOBILIZE PHAGE (E.G. FLUOROQUINOLONES, TMP-SMX), AZITHROMYCIN AND RIFAXIMIN DO NOT
- A1 SUBUNIT OF *STX*2 HAS HIGHER AFFINITY FOR RIBOSOMES AND *STX*2 IS 400 X MORE TOXIC THAN *STX*1, *STX*2 IS ASSOCIATED WITH DYSENTERY AND HUS
- ANTIBIOTICS ARE NOT INDICATED IN THIS INFECTION BUT STAY TUNED
- HUS BEGINS ~1 WEEK AFTER ILLNESS BEGINS AS DIARRHEA IS IMPROVING ~15% OF CHILDREN DEVELOP, LESS IN ADULTS WITH INCREASING RATE IN ELDERLY. DEATH RATE 3-5%
- WHILE COMPLEMENT IS INVOLVED IN TYPICAL HUS, ANTI-COMPLEMENT MONOCLONAL ANTIBODIES (ECULIZUMAB AND RAVULIZUMAB) ARE NOT APPROVED FOR TYPICAL HUS
- TREATMENT IS SUPPORTIVE: DIALYSIS, ACE INHIBITORS, ARBS FOR CONTROL OF HYPERTENSION, BLOOD, PLATELETS, AND ANTI-SEIZURE DRUGS

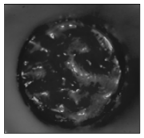
NON-TYPHOID SALMONELLOSIS

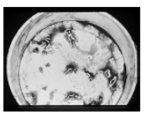


- ANTIBIOTICS ARE NOT HELPFUL IN NON-BACTEREMIC FORMS BUT ARE LIFE SAVING IN BACTEREMIA
- THE HIGHEST INCIDENCE OF INFECTION IS IN INFANTS
- BECAUSE OF DEEPER MUCOSAL PENETRATION BACTEREMIA RATE IN HEALTHY OCCURS IN 8% OF HEALTHY PEOPLE IN U.S., HIGH-RISK GROUPS: ELDERLY, INFANTS 1-3 MONTHS, SS DISEASE, INFLAMMATORY BOWEL DISEASE, IMMUNOCOMPETENCE OR ON STEROIDS) RATE UP TO 50%

WHAT'S NEW IN *SHIGELLA*?

- THE CDC HAS ISSUED A WARNING TO PHYSICIANS ABOUT DRUG RESISTANT (XDR) *SHIGELLA* SEEN CURRENTLY IN 5% OF THE 450,000 ANNUAL CASES SEEN
- THE ORGANISMS ARE RESISTANT TO ALL 5 ANTI-*SHIGELLA* ANTIBIOTICS AND ARE INCREASINGLY BEING SEEN IN MEN HAVING SEX WITH MEN, PEOPLE EXPERIENCING HOMELESSNESS, INTERNATIONAL TRAVELERS AND PEOPLE LIVING WITH HIV
- SUPPORTIVE TREATMENT WITHOUT ANTIBIOTICS IS THE TREATMENT





PROTOZOAL PATHOGENS CAUSE PROTRACTED DIARRHEA

- PERSISTENT DIARRHEA (≥ 14 DAYS)
- DIAGNOSTIC CHALLENGES

NEGATIVE TEST *GIARDIA*, EIA/PCR FOR *E. HISTOLYTICA*, ACID FAST STAINING NOT ROUTINE, MULTIPLEX PCR SOLVES

- SPORULATION REQUIRED FOR *CYCLOSPORA* FOR INFECTIVITY
- *CRYPTOSPORIDIUM*

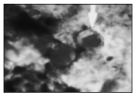
OFTEN HAS AN ANIMALS RESERVOIR, WATER VEHICLE OF TRANSMISSION

- *E. HISTOLYTICA* PRODUCES LIVER ABSCESS MOST IMPORTANTLY IN MALES

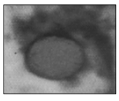
SEROLOGY HELPFUL IN HEPATIC ABSCESS AS STOOLS OFTEN NEGATIVE

Giardia

E. histolytica



Cryptosporidium



Cyclospora

12 – Gastrointestinal Disease: Etiologic Agents

Speaker: Herbert Dupont, MD

DIAGNOSTIC APPROACHES IN INFECTIOUS DISEASES MOVING TO PCR

Requires clinical judgement & correlation

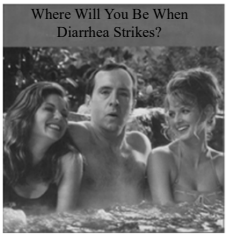
- Syndromic approach detects organisms that clinicians may have not thought about/ordered or are difficult to isolate in the lab
- Rapid diagnosis may allow earlier initiation of therapy
- For larger centers, is cost effective
- Has potential to re-define epidemiology and treatment
- In positives, culture of stool yields pathogen in <60%
- Colonizing *C. difficile* in patients associated with false (+), require confirmation with second step
- Interpretation for some pathogens is difficult (e.g. enteropathogenic *E. coli* (EPEC), enteroaggregative *E. coli* (EAEC), enterotoxigenic *E. coli* (ETEC)

ORGANISM-SPECIFIC THERAPY

- Shigellosis – Fluoroquinolone or azithromycin
- Non-typhoid salmonellosis – only with sepsis - fluoroquinolone or 3rd generation cephalosporin
- Campylobacteriosis – Azithromycin or erythromycin
- STEC diarrhea – none
- Non-cholera *Vibrio* diarrhea – as shigellosis
- Cholera – doxycyline
- Viral gastroenteritis – ORT, ? Bismuth subsalicylate
- Giardiasis – Tinidazole or nitazoxanide
- Cryptosporidiosis - nitazoxanide
- Cyclosporiasis or Cystoisosporiasis – TMP/SMX
- Enterocytozoon diarrhea – Albendazole
- Intestinal amoebiasis – metronidazole plus diloxanide furoate or paromomycin

CONCLUSIONS PART 1

- Infectious dose influences attack rate and incubation period
- Noroviruses – most communicable pathogen, causes half of the cases of foodborne disease, replacing rotavirus as the major pediatric enteropathogen
- It is important to understand STEC as a pathogen, pathogenesis and diagnosis
- Non-typhoid Salmonella is causing epidemic bacteremia in all age groups in Sub Saharan Africa due to host and microbial factors
- Antibiotics taken while in a developing regions will encourage colonization of ESBL coliforms
- Multiplex PCR diagnostics have the potential to revolutionize diagnosis and epidemiology of infectious diarrhea but needs to be quantitative to determine infection from colonization



13

Gastrointestinal Disease: Clinical Syndromes

Dr. Herbert Dupont

13 – Gastrointestinal Disease: Clinical Syndromes

Speaker: Herbert Dupont, MD

IDBR INFECTIOUS DISEASE BOARD REVIEW AUGUST 19-23 2023

Gastrointestinal Disease: Clinical Syndromes

Herbert L. DuPont, MD, MACP
Mary W. Kelsey Chair in the Medical Sciences
Professor, Infectious Diseases & Epidemiology
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Clinical Professor, Infectious Diseases
Baylor College of Medicine and MD Anderson Cancer

6/17/2023

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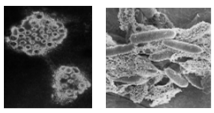
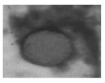
OBJECTIVES


Noroviruses

E. coli


Shigella


Cyclospora

- Describe clinical characteristics of various forms of Enteric infection syndromes and seafood-associated illnesses
- Outline methods employed in foodborne outbreak investigation
- Define the complications in therapy of travelers' diarrhea
- Explain the important chronic post-Enteric Infection Syndromes
- Explain principles of workup of persistent diarrhea for treatable causes

VOMITING AS THE PRIMARY SYMPTOM

- Viral gastroenteritis with incubation period: 24 – 48 hours
  (19-21 million cases/year)
- Food poisoning Performed toxin* of *Staphylococcus aureus* 2-7 hours
  (240,000 cases/year)
- *Bacillus cereus* with incubation period: 2-7 hours
  (63,000 cases/year)

FOOD POISONING WITHOUT VOMITING

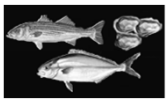
Clostridium perfringens food poisoning preformed toxin causes

watery diarrhea without vomiting,

incubation period of 8-14 hours

(1 million cases/year)

FOOD POISONING FROM MARINE TOXINS



Dinoflagellates, a group of phytoplankton, produce marine toxins that are either ingested by herbivorous fish or ingested and concentrated in in filter-feeding bivalve mollusks

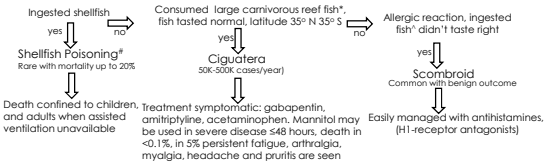
Fish that have a high amount of Histidine, a precursor of histamine can lead to excessive levels of histamine and an allergic reaction if not properly refrigerated after harvesting

Cooking and freezing does not inactivate the neurotoxins or histamine

13 – Gastrointestinal Disease: Clinical Syndromes

Speaker: Herbert Dupont, MD

SUDDEN ONSET OF NEUROLOGIC, CARDIOVASCULAR, ALLERGIC OR GI SYMPTOMS WITHIN 3 HOURS OF EATING A SEAFOOD MEAL



#Raw oysters should be avoided especially during or after algal blooms – red tide)

*amberjack, barracuda, grouper, moray eel, sea bass, sturgeon (reef fish not recommended for travelers)

^amberjack, anchovies, bluefish, herring, mackerel, mahi mahi (dolphin fish), marlin, sardines, and tuna

QUESTION #1

INFECTIOUS DISEASE BOARD REVIEW AUGUST 18-23 2023 PREVIEW QUESTION

WHICH OF THE FOLLOWING IS THE MAJOR SOURCE OF SHIGATOXIN-PRODUCING *E. COLI* INFECTION?

A. LEAFY GREEN VEGETABLES
B. INCOMPLETELY COOKED BURGERS
C. PETTING ZOOS
D. *UNPASTEURIZED FRUIT JUICES*
E. *STEAKS NOT COMPLETELY COOKED*

QUESTION #2

A PATIENT DEVELOPS NUMBNESS OF LIPS, BURNING AND TINGLING OF HIS EXTREMITIES, AND ABDOMINAL PAIN AND VOMITING 30 MINUTES AFTER A MEAL IN JAMAICA, PROGRESSING TO RESPIRATORY FAILURE.

WHAT IS THE LIKELY DIAGNOSIS?

A. SCOMBROID
B. PARALYTIC SHELLFISH POISONING
C. CIGUATERA
D. NEUROTOXIC SHELLFISH POISONING
E. MONOSODIUM GLUTAMATE TOXICITY

QUESTION 3

INFECTIOUS DISEASE BOARD REVIEW AUGUST 18-23 2023 PREVIEW QUESTION

- A 65-YEAR OLD CHAIRMAN OF MEDICINE AT A MEDICAL SCHOOL WITH 15 DAYS OF DIARRHEA, PASSING 4-8 WATERY STOOLS PER DAY WITHOUT FEVER OR PASSAGE OF BLOODY STOOLS. HE HAS NOT TRAVELED AND HAD AN INITIAL WORKUP FOR DIARRHEA: STANDARD STOOL CULTURE AND AN ORDER FOR PARASITES THAT INCLUDES A SCREEN FOR *GIARDIA*, *CRYPTOSPORIDIUM* AND *ENTAMOEBA*.

WHICH OF THE FOLLOWING IS THE BEST NEXT APPROACH?

A. COLLECT 3 STOOLS FOR PARASITES BY EIA
B. COLLECT 3 STOOLS FOR PARASITES BY PCR
C. PERFORM MULTIPLEX PCR FOR ENTERIC VIRAL, BACTERIAL AND PARASITIC PATHOGENS
D. ASK THE LABORATORY TO PERFORM ACID-FAST STAINING OF STOOL FOR PARASITES
E. GIVE THE PATIENT 1,000 MG AZITHROMYCIN IN SINGLE DOSE

QUESTION #4

INFECTIOUS DISEASE BOARD REVIEW AUGUST 18-23 2023 PREVIEW QUESTION

- A 65-YEAR OLD CHAIRMAN OF MEDICINE AT A MEDICAL SCHOOL IN TEXAS WITH 15 DAYS OF DIARRHEA, PASSING 4-8 WATERY STOOLS PER DAY WITHOUT FEVER OR PASSAGE OF BLOODY STOOLS. HE HAS NOT TRAVELED AND HAD AN INITIAL WORKUP FOR DIARRHEA: STANDARD STOOL CULTURE AND AN ORDER FOR PARASITES THAT INCLUDES A SCREEN FOR *GIARDIA*, *CRYPTOSPORIDIUM* AND *ENTAMOEBA*.

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D. ASK THE LABORATORY TO PERFORM ACID-FAST STAINING OF STOOL FOR PARASITES
E. GIVE THE PATIENT 1,000 MG AZITHROMYCIN IN SINGLE DOSE

COMPLICATED CASE OF TRAVELERS' DIARRHEA

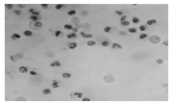
A 35-YEAR OLD WOMAN DEVELOPS DIARRHEA, CRAMPS AND IS PASSING BLOODY STOOLS WITH FEVER WHILE SNORKELING WITH HER FAMILY IN COZUMEL, MEXICO

13 – Gastrointestinal Disease: Clinical Syndromes

Speaker: Herbert Dupont, MD

QUESTION 4

Grossly bloody stool



Many leukocytes of stool microscopically indicate diffuse colonic inflammation

What is the preferred treatment for this patient With dysenteric traveler's diarrhea?

A. Azithromycin 1,000 mg
B. Ciprofloxacin 500 mg twice daily X 3 days
C. Levofloxacin 500 mg
D. Rifaximin 200 mg three times/d for 3 days
E. Oral fluids only

QUESTION 5

She takes three days of ciprofloxacin, a drug she has with her for recurrent urinary tract infection.

Which of the following concerns you the most about this treatment?

A. Colonization by ESBL-producing coliforms
B. Achilles tendon damage
C. C. *difficile* infection
D. Insomnia and irritability
E. She will run out of drugs for future UTI

SCREENING FOR ESBL-PRODUCING COLIFORMS

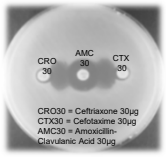
ESBL or MDR Enterobacteriaceae Risk Factors:

- Travel to tropical and semitropical areas, especially Asia (highest for travel to India)
- Diarrhea increases rate and receipt of antibiotics further increases risk

Endogenous Infections* or Spread to Family Duration of Colonization After Returning Home

- < 3 months to 12 months
- Shorter than when acquired in a hospital
- Treat only more severe Travelers' diarrhea

Extended spectrum beta lactamase-producing Enterobacteriaceae



Jiang Z-D, DuPont HL

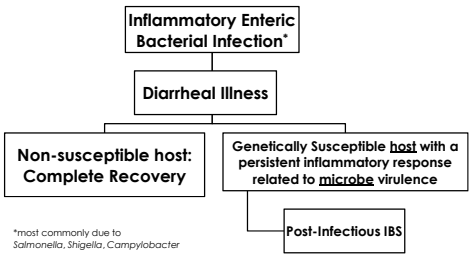
POST-ENTERIC INFECTION DISORDER

THE PATIENT EXPERIENCES A PROTRACTED COURSE

Abdominal discomfort and pain & bloating are near constant problems present 6 months later – she has never become well, although the illness has changed in character from diarrhea to abdominal discomfort with change in bowel pattern (eating increases Pain and decreases stool form)

POST-INFECTIOUS IRRITABLE BOWEL SYNDROME 5-10% AFTER BACTERIAL DIARRHEA

PATHOGENESIS OF POST-INFECTIOUS IBS



POST-ENTERIC INFECTION DISORDER 2

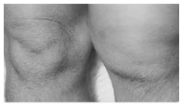
QUESTION 6

Which one of the following represents an antibody-Mediated post- enteric autoimmune complication?

A. Crohn's disease
B. Functional constipation
C. Reactive arthritis
D. Celiac disease
E. Whipple's disease

Post-Enteric Infection Disorder 2

- Reactive arthritis after infection by *Salmonella*, *Shigella* or *Yersinia* due to autoimmune responses targeting epitopes common to pathogen and joint tissues



QUESTION 7

What is another antibody-mediated post-enteric infection syndrome?

A. Aseptic Meningitis
B. Guillain Barré Syndrome
C. Post-infectious IBS
D. Post-Infectious inflammatory bowel disease
E. Diverticulitis

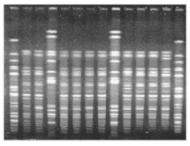
OUTBREAK INVESTIGATIONS

STEPS
EPIDEMIC CURVE ESTABLISH AN OUTBREAK
CLINICAL FEATURES TO DEVELOP A CASE DEFINITION
INCUBATION PERIOD IN THE CASE OF A COMMON EXPOSURE
CASE-CONTROL STUDIES OF CAUSE

AN EPIDEMIC OF SHIGA-TOXIN (STX) PRODUCING *E. COLI* (STEC) O157:H7

- On May 19, 2009, the PulseNet national molecular subtyping network identified a cluster of 77 cases of *E. coli* infection from 30 states with identical PFGE pattern
- Cases occurred between March 1 and July 31, 2009
- The median age was 15 years, 71% were females
- 55% were hospitalized, 18% developed HUS and none died

PulseNet*



- Developed in 1996, two enzymes cut bacterial DNA, with an electrical
- Current moves DNA according to size showing unique banding patterns

PFGE being combined with WGS

CASE CONTROL STUDY PERFORMED TO IDENTIFY THE SOURCE

Step 3: Case Control Study

- Controls were found from corresponding health departments with non-STEC enteric infection
- Conventional STEC risk factors* were not found

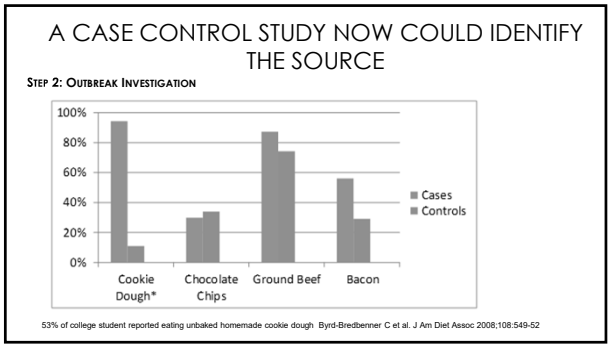
**Ground beef, raw dairy products, leafy green vegetables, wading pools and animal contact*

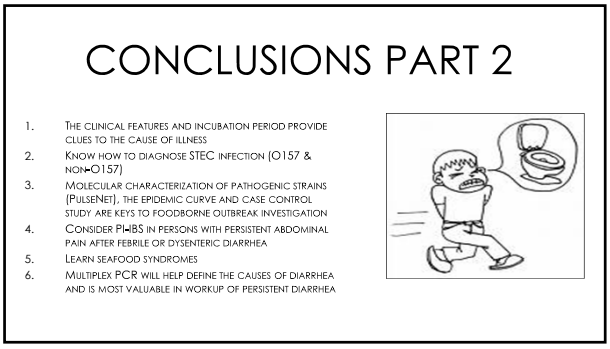
CONVENTIONAL SOURCES RULED, LOOK FOR UNUSUAL EXPOSURES

- Opened questions in one health region found 5/5 ate ready-to-bake cookie dough

13 – Gastrointestinal Disease: Clinical Syndromes

Speaker: Herbert Dupont, MD





14

CMV, EBV, HHV6, and HHV8 in Immunocompetent and Immunocompromised Patients

Dr. Camille Kotton

14 – CMV, EBV, HHV6 and HHV8 in Immunocompetent and Immunocompromised Patients

Speaker: Camille Kotton, MD

IDBR INFECTIOUS DISEASE BOARD REVIEW LIVE/VIRTUAL AUGUST 19-23 2023

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

7/2/2023

INFECTIOUS DISEASE BOARD REVIEW AUGUST 19-23 2023

Disclosures of Financial Relationships with Relevant Commercial Interests

Consulting: Hookipa (CMV Vaccine trial), Merck (CMV), Takeda (CMV), Natera

Scientific Advisory Board: Roche Diagnostics, ResTORBio, Evrys

Research Funding: Beigene

Speaker: Oxford Immunotec

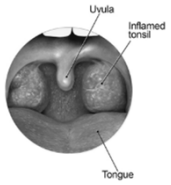
Human Herpesviruses Family

1. Herpes simplex virus type I (HSV-1)
2. Herpes simplex virus type 2 (HSV-2)
3. Varicella-zoster virus (VZV)
4. **Epstein-Barr virus (EBV)**
5. **Cytomegalovirus (CMV)**
6. **Human herpesvirus type 6 (HHV-6)**
7. Human herpesvirus type 7 (HHV-7)
8. **Human herpesvirus type 8 (HHV-8)**

3

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
Lymphocytosis (>50%; >4500/mm3)				
Atypical lymphocytes (>10%)	++++	+++	+	++
Elevated LFTs	++++	+++	0	+



4

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 (40%)
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
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 Bravo.[19]
† 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.

*

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**

14 – 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 dz (infectious mononucleosis)
- 500 cases/100,000 population/year in USA
  - incidence rate for those 15--19yo estimated 200 – 800 cases per 100,000
- Occasionally transmitted by transfusion or organ/stem cell transplant
- Latently infected memory B lymphocytes serve as lifelong viral reservoirs
  - EBV is capable of transforming B lymphocytes, resulting in malignancy

8

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 - **lymphocytosis** with atypical lymphocytes
- Diagnosis - **serology**. Non-specific heterophile Ab ("**monospot**") & EBV specific Ab
- 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 on horizon?)
- EBV reactivation mostly asymptomatic; can reflect extent of immunosuppression

9

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

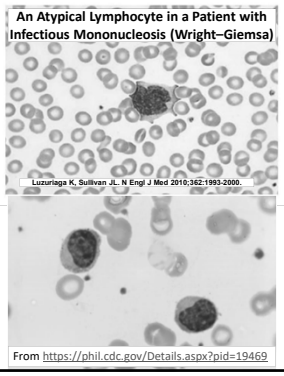
Heme syndromes:

- Neutropenia
- TTP-HUS
- DIC
- Acquired hypogammaglobulinemia
- X-linked lymphoproliferative disease (EBV as trigger)
- Hemophagocytic lymphohistiocytosis (HLH) (estimated 50% of all HLH cases from EBV)

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

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:

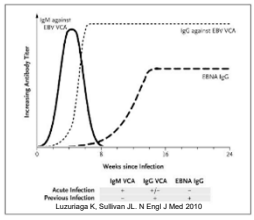
- Low nuclear / cytoplasmic ratio
- Indented or lobulated nuclei with nucleoli
- Cytoplasm often basophilic; can be "sky blue", with vacuoles and granules

14 – 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.**
- **EBV nuclear antigen (EBNA)**
  Antibody to EBNA, determined by the standard immunofluorescent test, is not seen in the acute phase of EBV infection but slowly **appears two to four months after onset of symptoms and persists for the rest of a person's life.**
- **Early antigen (EA)**
  Anti-EA IgG appears in the acute phase of illness and generally falls to undetectable levels after three to six months. In many people, detection of antibody to EA is a sign of active infection. However, 20% of healthy people may have antibodies against EA for years.
- **Monospot test**
  The Monospot test is not recommended for general use, poorly sensitive/specific. The antibodies detected by Monospot can be caused by conditions other than infectious mononucleosis.
- The antibody response occurs rapidly during primary EBV infection



Luzuriaga K, Sullivan JL. N Engl J Med 2010

https://www.cdc.gov/epstein-barr/laboratory-testing.html

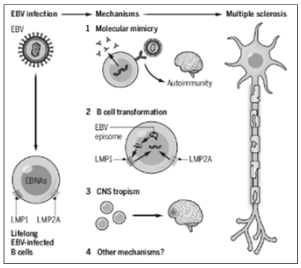
Longitudinal analysis reveals high prevalence of Epstein-Barr virus associated with multiple sclerosis

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. Nichols[10]; Ann I. Schw[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 level EBV viremia (<5,000 IU/ml) may reflect immunosuppressed state
- No evidence that any current antiviral therapy is helpful
  - Valganciclovir only works in lytic phase (small %)
- WHO pathology classification of a tissue biopsy remains the gold standard for PTLD diagnosis
- PTLD treatment may include (in order): reduction of immunosuppression, rituximab, and cytotoxic chemotherapy

Allen and Preiksaitis, Post-transplant lymphoproliferative disorders, Epstein-Barr virus infection, and disease in solid organ transplantation: Guidelines from the American Society of Transplantation Infectious Diseases Community of Practice, Clin Trans 2019

Question

IDBR 2023 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	-	-	+	-

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CMV

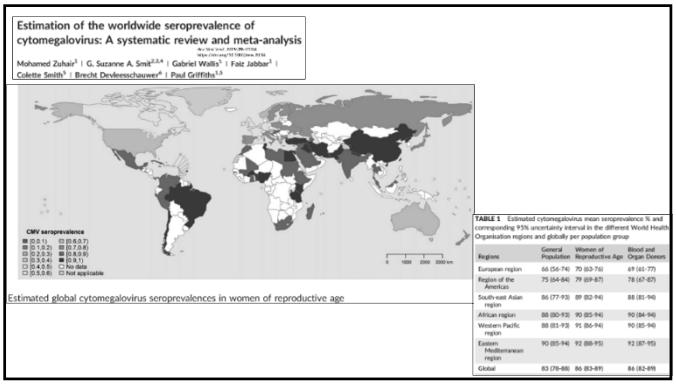
Epidemiology of CMV Infection

- 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

18

14 – 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)

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CMV Mononucleosis Syndrome

- CMV causes ~20% of mono syndrome cases in adults
- Presentation: fever, myalgias, atypical lymphocytosis.
  - High fever ("typhoidal"). Pharyngitis and lymphadenopathy (13-17%) less common than with EBV (80%).
  - Rash in up to 30% (variety of appearances)
  - May be clinically indistinguishable from mono syndrome caused by other pathogens
  - Complications: colitis, hepatitis, encephalitis, GBS, anterior uveitis
- Symptoms may persist > 8 weeks
- Diagnosis: IgM/IgG seroconversion (CMV blood PCR - can be confusing)
- Antiviral therapy not indicated (except for severe complications or in immunocompromised)

21

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%

22

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.

23

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

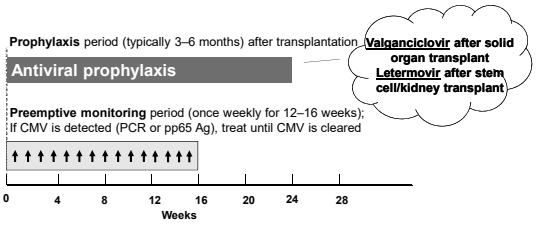
Tissue-Invasive Disease
- GI diseases: Colitis, Hepatitis
- Pneumonitis
- Myocarditis
- Myocarditis
- Nephritis
- Encephalitis, retinitis

Torres-Madriz G, Boucher HW. Clin Infect Dis. 2008;47(5):702-711;
Kotton CN, CMV: Prevention, Diagnosis and Therapy, AJT 2013

14 – CMV, EBV, HHV6 and HHV8 in Immunocompetent and Immunocompromised Patients

Speaker: Camille Kotton, MD

PREVENTION: Prophylaxis vs. Preemptive Therapy

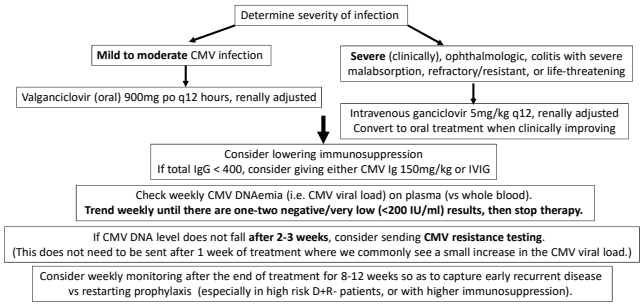


Humar A, Snydman D; AST Infectious Diseases Community of Practice. *Am J Transplant.* 2009;9 (Suppl 4):S78-S86.

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

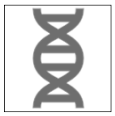


* Kotton et al, International CMV Guidelines, Transplantation 2018

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 IIDNUM$ / 4 PIN@<N@

14 – 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

2023

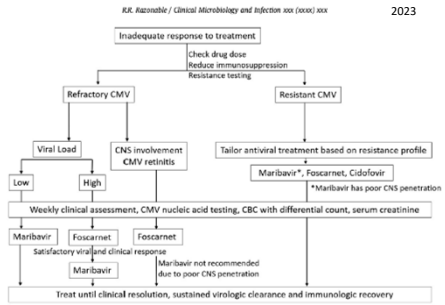


Fig. 2. Suggested algorithm for the treatment of refractory and resistant CMV disease. CMV, cytomegalovirus; CBC, complete blood count; CNS, central nervous system.

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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

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[2] | Marcel Doerflinger[2] | Marc Pellegrini[2] | Danny Rischin[3] | Alesha Thal[4] | Monica A. Slavin[2,5] | Camille N. Kotton[2]

"Cytomegalo-tumor"

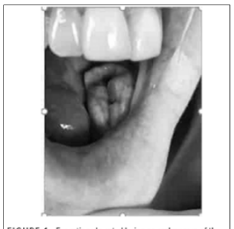

FIGURE 1 Fungating ulcerated lesion on oral mucosa of the left lower mandible at the site of prior SCC resection and marginal mandibulectomy

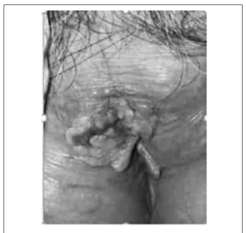

FIGURE 3 Six centimeter cluster of verrucous papules in a cluster encompassing the entire right labia minora, the right clitoral hood, and the margin of the right labia majora and sparing the periurethral area

A kidney transplant recipient (D+R-) gets 6 months of valganciclovir prophylaxis. Three months later, presents with fevers, malaise, low WBC, atypical lymphocytes, low platelets, hepatitis. What do you recommend?

A. Could be many things – send for many different cultures and viral load testing
B. This is probably CMV – send CMV viral load testing and routine cultures, and start treatment with valganciclovir 900mg po twice a day (renally adjusted as needed) (plan if not better, will check additional diagnostics)
C. Call a transplant ID colleague for guidance

14 – 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

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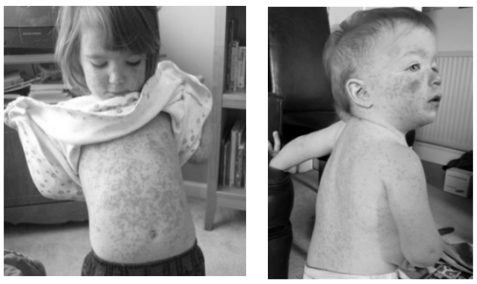
Exanthem subitum (roseola, sixth disease)



Slide courtesy of John W. Gnann Jr., MD, Medical University of South Carolina

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Human Herpesvirus Type 6: Normal hosts

- Associated syndromes
  - Exanthem subitum (roseola infantum, sixth disease)
    - children <4 y.o.; high fever for 5 days (febrile seizures), followed by a rash
  - Primary infection in adults (very rare) – mononucleosis syndrome
  - *Reactivation disease in transplant patients, esp. encephalitis and pneumonitis*
  - Mesial temporal lobe epilepsy association
  - Not the cause of MS, chronic fatigue, myocarditis, some others
- Diagnosis
  - Classic rash and clinical setting (early childhood)
  - IgG seroconversion
  - PCR from plasma (cell free), CSF, tissue → *immunocompromised patients*
- Therapy
  - Supportive care

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HHV-6: Immunocompromised Hosts

- Associated syndromes
  - Reactivation disease in transplant patients
  - **Encephalitis – mostly allogeneic HCT recipients (1-3%), often in first 60 days**
  - Bone marrow suppression (maybe also GVHD?)
  - Pneumonitis (rare, harder to prove)
- Diagnosis
  - PCR from plasma (cell free), CSF, tissue
    - High prevalence of viral DNA in peripheral blood mononuclear cells limits the use of PCR to discriminate between latency and active infection, chromosomal integration can be confusing
    - CSF typically normal or only mildly abnormal, slightly elevated WBC and protein, HHV-6 PCR 15,000-30,000 copies/ml
  - Encephalitis – MRI, EEG
- Therapy
  - Ganciclovir or foscarnet; likely decide based on toxicities; cidofovir last choice
  - Treat encephalitis; not all need treatment, not low level HHV-6+ in blood
  - Reduce immunosuppression if possible

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HHV-8

14 – CMV, EBV, HHV6 and HHV8 in Immunocompetent and Immunocompromised Patients

Speaker: Camille Kotton, MD

Human Herpesvirus Type 8

- Gamma herpesvirus, discovered 1994
- Kaposi sarcoma-associated herpesvirus (KSHV)
- Four variants have been described:
  - classic
  - endemic (Africa, Mediterranean regions)
  - iatrogenic or immunosuppression-associated
  - epidemic or AIDS- associated
- HHV-8 seroprevalence in the US (highly variable internationally):
  - Blood donor populations: 1-5%
  - MSM: 8-25%
  - HIV-positive MSM: 30-77%
  - HIV-positive with KS: 90%
- Route of transmission unknown – Sexual, saliva?
  - Transmission via SOT documented (rare).
- 1° infection usually asymptomatic, some with febrile rash syndrome

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HHV-8 Associated Diseases

- **Kaposi sarcoma**. 4 types:
  - Classic: indolent cutaneous proliferative disease, mainly affecting the lower extremities of elderly men of Mediterranean and Ashkenazi Jewish origin
  - Endemic: all parts of equatorial Africa, affecting both children and adults, can be more aggressive than classic
  - Transplant-associated: more often donor-derived (D+R-), can be reactivation
  - Epidemic/AIDS-related): KS is the most common tumor arising in people living with HIV; an AIDS-defining illness
- **Primary effusion lymphoma (body cavity-based lymphoma)**
  - Non-Hodgkin B-cell lymphoma, usually in HIV+. Involves pleural, pericardial, or peritoneal spaces
- **Castleman's disease (HIV+ and HIV-)**
  - Unicentric or Multicentric; hyaline vascular or plasma cell variants – all HHV-8 related. Fever, hepatomegaly, splenomegaly, massive lymphadenopathy
- **KSHV Inflammatory Cytokine Syndrome (KICS) in HIV+.**
  - Fever, elevated IL-6 & IL-10, high HHV-8 VL. High mortality rate.

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HHV-8 Diagnosis and Treatment

- Diagnosis
  - HHV-8 IgG
  - HHV-8 PCR on plasma, tissue
  - Biopsy/pathology for primary effusion lymphoma, Castleman's disease, etc
    - HHV-8 immunohistochemistry
- Treatment
  - Reduction of immunosuppression (watch for rejection)/start antiretroviral therapy
  - mTor inhibitors (sirolimus/rapamycin, etc) for transplant patients
  - Antiviral therapies +/- efficacy, not usually recommended, can be considered
  - Intralesional therapy or adjuvant chemotherapy may be required if unresponsive to these conservative measures or for more aggressive disease
  - Kaposi's sarcoma treated as a cancer

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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

Questions? ckotton@mgh.Harvard.edu

@KottonNelson

MASSACHUSETTS GENERAL HOSPITAL
TRANSPLANT CENTER

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%) Mucocutaneous lesions, rash, diarrhea
Human herpesvirus 6	Adolescents and adults	Any	Heterophile antibody–negative (<10%)
Bacteria			
Group A streptococci	School-age children, adolescents, and young adults	Winter and early spring	Scarlatiniform rash, no hepatosplenomegaly
Group C and group G streptococci	School-age children, adolescents, and young adults	Winter and early spring	Scarlatiniform rash
Arcanobacterium haemolyticum	Adolescents and young adults	Fall and winter	Scarlatiniform rash
Corynebacterium diphtheriae		Fall and winter	Tonsillar, pseudomembrane myocarditis
Neisseria gonorrhoeae	Adolescents and adults	Any	Tonsillitis
Mycoplasma pneumoniae	School-age children, adolescents, and young adults	Any	Pneumonia, bronchitis
Parasites			
Toxoplasma gondii	Adolescents and adults	Any	Heterophile antibody–negative (<3%) Small, nontender anterior lymphadenopathy

* Data are from Alcaide and Bisno.[29]
† 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.

Treatment of CMV after Transplant

Determine severity of infection

Mild to moderate CMV infection

Valganciclovir (oral) 900mg po q12 hours, renally adjusted

Severe (clinically), ophthalmologic, colitis with severe malabsorption, refractory/resistant, or life-threatening

Intravenous ganciclovir 5mg/kg q12, renally adjusted
Convert to oral treatment when clinically improving

Consider lowering immunosuppression
If total IgG < 400, consider giving either CMV Ig 150mg/kg or IVIG

Check weekly CMV DNAemia (i.e. CMV viral load) on plasma (vs whole blood).
Trend weekly until there are one-two negative/very low (<200 IU/ml) results, then stop therapy.

If CMV DNA level does not fall **after 2-3 weeks**, consider sending **CMV resistance testing**.
(This does not need to be sent after 1 week of treatment where we commonly see a small increase in the CMV viral load.)

Consider weekly monitoring after the end of treatment for 8-12 weeks so as to capture early recurrent disease vs restarting prophylaxis (especially in high risk D+R- patients, or with higher immunosuppression).

* Kotton et al, International CMV Guidelines, Transplantation 2018

Clinically significant drug interactions with maribavir

Cytochrome-P450 (CYP)/P-glycoprotein	Concomitant medication	Clinical implication of interaction	Clinical management of interaction
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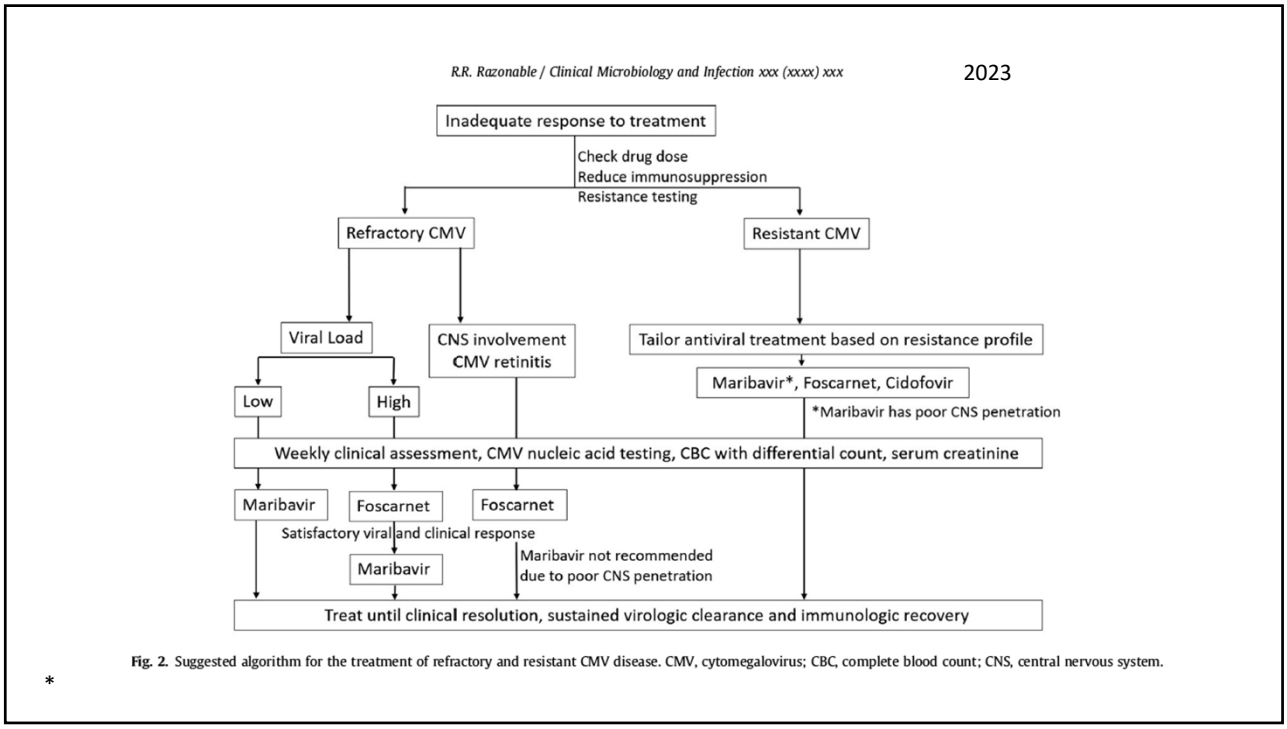

Fig. 2. Suggested algorithm for the treatment of refractory and resistant CMV disease. CMV, cytomegalovirus; CBC, complete blood count; CNS, central nervous system.

*

BR2

Board Review Session 2

Drs. Kotton (Moderator), Aronoff, Bennett, Chambers, DuPont, and Tunkel

BR2 – Board Review: Day 2

Moderator: Camille Kotton, MD

Board Review: Day 2

Moderator: Camille Nelson Kotton, MD, FIDSA, FAST
Faculty: Drs. Aronoff, Bennett, Chambers, Dupont, and Tunkel

8/2/2023

BOARD REVIEW DAY 2 INFECTIOUS DISEASE BOARD REVIEW 2023

#16 **A 30-year-old man from Washington, DC and no recent travel and without history of antibiotic use developed non-bloody diarrhea with abdominal cramps so severe that an acute abdominal emergency was considered.**

After a day or two, gross blood became visible in the stools.

He had no fever, his leukocyte count was mildly elevated, and he had only rare leukocytes found in the stool by microscopy after methylene blue staining.

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BOARD REVIEW DAY 2 INFECTIOUS DISEASE BOARD REVIEW 2023

#16 **Colonoscopy with biopsy revealed submucosal edema, hemorrhage and ulcerations.**

A stool sample sent to the laboratory was negative for the Clostridium difficile toxin B gene by PCR and for giardia by EIA.

Stool cultures at 48 hours are negative for Shigella, Salmonella, and Campylobacter.

Stool culture on sorbitol McConkey agar did not detect O157:H7.

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BOARD REVIEW DAY 2 INFECTIOUS DISEASE BOARD REVIEW 2023

#16 **Which of the following tests would most likely be useful?**

A) EIA for shigatoxin in stool

B) Stool antigens for Entamoeba histolytica

C) PCR for C. difficile toxin A gene in stool

D) Stool Gram stain for microsporidia

E) PCR on stool for enteroinvasive E. coli

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BOARD REVIEW DAY 2 INFECTIOUS DISEASE BOARD REVIEW 2023

#17 **An 86-year-old man is admitted to the hospital for treatment of community-acquired pneumonia and receives IV ceftriaxone followed by oral moxifloxacin.**

By day 4, his temperature is normal and he is ready for discharge when he develops loose stools with some abdominal cramping.

He is having 6-8 watery bowel movements a day. There is no blood in the stool.

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BOARD REVIEW DAY 2 INFECTIOUS DISEASE BOARD REVIEW 2023

#17 **His albumin is 3.0, creatinine has risen from 1.2 to 1.9, and white blood cell count is 18,000/mm^3.**

A stool specimen is submitted and is positive for *Clostridioides difficile* toxin using PCR for the toxin B gene and detection of toxin B by immunoassay.

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BOARD REVIEW DAY 2 | INFECTIOUS DISEASE BOARD REVIEW 2023

#17 **Which of the following drugs would you use to treat this patient assuming you were choosing monotherapy?**

A) IV Metronidazole

B) PO Metronidazole

C) PO Fidaxomicin

D) PO Rifaxamin

E) IV Vancomycin

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BOARD REVIEW DAY 2 | INFECTIOUS DISEASE BOARD REVIEW 2023

#18 **A 26-year-old man presents to the emergency room with fever, chills, and shortness of breath for three days. He is found to be febrile (T 102.3F), tachycardic (HR 110 bpm), with scattered rhonchi on an exam. WBC is 16,000 cells/cc^3.**

Blood cultures are drawn, and a chest x-ray reveals multiple scattered nodules. The patient is empirically started on vancomycin plus piperacillin/tazobactam and admitted.

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BOARD REVIEW DAY 2 | INFECTIOUS DISEASE BOARD REVIEW 2023

#18 **On exam, the inpatient team noticed an ulcerated area with an associated abscess on his left leg and several scars along his upper extremities' veins.**

On questioning, he endorses active injecting drug use with heroin and last injected two hours before presenting to the emergency department.

A transthoracic echo (TTE) is performed, revealing a 1.5 cm mass on the tricuspid valve. After 48 hours, 4/4 bottles of blood cultures grow *Eikenella corrodens*.

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BOARD REVIEW DAY 2 | INFECTIOUS DISEASE BOARD REVIEW 2023

#18 **What is the likely cause of infection with this particular organism?**

A) Aerosolization exposure from a water cooling system

B) Wound contamination from urine and stool

C) Ingestion of contaminated food or water

D) Using toilet water to dilute opioid

E) Licking the injecting needle before injection

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BOARD REVIEW DAY 2 | INFECTIOUS DISEASE BOARD REVIEW 2023

#19 **A patient with HIV infection (CD4 count =50 cells/μL, VL =2 million copies/ml) is referred to you from an HIV screening program.**

He has been asymptomatic except for a faltering gait and trouble being attentive at work over the past several months.

He is afebrile and has a normal complete blood count and chemistry profile.

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BOARD REVIEW DAY 2 | INFECTIOUS DISEASE BOARD REVIEW 2023

#19 **An MRI of his central nervous system shows several white matter lesions which do not enhance with gadolinium.**

The radiologist thinks the lesions are suspicious for progressive multifocal leukoencephalopathy/JC virus encephalitis.

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BOARD REVIEW DAY 2 INFECTIOUS DISEASE BOARD REVIEW 2023

#19 **A CSF analysis show 10 mononuclear leukocytes, protein 50 mg/dl, and normal glucose.**

JC PCR is negative as is a multiplex PCR for 14 likely viral/bacterial/fungal CSF pathogens.

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BOARD REVIEW DAY 2 INFECTIOUS DISEASE BOARD REVIEW 2023

#19 **What is the most likely interpretation of these results?**

A) The negative PCR rules out PML/JC

B) A blood PCR should be obtained to provide more diagnostic information

C) A urine PCR for JC virus should be obtained to provide more diagnostic information

D) A brain biopsy is indicated

E) The patient should be treated with ART (and no specific therapy for JC) and followed for progression/regression of neurologic disease

4 of 5

BOARD REVIEW DAY 2 INFECTIOUS DISEASE BOARD REVIEW 2023

#20 **A 42-year-old male presents with a deformed foot and draining sinuses.**

The patient is a native of Mexico, where he does manual labor.

He noted the onset of persistent swelling 2 years earlier in Mexico after dropping a heavy wooden box on his foot.

He received various treatments, but his foot has become more deformed.

1 of 5

BOARD REVIEW DAY 2 INFECTIOUS DISEASE BOARD REVIEW 2023

#20 **He is visiting family in the United States and comes to you for advice.**

He is afebrile, with normal vital signs. He looks well.

His exam is normal except for his left foot, which is swollen and firmly indurated, particularly over the metatarsals, but not very tender.

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BOARD REVIEW DAY 2 INFECTIOUS DISEASE BOARD REVIEW 2023

#20 **Several draining sinuses are present.**

His routine lab work, including CBC, is normal.

An x-ray of his foot shows soft tissue defects without bony erosions.

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BOARD REVIEW DAY 2 INFECTIOUS DISEASE BOARD REVIEW 2023

#20 **The appropriate approach would be:**

A) An empiric course of trimethoprim-sulfamethoxazole

B) An empiric course of amphotericin

C) An empiric course of itraconazole

D) Smear and culture of the sinus discharge before initiating therapy

E) Surgical biopsy and culture of deep tissue

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BOARD REVIEW DAY 2 | INFECTIOUS DISEASE BOARD REVIEW 2023

#21 **A 52-year-old male received a heart transplant two years ago and is doing well on cyclosporine, mycophenolate and prednisone maintenance therapy.**

His 12-month-old son is scheduled for routine immunizations including varicella vaccine.

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BOARD REVIEW DAY 2 | INFECTIOUS DISEASE BOARD REVIEW 2023

#21 **The father, who grew up in rural Mexico, is seronegative for varicella.**

He never received varicella vaccine and does not remember ever having chickenpox or zoster.

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BOARD REVIEW DAY 2 | INFECTIOUS DISEASE BOARD REVIEW 2023

#21 **What should you advise regarding management?**

A) The child should not be immunized.

B) The child should be immunized and the father given VariZig (zoster immune globulin).

C) The child should be immunized and removed from contact with the father if the child develops a rash associated with the vaccine.

D) The child should be immunized at which time the father should be given a 10-14 day course of valacyclovir.

E) The father should be immunized prior to immunizing the child.

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BOARD REVIEW DAY 2 | INFECTIOUS DISEASE BOARD REVIEW 2023

#22 **A husband and a wife share a sandwich bought at a fast-food location on a trip to a park near their home in southeastern US.**

Three hours later the wife develops chills and fever (101°F) and five hours after consuming the food the husband has watery diarrhea that progresses to the passage of bloody stools with copious mucus.

1 of 3

BOARD REVIEW DAY 2 | INFECTIOUS DISEASE BOARD REVIEW 2023

#22 **Which of the following explains the most likely cause of the illnesses:**

A) The sandwich did not cause the two illnesses

B) They both have probably acquired a bacterial infection from either Shigella or Campylobacter from the sandwich

C) They both likely have norovirus infection

D) Both should be followed for development of HUS

E) They should be studied for SARS-CoV-2 infection

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BOARD REVIEW DAY 2 | INFECTIOUS DISEASE BOARD REVIEW 2023

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

There is a family history of gastric cancer.

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

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BOARD REVIEW DAY 2 | INFECTIOUS DISEASE BOARD REVIEW 2023

#23 **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

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BOARD REVIEW DAY 2 | INFECTIOUS DISEASE BOARD REVIEW 2023

#24 **A 57-year-old man presents with 1 week of fever, chills, and low back pain.**

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

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

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

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BOARD REVIEW DAY 2 | INFECTIOUS DISEASE BOARD REVIEW 2023

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

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

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

Renal function is normal.

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BOARD REVIEW DAY 2 | INFECTIOUS DISEASE BOARD REVIEW 2023

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

A) Cefazolin 2 gm IV every 8 hours

B) Ceftriaxone 2 gm IV every 12 hours

C) Linezolid 600 mg IV every 12 hours

D) Nafcillin 1 gm IV every 4 hours

E) Vancomycin 1 gm IV every 12 hours

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BOARD REVIEW DAY 2 | INFECTIOUS DISEASE BOARD REVIEW 2023

#25 **A 31-year-old woman is brought to the emergency department by her husband for fever and neurological symptoms.**

She was completely well until 3 days earlier, when she felt nauseated and vomited twice.

During the next two days she had fever, felt "achy," developed a headache, and continued to have nausea and vomiting.

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BOARD REVIEW DAY 2 | INFECTIOUS DISEASE BOARD REVIEW 2023

#25 **Upon awakening this morning, she complained of double vision, and her husband noted her eyes "weren't looking in the same place."**

In the emergency room, she was found to have a temperature of 102.4°F.

There was no rash.

She had mild nuchal rigidity, right 6th cranial nerve palsy, and a sensory deficit over most of the left side of her body.

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BOARD REVIEW DAY 2 INFECTIOUS DISEASE BOARD REVIEW 2023

#25 **Her gait was very unsteady.**

The rest of the exam was unremarkable.

An MRI of the head demonstrated inflammation of the pons and medulla.

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BOARD REVIEW DAY 2 INFECTIOUS DISEASE BOARD REVIEW 2023

#25 **Which one of the following organisms is the most likely cause of her illness?**

A) Streptococcus pneumoniae

B) Nocardia nova

C) Mycobacterium tuberculosis

D) Listeria monocytogenes

E) Cryptococcus neoformans

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BOARD REVIEW DAY 2 INFECTIOUS DISEASE BOARD REVIEW 2023

#26 **A 42-year-old male had a heart lung transplant 2 years prior and was doing well when he presented to his transplant team complaining of diffuse body aches, particularly in the extremities.**

He had no arthritis on examination and full range of motion in joints.

The patient was afebrile, and his routine CBC, chemistry profile, cardiac echo, and pulmonary function tests were unchanged except for a serum alkaline phosphatase which was for the first time twice the upper limit of normal.

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BOARD REVIEW DAY 2 INFECTIOUS DISEASE BOARD REVIEW 2023

#26 **Other liver function tests were normal.**

A bone scan showed numerous scattered areas of uptake. Routine films of the extremities showed patches of periosteal thickening and a few calcified excrescences.

He had been diagnosed with probable pulmonary aspergillosis based on the presence of pulmonary nodules and an elevated serum galactomannan test and had been taking voriconazole for the past 18 months.

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BOARD REVIEW DAY 2 INFECTIOUS DISEASE BOARD REVIEW 2023

#26 **He was receiving tacrolimus (Prograf) and mycophenolate mofetil (CellCept) plus trimethoprim-sulfamethoxazole prophylaxis for PCP, acyclovir for recurrent orolabial Herpes simplex and once daily multivitamins with vitamins A and D.**

A repeat chest CT showed no change from the small nodules seen two months prior.

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BOARD REVIEW DAY 2 INFECTIOUS DISEASE BOARD REVIEW 2023

#26 **The most likely cause of these joint manifestations is:**

A) Drug interaction with Vitamin D

B) Drug interaction with Vitamin A

C) Voriconazole toxicity

D) Tacrolimus toxicity

E) Mycophenolate mofetil toxicity

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BOARD REVIEW DAY 2 | INFECTIOUS DISEASE BOARD REVIEW 2023

#27 **A 53-year-old man has received CAR CD19 T cell therapy with Axicabtagene ciloleucel (Yescarta- a CD19-directed genetically modified autologous T cell immunotherapy) for his refractory Diffuse Large B Cell Lymphoma (DBCL).**

He had failed prior regimens of standard chemotherapy.

Seven days after infusion of the Axicabtagene ciloleucel (Yescarta), he developed fever to 38.3°C, hypotension, hypoxemia, pulmonary infiltrates, and oliguria.

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BOARD REVIEW DAY 2 | INFECTIOUS DISEASE BOARD REVIEW 2023

#27 **On physical examination, other than his vital signs there are no new findings other than diffuse crackles.**

He has a port in place that looks unremarkable.

His absolute neutrophil count in 50 cells/ul.

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BOARD REVIEW DAY 2 | INFECTIOUS DISEASE BOARD REVIEW 2023

#27 **Which of the following would most accurately describe how to distinguish septic shock from a CAR-T cell cytokine release syndrome in this patient?**

A) IL-1 level

B) IL-6 level

C) CH50

D) C Reactive protein

E) There is currently no clinical or laboratory test that will distinguish sepsis from CAR-T cytokine release syndrome

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BOARD REVIEW DAY 2 | INFECTIOUS DISEASE BOARD REVIEW 2023

#28 **Two hours after eating at a hotel buffet in Hawaii, a 56-year-old man experiences abdominal pain, vomits once, and has one loose stool.**

Two days later he experiences numbness of his extremities, tongue, and throat.

He finds that cold objects feel hot and hot objects feel cold, and his teeth feel numb and loose.

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BOARD REVIEW DAY 2 | INFECTIOUS DISEASE BOARD REVIEW 2023

#28 **He develops weakness, gait ataxia, and vertigo.**

He is hospitalized where he has a slow convalescence.

Neurological symptoms persist for one month before he is completely well.

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BOARD REVIEW DAY 2 | INFECTIOUS DISEASE BOARD REVIEW 2023

#28 **What is the likely diagnosis?**

A) Ciguatera

B) Scombroid

C) Paralytic Shellfish Poisoning

D) Botulism

E) Staphylococcal food poisoning

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BOARD REVIEW DAY 2 | INFECTIOUS DISEASE BOARD REVIEW 2023

#29 **A 52-year-old otherwise healthy woman was admitted with a 4 x 5 cm abscess of the right buttock which she says started as a tender bump about a week ago.**

She has had subjective fevers beginning the day prior to admission.

Vital signs on admission were a temperature of 38.5°C, pulse 100, respiratory rate 16, blood pressure 125/80.

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BOARD REVIEW DAY 2 | INFECTIOUS DISEASE BOARD REVIEW 2023

#29 **Except for the buttock abscess the physical examination was unremarkable including no cardiac murmur, no rash or other skin findings.**

Admission chest x-ray was normal.

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

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

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BOARD REVIEW DAY 2 | INFECTIOUS DISEASE BOARD REVIEW 2023

#29 **The abscess was drained and empiric vancomycin was administered on hospital day 1.**

She has had no further fevers since drainage of the abscess and feels much improved.

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

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

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BOARD REVIEW DAY 2 | INFECTIOUS DISEASE BOARD REVIEW 2023

#29 **What should be your recommendation for echocardiography?**

A) Obtain transthoracic echocardiogram (TTE) to rule out endocarditis

B) Obtain a transesophageal echocardiogram (TEE) to rule out endocarditis

C) Echocardiography need not be performed; the patient has uncomplicated MSSA bacteremia and will do well with two weeks of antimicrobial therapy

D) Echocardiography need not be performed as long as the patient is given four weeks of antimicrobial therapy

E) Obtain a transthoracic echocardiogram (TTE) and proceed to transesophageal echocardiography if TTE is negative for evidence of endocarditis

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BOARD REVIEW DAY 2 | INFECTIOUS DISEASE BOARD REVIEW 2023

#30 **A 31-year-old female (EBV IgG negative, CMV seropositive) with acute myelogenous leukemia-M2 in relapse was given a T cell depleted myeloablative allogeneic hematopoietic stem cell transplant from an EBV and CMV antibody positive donor.**

She engrafted with 100% myeloid chimerism and was doing well on day 79 with a WBC of 3,700/cu ml at which time she developed fever, severe sore throat and tender cervical lymphadenopathy.

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BOARD REVIEW DAY 2 | INFECTIOUS DISEASE BOARD REVIEW 2023

#30 **She had been receiving cyclosporine and prophylactic trimethoprim-sulfamethoxazole and valacyclovir. Cultures of the pharynx for HSV and Streptococcus pyogenes were negative.**

High resolution chest CT found a 3cm well defined nodule in the left upper lobe.

Aspiration of a lymph node found predominately B cells with plasmacytoid differentiation, numerous mitotic figures and polyclonal light chain expression.

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BOARD REVIEW DAY 2 INFECTIOUS DISEASE BOARD REVIEW 2023

#30 **Immunochemical stains for EBV were positive. Quantitative PCR of peripheral blood found 3,200,000 genome copies of EBV per ml and she had developed a positive IgG antibody to EBV VCA.**

PCR of peripheral blood was negative for CMV.

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BOARD REVIEW DAY 2 INFECTIOUS DISEASE BOARD REVIEW 2023

#30 **Which of the following best describes this patient's condition?**

A) Infectious mononucleosis

B) Uncontrolled proliferation of EBV infected B cells

C) EBV infection that will respond to ganciclovir

D) CMV infection that will respond to ganciclovir

E) Multicentric Castleman's disease

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15

Nocardia, Actinomycosis, Rhodococcus, and Melioidosis

Dr. David Aronoff

15 – Nocardia, Actinomycosis , Rhodococcus, and Melioidosis

Speaker: David M. Aronoff, MD

IDBR INFECTIOUS DISEASE BOARD REVIEW AUGUST 19-23 2023

Nocardia, Actinomycosis, Rhodococcus, and Meliodosis

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

6/11/2023

IDBR INFECTIOUS DISEASE BOARD REVIEW AUGUST 19-23 2023

Disclosures of Financial Relationships with Relevant Commercial Interests

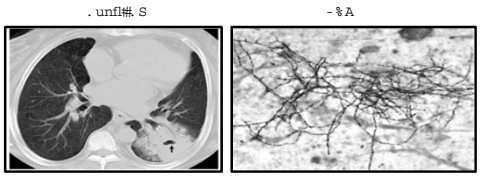
- **None**

Case

IDBR INFECTIOUS DISEASE BOARD REVIEW AUGUST 19-23 2023 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).

IDBR INFECTIOUS DISEASE BOARD REVIEW AUGUST 19-23 2023 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.

IDBR INFECTIOUS DISEASE BOARD REVIEW AUGUST 19-23 2023 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

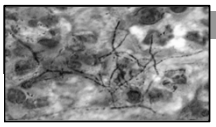
What are the most appropriate next steps in this patient's care?

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

15 – Nocardia, Actinomycosis , Rhodococcus, and Melioidosis

Speaker: David M. Aronoff, MD

Nocardia Infections



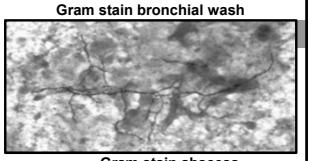
- **Microbiology:**
  - Beaded & branching gram-positive rods
  - Partially acid-fast
  - Aerobic (unlike anaerobic *Actinomyces*)
  - More than 80 species & >40 cause disease in humans
    - New phylogeny based on DNA sequence (*formerly*, *N. asteroides* complex): **species names are *lookups***.
-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

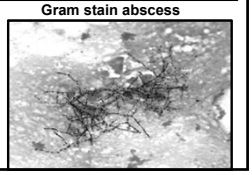
Images of *Nocardia*

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

Gram stain bronchial wash



Gram stain abscess



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

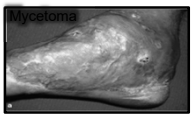
Clinical Features of *Nocardia*

- **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). "Madura foot"

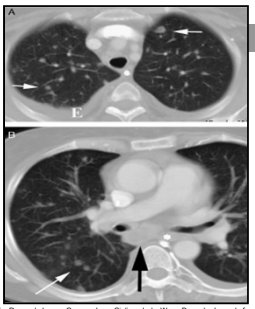


Baradkar V P, *et al. Indian J Pathol Microbiol* 2008;51:432-4 Sharma NL, *et al. Indian J Dermatol Venereol Leprol* 2008;74:635-40

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)

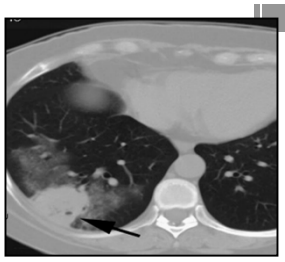


Pulmonary Nocardiosis: Computed Tomography Features and Diagnosis. Blackmon, Kevin; Ravenel, James; Gomez, Juan; Ciolino, Jody; Wray, Dannah. *Journal of Thoracic Imaging*. 26(3):224-229, August 2011. DOI: 10.1097/RTI.0b013e3181f45dd5

15 – Nocardia, Actinomycosis , Rhodococcus, and Melioidosis

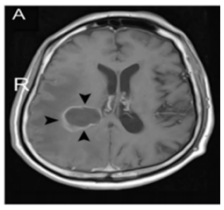
Speaker: David M. Aronoff, MD

- 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

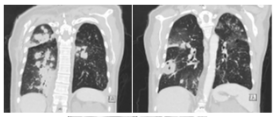
- Right frontoparietal subcortical ring lesion with a central dark signal & bright **ring enhancement** (black arrowheads) in postcontrast T1-weighted image.

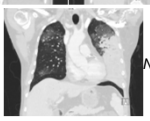


Nandhagopal, Ramachandiran, Zakariya Al-Muharrmi, and Abdullah Balkhair. "Nocardia brain abscess." *QJM* 107.12 (2014): 1041-1042.

Case

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

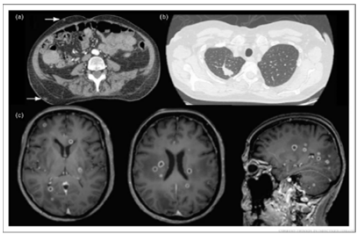




Nocardia nova

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).

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)

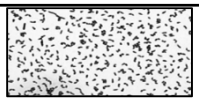
15 – Nocardia, Actinomycosis , Rhodococcus, and Melioidosis

Speaker: David M. Aronoff, MD

Nocardia Buzzwords

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

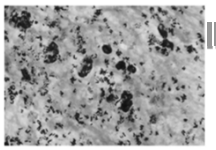
Rhodococcus



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

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

Rhodococcus

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

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

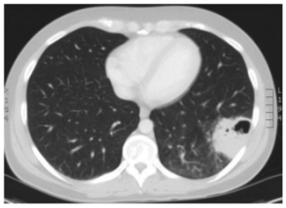


Image from Stewart A., *et al. IDCases.* (2019)

Rhodococcus

- **Diagnosis:**
  - **Culture** followed by 16S rRNA, MALDI-TOF
  - Tissue: gram stain, **necrotizing granulomatous** reaction; microabscess
  - Blood cultures may be positive (>25%)
- **Treatment:**
  - Combination therapy 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**
- **Horse** / manure exposure

15 – Nocardia, Actinomycosis , Rhodococcus, and Melioidosis

Speaker: David M. Aronoff, MD

Case

2023 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

2023 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.

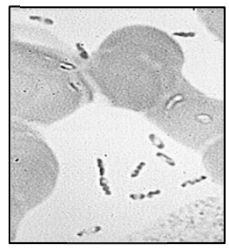
Melioidosis Take-Aways

- Microbiology lab:
  - Facultative intracellular gram-negative rod, *Burkholderia pseudomallei*
  - Oxidase positive
  - Characteristic bipolar staining with a "safety pin" appearance
- Typical patient:
  - SE Asia, northern Australia
    - *Esp.* Northeastern Thailand & northern Australia

Chakravorty A, Heath CH. *Australian Journal of General Practice* (2019)

Bacteria with “safety pin” appearance

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



Melioidosis Take-Aways

- **Clinical findings:**
  - **Acute** or chronic pneumonia or sepsis
  - Transmission via percutaneous inoculation, **inhalation**
  - Risk factors = **diabetes**, alcoholism, chronic renal & lung disease
  - Acute infection more common than chronic infection

Chakravorty A, Heath CH. *Australian Journal of General Practice* (2019)

Melioidosis Take-Aways

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

Wiersinga WJ, *et al. Nat Rev Dis Primers.* 2018

Melioidosis Take-Aways

- **Diagnosis: Culture**
  - **Alert the lab you are concerned about this pathogen!**
  - Ashdown's media
- **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
https://jcm.asm.org/content/54/12/2866
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2600349/

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 stain; Gram negative rods
- **Ashdown media**

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

Melioidosis: **Bonus Material**

- Small outbreak (n=4, 2 deaths) in US associated with a contaminated **aromatherapy product**


BRIEF REPORT

Multistate Outbreak of Melioidosis Associated with Imported Aromatherapy Spray


United States CONSUMER PRODUCT SAFETY COMMISSION

Walmart Recalls Better Homes and Gardens Essential Oil Infused Aromatherapy Room Spray with Gemstones Due to Rare and Dangerous Bacteria; Bacteria Identified in this Outbreak Linked to Two Deaths

FUTURE BOARD EXAM?

https://www.cdc.gov/melioidosis/outbreak/2021/index.html
N Engl J Med 2022;386:861-8. DOI: 10.1056/NEJMoa2116130

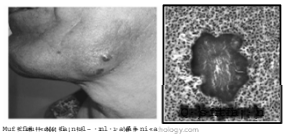
Glanders

- 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)

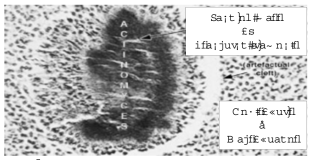


Actinomyces Take-Aways

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

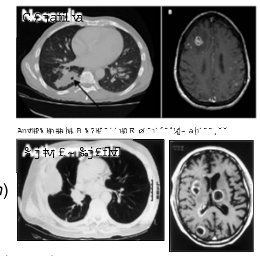
Actinomyces: **Buzzwords**

- **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

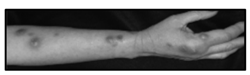


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Photo: eScholarship

THANK YOU

aronoff@iu.edu
@DMAronoff

15 – Nocardia, Actinomycosis , Rhodococcus, and Melioidosis

Speaker: David M. Aronoff, MD

Nocardia Treatment

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

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

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

16

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

Dr. Henry Chambers

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

Speaker: Henry Chambers, MD

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

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

7/2/2023

Disclosures of Financial Relationships with Relevant Commercial Interests

- **Data monitoring committee: Merck**
- **Stock: Merck, Moderna**
- **Medical expert, product liability: Lilly**
- **Medical expert, patent dispute: Nexus Pharmaceuticals**

Topics for Discussion

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

Diagnosis of Endocarditis

Clinical Signs and Symptoms

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

Arch Intern Med. 2009;169:463-473

Q1. Which one of the following statements is correct?

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

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

Speaker: Henry Chambers, MD

Microbiology

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

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

Clinical Infectious Diseases
VIEWPOINTS

The 2023 Duke-International Society for Cardiovascular Infectious Diseases Criteria for Infective Endocarditis: Updating the Modified Duke Criteria

Vance G. Fowler, Jr.,[1,2,3] David T. Durack,[1] Christine Selton-Suty,[3] Eugene Athan,[4] Arnold S. Bayer,[5,6] Anna Lisa Chamis,[1] Anders Dahl,[7] Louis DiBernardo,[1] Emanuele Durante-Mangoni,[8] Xavier Duval,[9] Claudio Querido Fortes,[10] Emil Fosbol,[11] Margaret M. Hannan,[12] Barbara Hasse,[13] Bruno Hoen,[14] Adolf W. Karchmer,[15] Carlos A. Mestres,[16] Cathy A. Petti,[1,17] Maria Nazarena Pizzi,[18] Stephen D. Preston,[19] Albert Roque,[20] Francois Vandenesch,[21,22] Jan T. M. van der Meer,[23] Thomas W. van der Vaart,[23] and Jose M. Miro[24,25]

Clin Infect Dis. 2023 May 4. PMID 37138445

Weaknesses of Modified Duke Criteria

- Reduced sensitivity for diagnosis of PVE, CIED-related endocarditis
- Reduced sensitivity for culture-negative endocarditis
- Poorly validated in pediatric populations
- Newer imaging modalities and molecular diagnostics not included in criteria

2023 Duke-ISCVID Criteria for Diagnosis of Endocarditis

Definite pathologic diagnosis	**Definite Clinical Diagnosis**	**Possible Clinical Diagnosis**
Microorganisms identified on cardiac tissue, vegetation, graft, device	Two major criteria	Three minor criteria
	OR	OR
OR	Five minor criteria	One major plus one minor criteria
Vegetation, leaflet destruction, or adjacent cardiac tissue showing inflammatory changes	OR	
	One major plus three minor criteria	

Rejected endocarditis: criteria for definite or possible endocarditis are not met **OR** firm alternative diagnosis established OR lack of recurrence with < 4 days antibiotic therapy

2023 Duke-ISCVID Major Criteria

Positive blood cultures

Typical microorganisms* from 2 separate blood cultures
OR
Non-typical organisms in 3 or more separate blood cultures
OR
+ PCR for Coxiella burnetti, Bartonella, T whipplei; Coxiella phase I IgG antibody titer >1:800, IFA IgG titer for Bartonella ≥ 1:800

Imaging

+ ECHO/Cardiac CT
1) Vegetation, leaflet perforation, aneurysm, abscess, pseudo-aneurysm, fistula OR
2) New regurgitation c/w prior imaging OR
3) NEW PVE dehiscence

+ PET/CT
PV, device, or graft

Surgical

Evidence of IE by direct inspection at surgery

**Staphylococcus aureus*, viridans group streptococci, *Streptococcus gallolyticus*, HACEK species (*Hemophilus* species, *Aggregatibacter*, *Cardiobacterium*, *Eikenella*, *Kingella*), *E. faecalis*, *S. lugdunensis*, *Granulicatella*, *Gamella*, *Abiotphia* and in addition for PVE CoNS, *C. acnes*, Corynebacterium, Serratia

2023 Duke-ISCVID Minor Criteria

- Predisposition: previous IE, PV, h/o valve repair, CHD, more than mild valve regurgitation or stenosis, CIED, hypertrophic cardiomyopathy, IVDU
- Fever, documented temperature >38.0°C (>100.4°F)
- Vascular phenomena: systemic arterial emboli, septic pulmonary emboli, mycotic aneurysm, intracranial hemorrhage, conjunctival hemorrhages, or Janeway lesions, cerebral or splenic abscess
- Immunologic phenomena: glomerulonephritis, Osler nodes, Roth spots, or rheumatoid factor
- Positive blood cultures that do not meet major criteria, OR +PCR/NGS for typical organism from sterile body site
- + PET/CT of PV, graft, or device within 3 mo of implantation
- New regurgitant murmur on exam and echocardiography unavailable

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

Speaker: Henry Chambers, MD

2023 Duke-ISCVID Criteria for Diagnosis of Endocarditis

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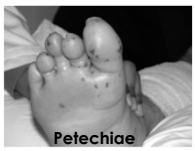
2023 Duke-ISCVID Criteria for Diagnosis of End

Definite pathologic diagnosis	Definite Clinical Diagnosis	Possible Clinical Diagnosis
Microorganisms identified on cardiac tissue, vegetation, graft, device	Two ma	
OR		One major plus one minor criteria
Ve		
	One major plus three minor criteria	

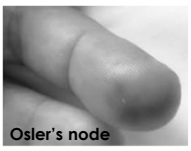
- Sensitivity: 85% (definite) to 95% (definite + possible)
- Specificity: 95%

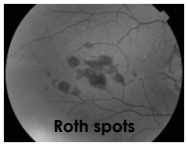
Re endocarditis: criteria for definite or possible endocarditis are not met **OR** firm alternative diagnosis established OR lack of recurrence with < 4 days antibiotic therapy

Microvascular/Immunologic Phenomena

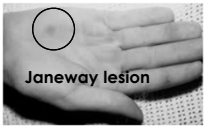

Petechiae


Splinter hemorrhages

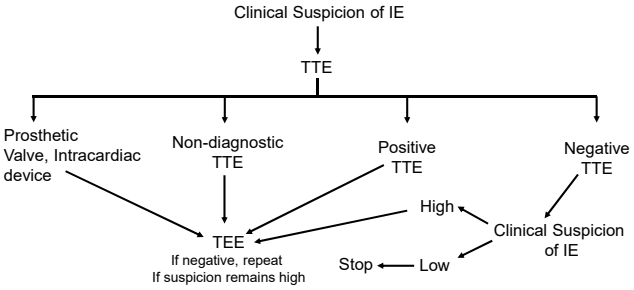

Osler's node


Roth spots


Subconjunctival hemorrhages


Janeway lesion

Role of Echocardiography



European Heart Journal (2015) 36, 3075–3123

Harmonic TTE vs TEE for Diagnosis of IE

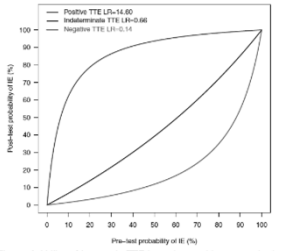


Figure 3 Utility of harmonic TTE in patients without prosthetic valves.

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

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

Native Valve Endocarditis

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

Speaker: Henry Chambers, MD

PREVIEW QUESTION

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

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

PREVIEW QUESTION

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

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

Native Valve Staph. aureus IE

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

No gentamicin, no rifampin

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

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

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

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

Treatment of VGS and Strep. gallolyticus Native Valve Endocarditis

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

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

Speaker: Henry Chambers, MD

PREVIEW QUESTION

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

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

PREVIEW QUESTION

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

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

Enterococcal Endocarditis

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

*Limited data that 2 weeks of gent is sufficient

HACEK Organisms

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

Antimicrobial Therapy of HACEK Endocarditis

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

Empirical Therapy for Endocarditis While Awaiting Culture Results

- Vancomycin 60 mg/kg/d in divided doses + ceftriaxone 2 gm Q24h
- Severe penicillin allergy: Vancomycin + aztreonam 2 gm q8h

Oral Therapy of Endocarditis

Principles Of Antimicrobial Therapy

- The regimen should kill the pathogen
- A prolonged course of therapy (i.e., weeks not days)
- Intensive dosing to ensure adequate drug exposure
- Source control

POET Trial of Oral Therapy

- Noninferiority trial, 10% margin, left-sided endocarditis, IV vs partial oral
- Streptococci, Enterococcus faecalis, Staph. aureus, coag-negative staphylococci
- All patients given IV antibiotics for at least 10 days
- Primary outcome: composite of all-cause mortality, unplanned cardiac surgery, embolic events, or relapse within 6 mo.

N Engl J Med 2019;380:415

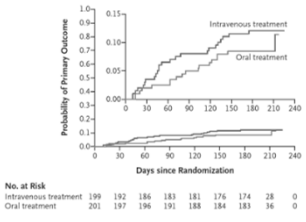
Outcomes: POET Trial of Oral Therapy

1954 assessed for eligibility
↓
1554 excluded (428 no Duke criteria)
↓
400 randomized

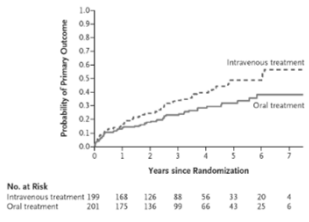
Outcome	IV (N=199)	PO (N=201)
Mortality	13 (6.5%)	7 (3.5%)
Unplanned surgery	6 (3.0%)	6 (3.0%)
Embolic event	3 (1.5%)	3 (1.5%)
Relapse	5 (2.5%)	5 (2.5%)

N Engl J Med 2019;380:415

Outcomes: POET Trial of Oral Therapy



N Engl J Med 2019;380:415



N Engl J Med 2019;380:1373

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Culture-Negative Endocarditis

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

Speaker: Henry Chambers, MD

Culture-Negative Endocarditis

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

Culture-Negative Scenarios

- **Coxiella burnetii (Q fever)**: Direct or indirect animal contact, hepatosplenomegaly, abnormal or prosthetic valve. Doxycycline + hydroxychloroquine >1 yr.
- **Bartonella**: Homeless, indolent, valve normal or abnormal, louse vector. **Rx:** 6 wks doxycycline plus two wks gentamicin or plus 2 wks rifampin if valve resected (otherwise 3 months more of doxy)
- **Tropheryma whippeli:** Indolent, protracted course with arthralgias, diarrhea, malabsorption, weight loss, CNS involvement

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Tools for Diagnosis of Culture-Negative Endocarditis

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

Prosthetic Valve and Device-Related Endocarditis

Q5. A 72 y/o man s/p AV replacement with a bioprosthetic valve for bicuspid AV with insufficiency. He reports sore throat, cough, congestion, fever, chills, sweats and malaise for 3 days

- Exam: T 100.2° F, Pulse 85 , BP 130/70mm Hg, RR 16
  - HEENT: oral cavity and tonsils red and swollen, no lymphadenopathy
  - Lungs: clear
  - Heart: No murmur
  - Skin: no rash
- Rapid rapid strep, rapid flu both negative

Q5. What is the best approach for managing this patient?

1. Obtain throat culture and prescribe Pen VK while awaiting results
2. Obtain throat culture and give a script for Pen VK to be filled if culture is positive for GAS
3. Prescribe azithromycin for treatment of acute URI
4. Obtain blood cultures and await results
5. Obtain blood cultures and initiate therapy with vancomycin, gentamicin, and rifampin

Speaker: Henry Chambers, MD

Microbiology of PVE

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

Adapted from Karchmer and Chu, UpToDate, 2020

Diagnosis of PVE

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

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

Antimicrobial Therapy of PVE

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

Cardiac Implantable Device Infections

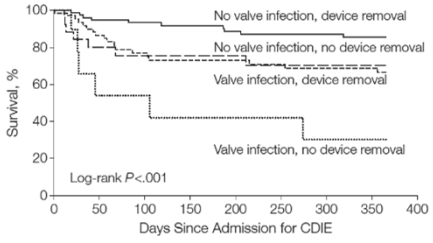
(permanent pacemakers, defibrillators)

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

Cardiac Implantable Device Infection Types

- Pocket site/generator only : ~ 60%
  - Blood culture positive <50%
  - Pocket infection or generator/lead erosion
- Occult bacteremia/fungemia: ~7-30%
- Lead infection +/- endocarditis: ~10-25%
- PET-CT may detect localized infection if work-up is inconclusive

Survival with and without Device Removal

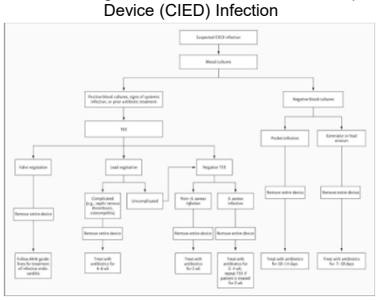


Athan, JAMA. 2012; 307:1727-1735

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

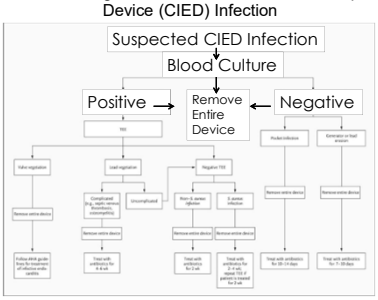
Speaker: Henry Chambers, MD

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



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

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



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

AHA Guidelines for Management of Cardiac Implantable Device Infections

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

Circulation 2010;121:458-77

AHA Guidelines for Device Reimplantation

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

Main Take-home Points

- Duke-ISCVID criteria is a valuable tool for assessing the likelihood of endocarditis
- TTE is acceptable to rule out endocarditis if of high quality and in a low probability setting
- Use a tried-and-true regimen, avoid aminoglycoside combination therapy for NVE
- Think prior antibiotics and Bartonella in culture-negative endocarditis
- Any fever is a patient with a prosthetic valve is endocarditis until proven otherwise

Time Permitting

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

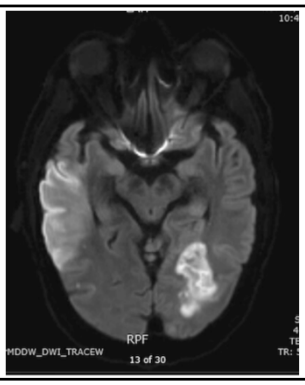
Speaker: Henry Chambers, MD

Case Presentation

- 52 yo M admitted from the ED with fever, chills, abdominal pain for 3 days
- PMH: HCV, cirrhosis, varices, injection drug use
- T 40.6ºC, HR 127, BP 125/88, no murmur; combative, disoriented, nuchal rigidity, nonfocal neuro exam

Initial Work-Up

- WBC 15K; Na+ 127, rest of BMP normal
- CSF: 388 white cells, 95% PMNs, Pro 71, Glu 69, Gram stain no organisms, culture positive for MRSA @ 18h
- CT abd: splenic infarcts
- CT head: without contrast: no blood & otherwise negative
- TTE: Thickened AV, mild AR, mild MR, possible R coronary cusp vegetation
- Rx: Vancomycin + ampicillin + ceftriaxone, then vancomycin



Hospital Course

MRI: Numerous areas of restricted diffusion in multiple vascular territories most notably in the L occipital lobe and R temporal lobe

Blood cultures persistently positive; CSF 19 WBCs and sterile

HD5: cold, pulseless RLE; heparin is administered, he is taken to the OR for thrombectomy and has a fatal cardiac arrest post-op

Embolic Events in IE

- Systemic embolization up 30-40%; CNS accounts for about half
- Highest rates in MV IE (anterior > posterior leaflet)
- 50% identified at presentation, prior to therapy
  - ~65% of the remainder during first 2 weeks of antibiotic therapy
  - ~3% suffer a stroke after 1 week of therapy (benefit of early surgery correspondingly less)
- Value of CNS imaging all patients with IE unknown, may be considered as part of pre-op evaluation
- Preventative systemic anticoagulation, antiplatelet therapy contraindicated (guidelines do not address anticoagulation for large, non-CNS emboli)

Anticoagulation

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

Surgical Management of NVE

- Optimal timing of surgery not known
- Early surgery (no standard definition)
  - Heart failure due to valvular dysfunction, fistula, shunt
  - Uncontrolled infection
    - MDR, fungal pathogens, persistently pos. BC (5-7d)
    - Paravalvular complication (abscess, heart block, fistula)
  - Prevention of systemic embolization
    - Vegetation > 10 mm, one or more embolic events on therapy

Speaker: Henry Chambers, MD

Valve Surgery with Stroke

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

Am Heart J 2019;216:102-112

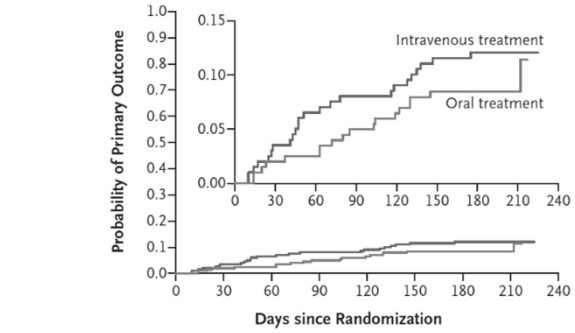
Pan-Scanning

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

Fever during Therapy of Endocarditis

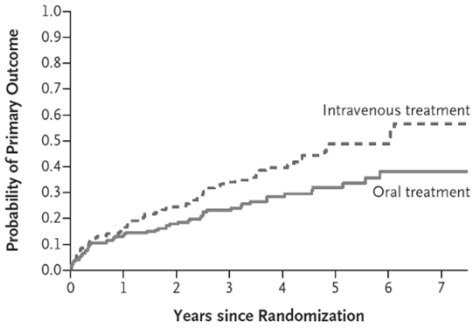
- Very common, lasts into the second week, a concern in PVE
- Cause (if one is found, often it is not)
  - Abscess: valve ring or elsewhere
  - Septic pulmonary emboli, pleural effusion
  - Another infection (e.g., IV site, fungal superinfection)
  - Polymicrobial endocarditis
  - Drug fever
- Work-up: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

Outcomes: POET Trial of Oral Therapy



No. at Risk									
Intravenous treatment	199	192	186	183	181	176	174	28	0
Oral treatment	201	197	196	191	188	184	183	36	0

N Engl J Med 2019;380:415



No. at Risk								
Intravenous treatment	199	168	126	88	56	33	20	4
Oral treatment	201	175	136	99	66	43	25	6

N Engl J Med 2019;380:1373

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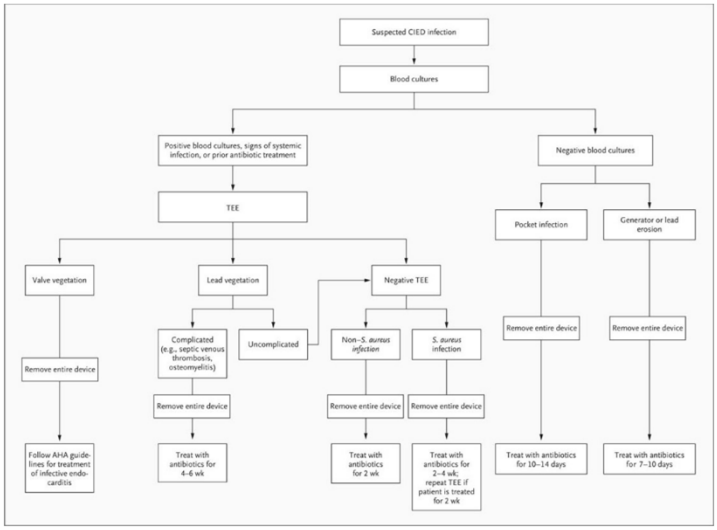
Algorithm for Management of an Infected Cardiac Implantable Device (CIED) Infection



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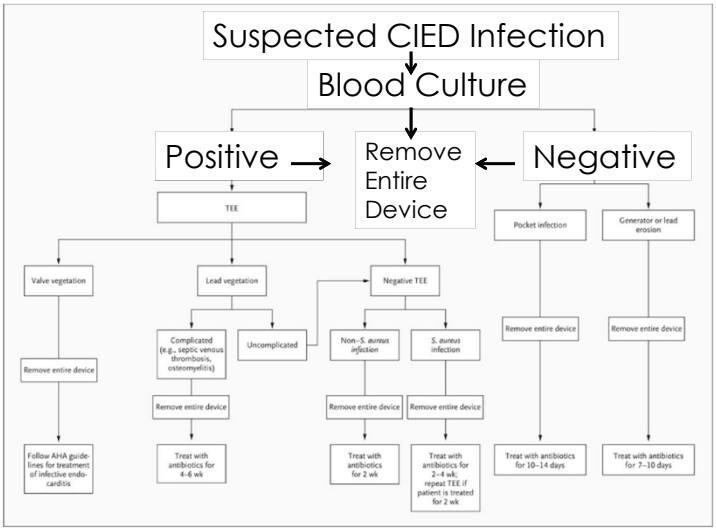

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17

Zoonoses

Dr. David Aronoff

17 – Zoonoses
Speaker: David M. Aronoff, MD

IDBR INFECTIOUS DISEASE BOARD REVIEW LIVE/VIRTUAL AUGUST 19-23 2023

Zoonoses

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

6/11/2023

IDBR INFECTIOUS DISEASE BOARD REVIEW AUGUST 19-23 2023

Disclosures of Financial Relationships with Relevant Commercial Interests

- **None**

Zoonoses: major infection route from animals in USA

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

Judson SD & Rabinowitz PM. *Curr Opin Infect Dis* 2021, 34:385-392

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 for later consumption. 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 any vomiting, diarrhea, chest pain, shortness of breath, adenopathy, or rash. The fever lasted for 9 days total primarily at night.

Case adapted from Cheung M, *et al. J Clin Micro* 61(4); 2023

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**.

Case adapted from Cheung M, *et al. J Clin Micro* 61(4); 2023

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

Case adapted from Cheung M, *et al. J Clin Micro* 61(4); 2023

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)

Judson SD & Rabinowitz PM. *Curr Opin Infect Dis* 2021, 34:385-392

★

THERE ARE MANY

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

Bacterial zoonoses transmitted by direct contact with animals or infected animal materials	Causative agent(s)
Anthrax	*Bacillus anthracis*
Brucellosis	*Brucella* spp.
Cat scratch disease	*Bartonella* spp.
Erysipelothrix infections	*Erysipelothrix rhusiopathiae*
Glanders and melioidosis	*Burkholderia mallei* and *Burkholderia pseudomallei*
Leptospirosis	*Leptospira interrogans* spp.
Mycobacterioses	*Mycobacteria* spp.
Q fever	*Coxiella burnetii*
Bacterial zoonoses transmitted principally by animal bites or scratches	
Pasteurellosis	*Pasteurella multocida* and other spp.
Capnocytophaga infections	*Capnocytophaga canimorsus*
Cat scratch disease	*Bartonella henselae*
Rat bite fever	*Spirillum minus* and *Streptobacillus moniliformis*
Vector-borne bacterial zoonoses	
Lyme borreliosis	*Borrelia burgdorferi* sensu lato (incl. *Borrelia garinii*, *Borrelia afzelii*)
Tick- and louse-borne relapsing fever borreliosis	*Borrelia recurrentis*, *Borrelia turicatae*, *Borrelia hermsii*, others
Plague	*Yersinia pestis*
Tularaemia	*Francisella tularensis*
Rickettsioses	Spotted fever and typhus group *Rickettsia* species
Ehrlichiosis and Anaplasmosis	*Ehrlichia chaffeensis*, *Anaplasma phagocytophilum*
Scrub typhus	*Orientia tsutsugamushi*
Foodborne bacterial zoonoses and intoxications	
Salmonellosis	*Salmonella enteritidis*
Campylobacteriosis	*Campylobacter* spp.
Listeriosis	*Listeria monocytogenes*
Escherichia coli O157:H7 infections	*Escherichia coli* STEC
Yersinia enterocolitica infections	*Yersinia enterocolitica*
Clostridium perfringens gastroenteritis	*Clostridium perfringens*
Botulism	*Clostridium botulinum*
Staphylococcal food poisoning	*Staphylococcus aureus*

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

CATS
- *Bartonella henselae*
- *Pasteurella multocida*

BIRDS
- *Chlamydia*
- *Chlamydophila psitacci*

FARM ANIMALS
(sheep, cows, 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
- *Campylobacter*
- *Capnocytophaga canimorsus*
- *Leptospira*
- *Pasteurella multocida*
- *Staph intermedius/pseudintermedius*

Adapted from *Comprehensive Review of Infectious Diseases* (2020), Elsevier.

LEECHES
- *Aeromonas hydrophila*

RABBITS
- *Francisella tularensis*

REPTILES
- *Salmonella*

BEARS
- *Trichinella spiralis*

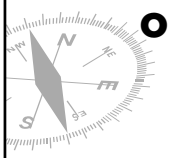
RODENTS
- *Leptospira*
- *Monkeypox*
- *Salmonella*
- *Spirillum minus*
- *Streptobacillus moniliformis*
- *Yersinia pestis*

Adapted from *Comprehensive Review of Infectious Diseases* (2020), Elsevier.

Zoonoses: major infection route from animals in USA

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

Direct contact with animal or animal tissue



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
  - But: he should be **systemically ill** (fevers, chills, malaise common)
  - **Uncommon**: 100-200 cases per year in the USA
- Chancroid: painful genital ulcer
- No suppurative lymph nodes in syphilis or granuloma inguinale (*Klebsiella granulomatis*) (painless ulcers)

Suppurative inguinal lymph nodes (continued)

- *Staphylococcus aureus*. Gram stain of pus & culture positive. Distal lesion may be present.
- Lymphogranuloma venereum (LGV)-
  - 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 or wound

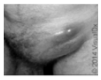


Image from https://www.skinsight.com/skin-conditions/adult/lymphogranuloma-venereum-lgv

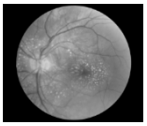
Cat Scratch Disease

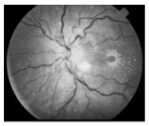
- *B. henselae* causes most cases
- >13,000 cases in the USA per year[1]
- Clinical findings:
  - 80% <21 yrs old, acute suppurative lymphadenitis proximal to bite, scratch, lick of young cat
  - Cats have chronic bacteremia but seem healthy
- Cat fleas may transmit between cats & occasionally to humans

1. Nelson CA, *at al. Emerging Infectious Diseases* 22 (2016); Photo from http://www.catscratchmed.com

Cat Scratch Disease

- Papule or pustule often at inoculation site if sought
- Often self-limited
- Encephalitis, **stellate retinitis**, uveitis rare





Lipid exudates forming a macular star

Photos from http://www.catscratchmed.com, http://imagebank.asrs.org/file/1173/cat-scratch-retinitis-with-macular-lipid, http://www.nejm.org/doi/full/10.1056/NEJMcm010038#t=article
Encephalitis reference: Fan J & Ali H.) *Proc Bayl Univ Med Cent*. 2020 Jul; 33(3): 440-441.

Cat Scratch Disease

Rx: 10% drain spontaneously

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

Treatment = AZITHROMYCIN x 5 d (TMP/SMX, clarithromycin, ciprofloxaxin or rifampin as alternatives)	Treat to prevent serious complications, since up to 14% of patients will have dissemination, with potential infection of the liver, spleen, eye, or CNS

Warthin Starry silver stain

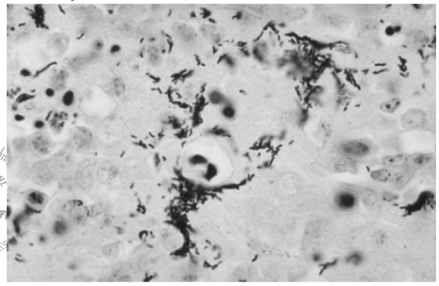
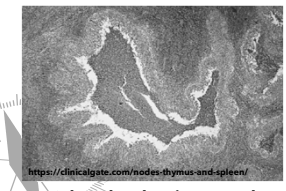


Photo by Andrew Margileth, MD., from http://emedicine.medscape.com/article/214100-workup#c8

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



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

Lymph nodes showing central abscess formation surrounded by palisaded histiocytes

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

Other Major Syndromes due to *Bartonella*

- *B. bacilliformis*- the **Andes, Peru, Equador, Columbia** & **sand fly** bite
  - Carrion's disease; biphasic illness
  - Oroya fever (acute phase: fever + anemia; high mortality)
    - Serious, life-threating illness
    - Mainly affects immunologically naïve populations, such as children.
    - Special concern in pregnant women, because high mortality rates have been described as well as miscarriages, preterm births, & fetal deaths
  - Verruga peruana (later; hemangioma-like nodules in the skin & mucous membranes)
  - Treatment = ciprofloxacin (Oroya); azithromycin (vp)

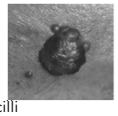
Pons MJ, *et al. PLoS Pathog*. 2016; Gomes C, Ruiz J. *Clin Microbiol Rev*. 2017; Garcia-Quintanilla M, *et al. Parasit Vectors*. 2019

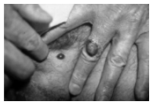
Other Major Syndromes due to *Bartonella*

- *B. quintana*
  - Human **body louse** *Pediculus humanus var. corporis* = vector
  - Bacteremia in persons experiencing **homelessness**, trench fever
  - **Endocarditis**

Other Major Syndromes due to *Bartonella*

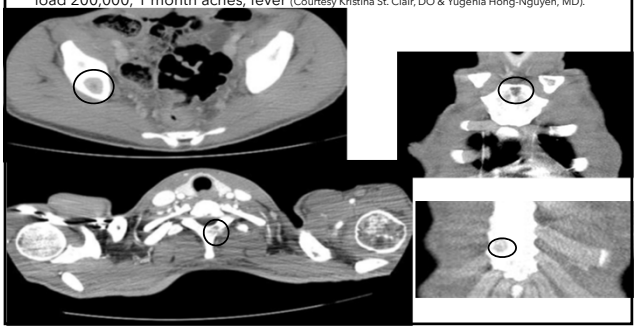
- HIV-associated (CD4<<100)
  - **Bacillary angiomatosis** (cutaneous)
    - Caused by either *B. henselae* or *B. quintana*
    - Lesions bleed easily
    - Biopsy: vascular proliferation, plump endothelial cells, bacilli
    - DDx = Kaposi sarcoma
  - Bacillary **peliosis** (*B. henselae*)
  - Osteomyelitis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





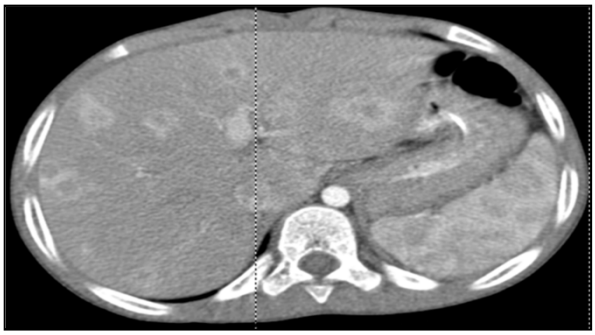
Images from http://mddk.com/bacillary-angiomatosis.html

Bartonella osteomyelitis: 30 yr old transgender female with HIV, CD 4=3, viral load 200,000, 1 month aches, fever (Courtesy Kristina St. Clair, DO & Yugenia Hong-Nguyen, MD).



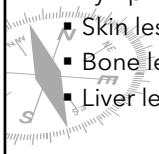
Bacillary peliosis

- *B. henselae*
- Hepatosplenic bacillary peliosis
- Fever, chills, hepatosplenomegaly
- CT: Hypodense dense center +/- contrast enhancing rim
- Ultrasound, MRI = masses
- Blood filled spaces. Numerous bacilli on Warthin Starry stain or immunostaining



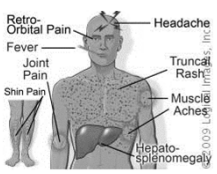
Solid Organ Transplantation

- SOT, like AIDS, can predispose to ALL the manifestations of bartonellosis
  - Lymphadenitis
  - Skin lesions (bacillary angiomatosis)
  - Bone lesions
  - Liver lesions



Bartonella quintana

- Transmitted by human body **lice**
- Crowded, unsanitary conditions: "trench fever" in WW1
- Splenomegaly, fever, arthropathy & arthritis, leg pains, rash, & severe weakness, thrombocytopenia
- Bacteremia, endocarditis in AIDS, **homelessness** +/- alcoholics

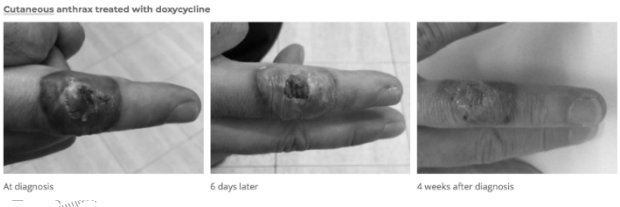


Brouqui P, *et al. NEJM* (1999)

Bartonella endocarditis

- <5% of all bacterial endocarditis
- Consider *B. quintana* or *B. henselae* in **homelessness** & with **culture negative** endocarditis
- Insidious or acute onset of fever, weight loss, anorexia.
- Serology: IgG>1:800 highly suggestive (not species specific)
- **PCR** of serum, valve tissue
- Lysis-centrifugation blood cult.
  - 35°C, fresh chocolate agar, hold 2-4 weeks
- Rx: doxycycline x 6 weeks + initial 2 weeks gentamicin or 2 weeks rifampin if valve resected

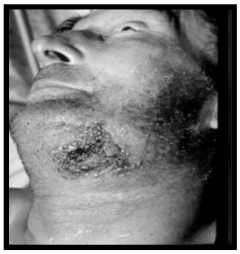
ANTHRAX



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

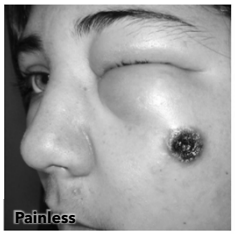
ANTHRAX

- Skin (95%): pruritic papule on skin exposed to goat hair, animal hides. Small **vesicles around an ulcer**. +/- pain. **Edema**. Mild systemic symptoms.
- DX: *Aerobic*, encapsulated, sporulating **Gram positive** bacillus seen on smear, culture of vesicle fluid (alert the lab!)
- RX: Penicillin but "weaponized" strains resistant to multiple antibiotics
- Inhalation (5%), ingestion (<1%)
- Anthrax rare in USA. Bioterrorism: see online lecture



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

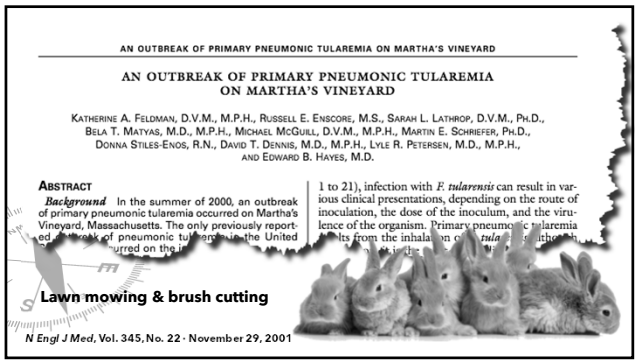
Edema
Vesicles
Necrotic ulcer



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

TULAREMIA

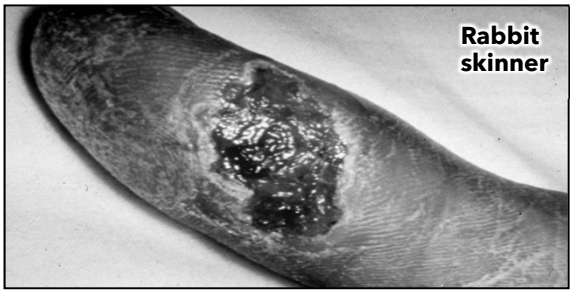
- Highly infectious gram-negative **coccobacillus** *Francisella tularensis*
- Vectors = **Ticks** (*Dermacentor variabilis* > *Amblyomma americanum*) & **Deerflies**
- Direct inoculation = rabbits, squirrels, muskrats, beavers, cats
- Hunters **skinning animals** (old days); farmers, veterinarians
- Red tender local lymph node inoculation site may form ulcer
- **Ulceroglandular >** glandular >> oculoglandular, pharyngeal, typhoidal, pneumonic = Bioterrorism, landscapers, mowers



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), **FQs**, **doxycycline**
- Prophylaxis (bioterrorism) doxycycline

Maurin & Gyuranecz. *Lancet* (2016); BCYE – buffered charcoal yeast extract



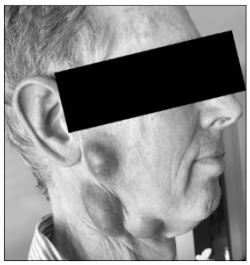
Glandular Tularemia

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



Marks, Laura, & Spec. "Glandular Tularemia." *New England Journal of Medicine* 379.10 (2018): 967-967.

Contact with insect vector

PLAGUE

PLAGUE

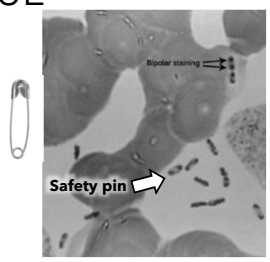
- *Yersinia pestis*
- New Mexico, California, Arizona & Colorado
  - Rodent **flea bite**
  - **Prairie dogs**
- Fever, nausea & swollen, painful lymph nodes
- Sepsis, pneumonia-hematogenous or aerosol in crowded conditions


(Michael Smith, Getty Images)

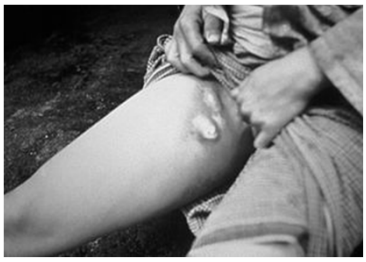

(Eye of Science/Science Source)

PLAGUE

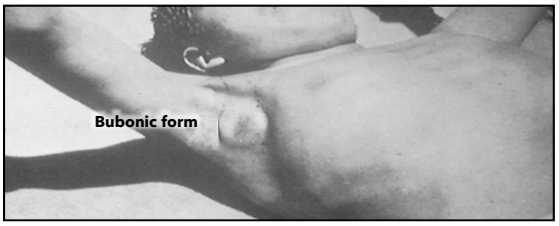
- Gram negative coccobacillus
- **Bipolar-staining** bacilli
- **Safety pin** appearance
  - *Yersinia pestis*: lab hazard
- Treatment: **Streptomycin** >> doxy, cipro

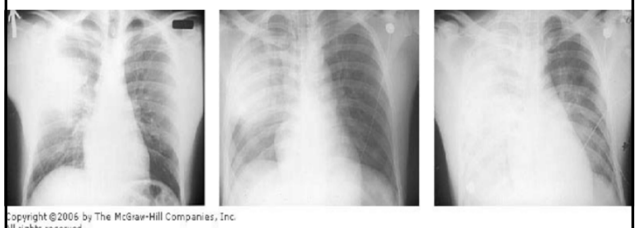


Bubonic form



Wikipedia image





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

Image from Canyon, Deon V. "Environmental Change and Human Health Case Studies I." (2008).

Large Outbreak in Madagascar

Plague is an endemic disease in Madagascar

Each year there is a seasonal upsurge between September – April

In 2017, an unprecedented pneumonic plague outbreak hit the main island

Nearly 2,500 reported or suspected cases (78% pneumonic)

https://www.sciencedaily.com/releases/2019/04/190416132101.htm
Randremanana R, *et al. Lancet ID*, 19(5) (2019)
Majumder MS, *et al. PLoS Curr.* (2018)

2019

Mongolian Couple Die of Plague after Eating Raw Marmot

THE INCIDENT SPARKED A QUARANTINE, STRANDING TOURISTS FOR DAYS

May 17, 2019

By Jonny Lupsha, News Writer

A couple in Western Mongolia have died of bubonic plague after eating raw marmot, *The Guardian* reported. There are people who believe eating the innards of the rodent is good for their health. Although people ignore health warnings not to eat uncooked meat, raw marmot can carry the plague germ *Yersinia pestis*. Plague is known for causing the Black Death in the 14th century—but was it that simple?

Intact skin contact with animal urine

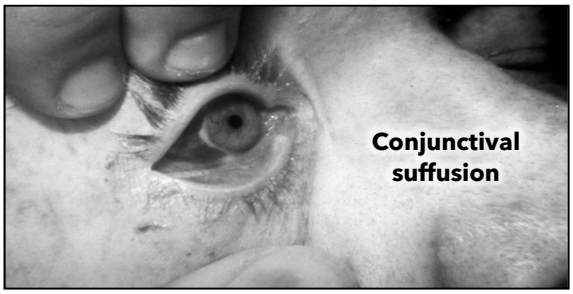
Question #3 PREVIEW QUESTION

- 28 yr old male presents with temp 39ºC, diffuse myalgia, headache, malaise. Returned 2 days ago from "Iron Man" race with running, biking, swimming in lake, climbing in Hawaii. Numerous mosquito bites. Exam: Conjunctival suffusion but no other localizing findings.
- WBC 14,500 with 80%PMN, no eos or bands. Platelets 210k.
- Bili 2.4, ALT 45, AST 52, Alk Phos 120, Cr 1.6. Hct 45%. BC neg. UA: normal

Question #3 PREVIEW QUESTION

Most likely diagnosis:

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



Ingestion of animal products

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:

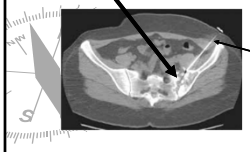
A. Home made sausage from Greece
B. Home made goat cheese from Greece
C. Cole slaw from a Baltimore delicatessen
D. Beef tartar, meat from the farmer's market
E. Lamb kabobs, meat from the farmer's market

BRUCELLOSIS

- Exposure to non-USA dairy or meat, **unpasteurized** cheese, uncooked meat,
- Slaughterhouse worker, meat packer, veterinarian
- 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

BRUCELLOSIS

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



Biopsy needle

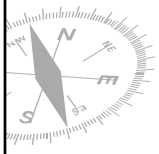
Malodorous perspiration (uncommon) "pathognomonic"[2]

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

BRUCELLOSIS (con't)

- WBC normal or low, anemia, plt can be low
- DX: 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

Inhalation of animal products

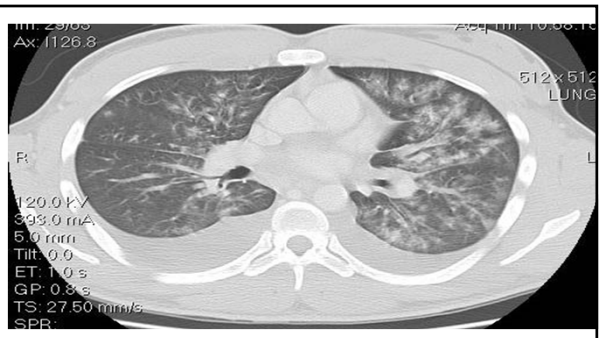


Case

- A 22 year old previously healthy male contractor returned from Afghanistan one week prior to presentation. He had a three day history of fever, myalgia, arthralgia, mild headache & cough. He had vomited once & had mild midepigastric, nonradiating pain.
- The facility he was hired to guard was adjacent to the path that the local sheep & goat herders used on their way to market & he had purchased a wool rug from one of the locals. He remembers shaking it hard to get rid of the dust.
- He reported that some members of his guard unit also had flu-like illness from which they recovered without treatment.

Case

- Examination was normal except for a variable temperature up to 102°F
- WBC **3.3**K, platelets **121**K, creatinine 1.2, AST **144**, ALT **154**, alk phos 88, total bilirubin 0.6
- Admission chest Xray was normal
- Ceftriaxone was begun but the patient remained febrile & had the chest CT shown on the next slide

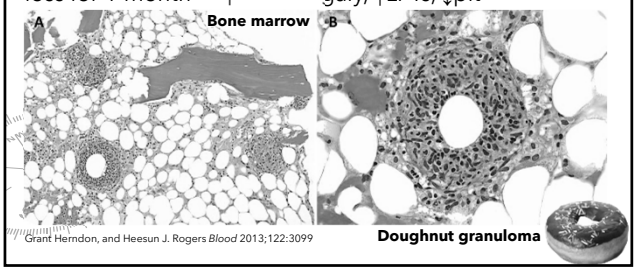


Question #5

Which of the following is the most likely diagnosis?

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

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



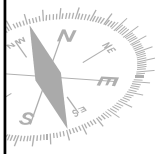
Grant Herndon, and Heesun J. Rogers *Blood* 2013;122:3099

Rat Bite Fever

- Rat-bite fever (RBF): infection caused by 2 different bacteria:
  - *Streptobacillus moniliformis*, the only reported bacteria that causes RBF in North America (streptobacillary RBF): fever, chills, myalgia, headache, & vomiting; rash
    - Gram negative facultative anaerobe; can culture
    - "Haverhill fever"
  - *Spirillum minus*, common in Asia: fever, ulceration at the bite site, lymphangitis, lymphadenopathy, distinct rash of purple or red plaques
    - Darkfield needed to diagnose; culture negative
- Most infected after contact with rodents carrying the bacteria
  - Consumption of food or water contaminated with the urine & droppings of rodents carrying the bacteria.
- **Penicillin** treatment

https://www.cdc.gov/rat-bite-fever/index.html

QUICK SUMMARIES



Summary of Key Exposures

- Flea bites from rodents or outdoor cats in contact with wild rodents:
  - *Yersina pestis* PLAGUE (New Mexico, Colorado, Arizona)
- Wild game or their ticks: handling, cleaning muskrats, beavers, rabbits, squirrels
  - TULAREMIA

Summary of Key Exposures

- Eating unpasteurized cheese from overseas, including goat cheese:
  - BRUCELLOSIS
  - Unpasteurized queso *could suggest* ***Listeria***
    - Stem likely to include pregnant patient

Summary of Key Exposures

- Animal **urine** on intact skin: hiker, farmer, forestry, veterinarian, swimming, falling in water or rafting in contaminated water
  - **Leptospirosis**
- Handling overseas animal **hair**, **hides**
  - **Anthrax**
- Slaughterhouses, veterinarians, parturient cat exposure, sheep handlers, living downwind of sheep/cattle farms
  - **Q Fever**

Key Clinical Syndromes

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

Kaposi-like skin lesions: *Bartonella henselae*

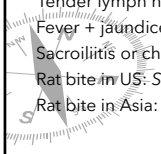
Tender lymph node: bartonellosis, tularemia, plague

Fever + jaundice: leptospirosis

Sacroiliitis or chronic illness w/ stinky sweat: brucellosis

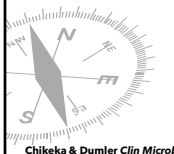
Rat bite in US: *Streptobacillus moniliformis*

Rat bite in Asia: *Spirillum minus*

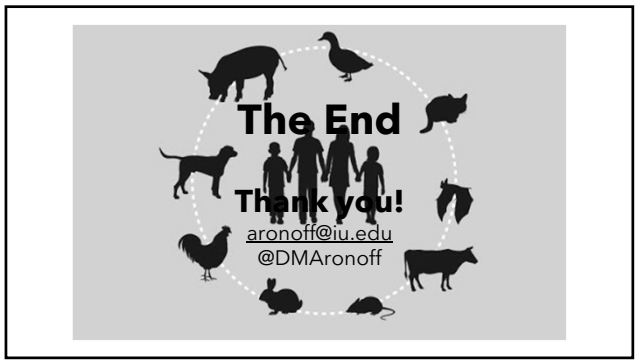


Other Zoonoses

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



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



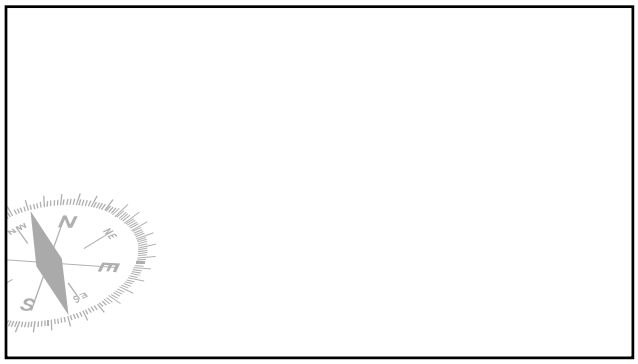


Table 1. Zoonotic pathogens causing recent epidemics

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)

Judson SD & Rabinowitz PM. *Curr Opin Infect Dis* 2021, 34:385–392

*

THERE ARE MANY

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

Bacterial zoonoses transmitted by direct contact with animals or infected animal materials	Causative agent(s)
Anthrax	*Bacillus anthracis*
Brucellosis	*Brucella* spp.
Cat scratch disease	*Bartonella* spp.
Erysipelothrix infections	*Erysipelothrix rhusiopathiae*
Glanders and melioidosis	*Burkholderia mallei* and *Burkholderia pseudomallei*
Leptospirosis	*Leptospira interrogans* spp.
Mycobacterioses	*Mycobacteria* spp.
Q fever	*Coxiella burnetii*
Bacterial zoonoses transmitted principally by animal bites or scratches	
Pasteurellosis	*Pasteurella multocida* and other spp.
Capnocytophaga infections	*Capnocytophaga canimorsus*
Cat scratch disease	*Bartonella henselae*
Rat bite fever	*Spirillum minus* and *Streptobacillus moniliformis*
Vector-borne bacterial zoonoses	
Lyme borreliosis	*Borrelia burgdorferi* sensu lato (incl. *Borrelia garinii, Borrelia afzelii*)
Tick- and louse-borne relapsing fever borreliosis	*Borrelia recurrentis, Borrelia turicatae, Borrelia hermsii,* others
Plague	*Yersinia pestis*
Tularaemia	*Francisella tularensis*
Rickettsioses	Spotted fever and typhus group *Rickettsia* species
Ehrlichiosis and Anaplasmosis	*Ehrlichia chaffeensis, Anaplasma phagocytophilum*
Scrub typhus	*Orientia tsutsugamushi*
Foodborne bacterial zoonoses and intoxications	
Salmonellosis	*Salmonella enteritidis*
Campylobacteriosis	*Campylobacter* spp.
Listeriosis	*Listeria monocytogenes*
Escherichia coli O157:H7 infections	*Escherichia coli* STEC
Yersinia enterocolitica infections	*Yersinia enterocolitica*
Clostridium perfringens gastroenteritis	*Clostridium perfringens*
Botulism	*Clostridium botulinum*
Staphylococcal food poisoning	*Staphylococcus aureus*

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

18

Staphylococcal Disease

Dr. Henry Chambers

18 – Staphylococcal Disease

Speaker: Henry F. Chambers, MD

Staphylococcal Diseases

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

7/2/2023

Disclosures of Financial Relationships with Relevant Commercial Interests

- **Data monitoring committee: Merck**
- **Stock: Merck, Moderna**
- **Medical expert, product liability: Lilly**
- **Medical expert, patent dispute: Nexus Pharmaceuticals**

Outline of the Talk

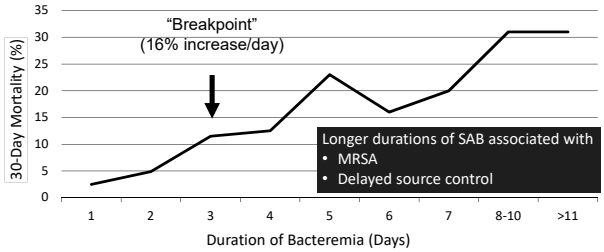
- Risk factors for poor outcome, complicated bacteremia
- Echocardiography
- Treatment of MSSA bacteremia
- Treatment of MRSA bacteremia
- Duration of Therapy
- Oral Therapy
- Combination therapy

Risk factors for poor outcome, complicated S. aureus bacteremia

Q1. Which one of the following risk factors is most predictive of complicated Staph. aureus bacteremia and mortality?

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

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



Clin Infect Dis. 2020; 70:566-573

Q2. A single positive blood culture for Staph. aureus…….

A. Represents contamination in a quarter or more of cases
B. Is associated with a significantly lower relapse rate than presence multiple positive blood cultures
C. Is associated with complicated bacteremia at a rate similar to multiple positive cultures
D. Excludes the need to perform echocardiography to rule out endocarditis
E. Is associated with a lower 60-day mortality than multiple positive blood cultures

Prediction Scores to Rule Endocar[illegible]s (and avoid an ECHO)

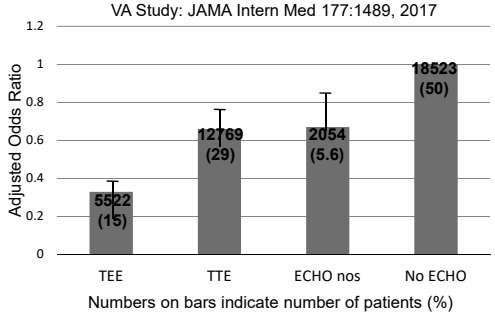
POSITIVE (Cutoff >4)	PREDICT (Cutoff ≥2)	[illegible]toff ≥3)
TTP < 9h – 13h (2,3,5)	ICD (2)	[illegible]boli (5)
IVDU (3)	Pacema[illegible]	Meningitis (5)
Vascular phenomena (6)	CA[illegible]	Intracardiac device (4)
Predisposing heart dis (5)	[illegible]BC > 72h (2)	Previous IE (3)
		IVDU (4)
		Positive BC > 48h (3)
		CA or HCA SAB (2)
		Sepsis or septic shock (1)
		CRP > 190 mg/L (1)

Prevalence of endocarditis 12%-18% overall
Prevalence of endocarditis with a negative score 2.2-4.9%

Clin Infect Dis 2022;74:1442, J Antimicrob Chemother 2022; 77: 2003, J. Clin. Med. 2022; 11: 1502.

ECHO and Mortality in S. aureus Bacteremia

VA Study: JAMA Intern Med 177:1489, 2017



Numbers on bars indicate number of patients (%)

Role of Echocardiography for S. aureus Bacteremia

- Prevalence of endocarditis 12%-18% overall
- Depends on the pre-test probability
  - Consider TTE (sensitivity 70%, specificity 95%) in all patients with SAB
  - Obtain TEE (sensitivity 90%, specificity 95%) in high risk patients
    - Embolic events, intracardiac device, IVDU, prior IE
    - Suspected endocarditis, negative TTE

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

FDG-PET/CT in Patients with Staph. aureus Bacteremia

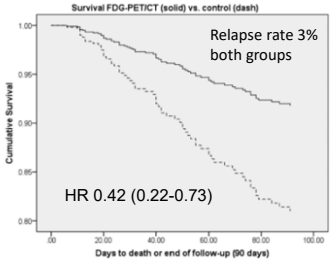
Matched Cohort Study of FDG-PET/CT in Patients with Staph. aureus Bacteremia

Detection of Infected Foci by PET/CT according to Clinically Suspicion

Clinically suspected sites (n=136)		PET/CT + sites (n=217)	
PET/CT +, confirmed	72 (53%)	PET/CT +, clinically unsuspected	145 (69%)
PET/CT -, excluded	64 (47%)	PET/CT +, clinically suspected	72 (31%)

Clin Infect Dis. 2021;73:e3859

Matched Cohort Study of FDG-PET/CT in Patients with Staph. aureus Bacteremia



Issues:
--Availability
--Reimbursement
--Observation studies only
--Goals of care?

Clin Infect Dis. 2021;73:e3859

Single positive blood culture for S. aureus

- Represents contamination in < 10% of cases
- Follow-up blood cultures will be positive in ~15% of cases in whom half will be afebrile
- Carries similar risks of mortality, relapse, and complicated bacteremia as multiple positive cultures
- Although the risk of endocarditis is less than with multiple positive cultures (~ 4% vs ~14%), an ECHO still should be obtained
- **Always obtain follow-up blood cultures**

Infect Dis 2020;52:207, OFID. 2021;9(2):ofab642

Treatment of MSSA Bacteremia

PREVIEW QUESTION 2023

Q3. On day 9 of nafcillin therapy for complicated methicillin-sensitive S. aureus bacteremia the patient has developed new neutropenia (1,000 neutrophils). MICs (μg/ml) of the blood isolate are penicillin 0.12 (S), cefazolin 0.5 (S), vancomycin 1 (S), daptomycin 0.5 (S), ceftaroline 0.5 (S).

Which one of the alternative agents would you recommend?

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

Penicillin for treatment of Staph. aureus endocarditis per AHA guidelines

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

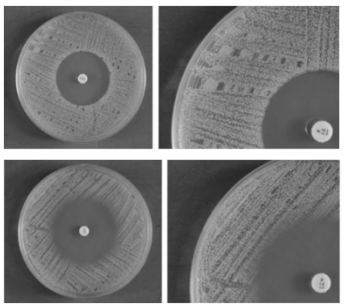
Pen MIC (μg/ml)	No. (%) of strains	
	Tested for blaZ	PCR + for blaZ
0.015	1 (100)	0
0.03	24 (100)	0
0.06	370 (100)	14 (3.4)
0.12	53 (100)	17 (32.1)

J Clin Micro 54:812, 2016

Zone edge test for β-lactamase

Positive

Negative



MSSA Bacteremia: Cefazolin vs. Antistaphylococcal Penicillins

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

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

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

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

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

AHA Guidelines for S. aureus Native Valve Endocarditis

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

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

Summary: MSSA bacteremia

- An ASP and cefazolin overall preferred agents for definite therapy
  - An ASP is first-line but less well tolerated than cefazolin
  - Observational studies suggest mortality, relapse, and treatment failures rates are similar with cefazolin
  - Anxiety over the inoculum effect, which may adversely impact outcome in a subset of cefazolin-treated patients
  - Start with an ASP until source control established
- Vancomycin, daptomycin if serious beta-lactam allergy or intolerance and possibly for OPAT (daptomycin > vancomycin)
- Ceftriaxone not 1st or 2nd line, should be avoided in patients with endocarditis, more serious infections, complicated/high risk SAB

*ASP = antistaphylococcal penicillin

Treatment of MRSA Bacteremia

2023 PREVIEW QUESTION

Q4. A patient with complicated MRSA bacteremia on day 9 of therapy with daptomycin q48h develops myalgias with a creatinine kinase of 1250 u/L (upper limit of normal 200). The last positive blood culture was on day 3 of therapy. MICs (µg/ml) of the isolate are as follows: vancomycin 2 (S), daptomycin 0.5 (S), dalbavancin 0.25 (S), telavancin 0.5 (S), ceftaroline 1 (S).

Which one of the following would you recommend?

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

First-line choices for MRSA bacteremia

- Vancomycin
  - 30-60 mg/kg/d in 2-3 divided doses
  - Nephrotoxic at higher trough concentrations (15-20 µg/ml)
  - Need for therapeutic drug monitoring
- Daptomycin
  - Non-inferior to vancomycin, better tolerated
  - Potential for emergence of resistance on therapy (mprF mutants), especially in high inoculum infections, poor source control
  - Do not use for primary pneumonia
  - Some cross-resistance with VISA

Holland et al: JAMA 312:1330, 2014

FDA-approved antibiotics for MRSA Infections

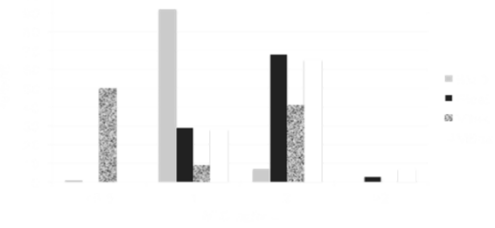
Antibiotic	Indications	Comments
Linezolid	SSTI, HAP, VAP	Serotonin syndrome: avoid use with SSRIs, MAO-Is; bacteriostatic Bone marrow suppression
Telavancin	SSTI, HAP, VAP	Vancomycin derivative Nephrotoxic, black box warning for ClCr ≤ 50 ml/min Artificially prolongs PT, PTT QTc prolongation, teratogenic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

FDA-approved antibiotics for MRSA Infections

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

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

Vancomycin MICs Vary by Method



Int J Antimicro Agent 32:378, 2008

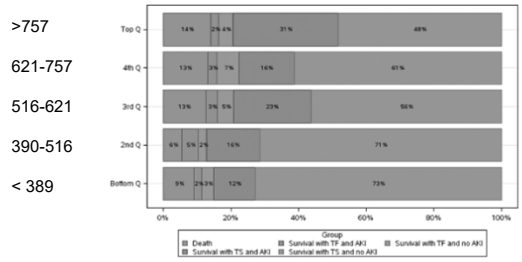
MIC is a Poor Predictor of Outcome

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

Kalil, et al. JAMA 312:1552, 2014.

Vancomycin Dosing: Higher AUC Correlates with Worse Outcome

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



Highlights of Modern Vancomycin Dosing for MRSA Infections

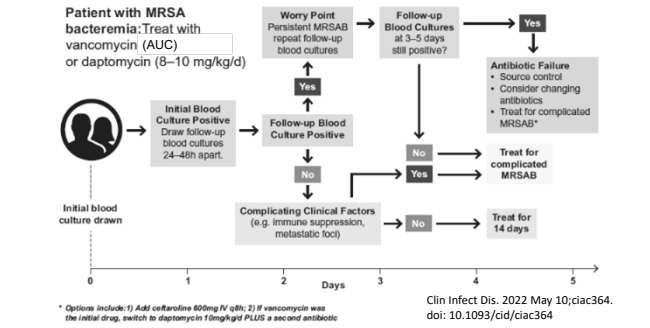
- Use of troughs no longer recommended
- Target AUC/MIC_{MBD} to 400-600 mg⋆h/L(assume MIC_{BMD} = 1 μg/ml)
  - Bayesian-derived monitoring, 1-2 samples (Cmax, Cmin)
  - 1st order PK equation with C_{max}, C_{min} at near steady-state
  - Continuous infusion: multiply steady-state concentration x 24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

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

AHA guidelines for therapy of native valve S. aureus endocarditis

- MSSA
  - Nafcillin (or Oxacillin) 2 gm q4h x 6 weeks
  - Cefazolin 2 gm q8h x 6 weeks, allergic or intolerant to naf
  - No aminoglycoside
- MRSA
  - Vancomycin 30-60 mg/kg/d divided q8-12h to achieve ~~trough of 15-20 µg/ml~~ AUC 400-600 x 6 weeks
  - Daptomycin 6-10 mg/kg q24h x 6 weeks
  - No aminoglycoside

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



Clin Infect Dis. 2022 May 10;ciac364. doi: 10.1093/cid/ciac364

Duration of Therapy for S. aureus BSI

14 days

- UNCOMPLICATED/LOW RISK (~10% of cases)
- Fever resolves by day 3
- Sterile blood culture after 2-3 days (DOCUMENT!)
- Easily removed focus of infection (no DVT)
- No metastatic infection (e.g., osteo)
- Negative echo, no evidence of endocarditis
- No predisposing valvular abnormalities
- (No implanted prosthetic devices, no DM, no immunosuppression)

4-6 weeks +

- COMPLICATED/HIGH RISK
- Failure to meet one or more of above criteria
- Osteomyelitis, endocarditis, epidural abscess, septic arthritis, pneumonia, complicated UTI

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

Outcomes of Partial Oral Antibiotic Treatment for Complicated *Staphylococcus aureus* Bacteremia in People Who Inject Drugs

John A. Wildenthal,[1,3,4] Andrew Atkinson,[2] Sophia Lewis,[3] Sena Sayood,[3,5] Nathanial S. Nolan,[3] Nicolo L. Cabrera,[3] Jonas Marschall,[3] Michael J. Durkin,[3] and Laura R. Marks[3,5]

[1]Medical Scientist Training Program, Washington University in St. Louis School of Medicine, St. Louis, Missouri, USA; [2]Department of Infectious Diseases, Bern University Hospital, Inselspital, University of Bern, Bern, Switzerland; [3]Division of Infectious Diseases, Washington University in St. Louis School of Medicine, St. Louis, Missouri, USA; and [4]Department of Computational and Systems Biology, Washington University in St. Louis School of Medicine, St. Louis, Missouri, USA

Endocarditis*	Epidural abscess	Septic Arthritis	Osteo	+BC, 5+ days*	MRSA
65%	15%	24%	19%	32%	42%

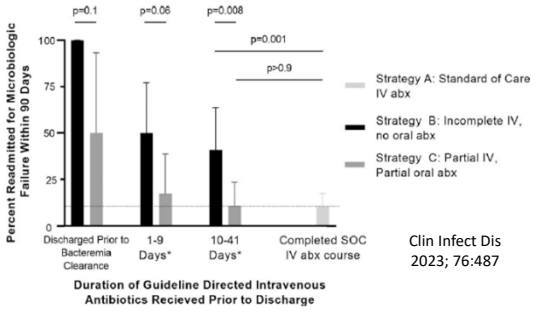
Clin Infect Dis 2023; 76:487

Outcomes of 3 Treatment Strategies

Outcomes	A: Standard of care IV N=122	B: Partial IV Discharged No PO N=36	C: Partial IV Discharged With PO N=69
Death, micro failure @ 90 days of D/C	11%	44%	13%
Readmission @ 90 days of D/C	31%	53%	26%

Clin Infect Dis 2023; 76:487

Readmissions with Treatment Failure



Clin Infect Dis 2023; 76:487

Oral Therapy of S. aureus Bacteremia

- Observational studies, low quality, subject to selection bias, confounding by indication
  - Relapse rates consistently higher with IV
  - Mortality rates consistently higher with IV
- May be an option for treatment of uncomplicated bacteremia in carefully selected patients, but there is a lack of standard definition
- Role in treatment of endocarditis, endovascular infections, complicated bacteremia not well defined but growing
- Prefer agents with good oral bioavailability: linezolid, T/S, FQ+rif, clindamycin, anti-staphylococcal beta-lactam, other combos

See Dagher, et al. Open Forum Infect Dis 2020 May 5;7(6):ofaa151.

Combination Therapy of S. aureus BSI

Q5. Which one of the following combinations have been shown to improve mortality of patients with S. aureus bacteremia or native valve endocarditis?

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

Overview of Studies of Combination Therapy for SAB

Regimen	Study	Population	Comments	PMID
Adjunctive rifampin	RCT	MRSA, MSSA	No benefit	1929035 29249276
Adjunctive aminoglycoside	Obs., RCT	MRSA, MSSA	1 d shorter SAB, toxic	Various
Adjunctive dapto	RCT	MSSA	No benefit	32667982
Adjunctive β-lactam + vanco/dapto	RCT	MRSA	↑↑ AKI, higher mortality	32044943
Dapto + ceftaroline	Obs., aborted RCT	MRSA	Low quality data	30858203, 31640977, 31404468
Dapto + fosfomycin	RCT	MRSA	No mortality benefit, ↓ micro failure, ↑ AEs	32725216 32887985

Overview of Studies of Combination Therapy for SAB

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Adjunctive aminoglycoside	Obs., RCT	MRSA, MSS	toxic	Various
Adjunctive dapto	RCT		No benefit	32667982
Adjunctive β-lactam + vanco/dapto	RCT	A	↑↑ AKI, higher mortality	32044943
Dapto + ceftar	aborted RCT	MRSA	Low quality data	30858203, 31640977, 31404468
Da	RCT	MRSA	No mortality benefit, ↓ micro failure, ↑ AEs	32725216 32887985

Consider for salvage therapy, not first line

Monotherapy versus combination therapy for *Staph. aureus* bacteremia

- No high quality RCT has demonstrated improved mortality with combination antimicrobial therapy over monotherapy
- Studies suggesting a possible benefit of combination therapy are mostly low quality, retrospective, subject to bias, and based on subjective outcomes (e.g., change in therapy) not mortality, recurrence, metastatic infections*
- Reserve for salvage therapy

Possible exception: Dapto + Fosfo vs Dapto, Pujol, et al. Clin Infect Dis 2021; 72:1517

De-Escalation of Combo Therapy for Complicated MRSA bacteremia

- Single center, retrospective study, 146 patients, ≥72h of dapto + ceftaroline combo
  - Combo: 66 on combo ≥ 10 days (IQR 13-21 days)
  - Mono: 74 on combo < 10 days (IQR 4-6 days)
    - De-escalated to dapto (n=30), ceftaroline (n=18), or vanco (n=26)
- Days of therapy prior to dapto + ceftaroline
  - Combo: 6 (IQR 4-9)
  - Mono: 7 (IQR 5-11)

Open Forum Infect Dis. 2021 Jun 22;8(7):ofab327.

De-Escalation of Combo Therapy for Complicated MRSA bacteremia

Outcome	Combo (n=66)	Mono (n=74)	P-value
Composite clinical failure	14 (21%)	8 (24%)	0.66
Recurrent bacteremia, 60d	2 (3%)	5 (7%)	0.45
In-patient mortality	1 (2%)	4 (5%)	1
Readmission, 60d	13 (20%)	13 (18%)	0.75
Duration of bacteremia, d	8 (IQR 6-11)	8 (IQR 5-12)	0.33
Adverse drug event	2 (4%)	1 (1)	0.47
Length of stay, d	26 (IQR 20-41)	24 (IQR 16-33)	0.08

Open Forum Infect Dis. 2021 Jun 22;8(7):ofab327.

Take-Home Points

- "Uncomplicated" Bacteremia is uncommon
  - 2 weeks of therapy for "uncomplicated" SAB, otherwise 4-6 weeks
- Community and HCA SAB do not differ in early mortality rates, but the former has a 2-fold increased risk of endocarditis
- Parenteral drugs of choice
  - MSSA: Nafcillin, cefazolin
  - MRSA: Daptomycin, vancomycin
- Monotherapy is effective in most cases, reserve combination therapy for MRSA salvage
- Role of oral therapy is an evolving area

Thanks

19

Helicobacter and Clostridioides Difficile

Dr. David Aronoff

19 – Helicobacter and Clostridium Difficile

Speaker: David Aronoff, MD

IDBR INFECTIOUS DISEASE BOARD REVIEW AUGUST 19-23 2023 LIVE/VIRTUAL

Helicobacter and Clostridioides difficile

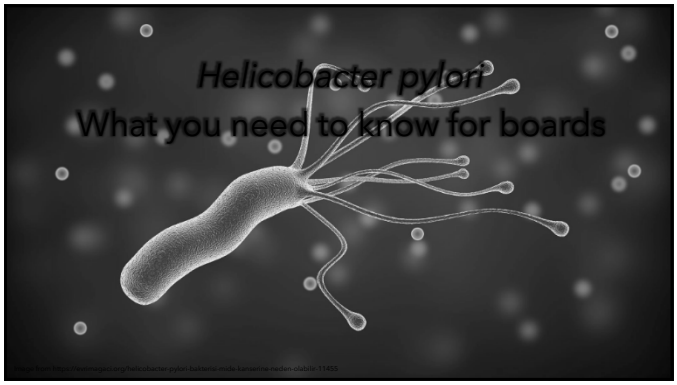
David M. Aronoff, MD, FIDSA, FAAM
John B. Hickam Professor of Medicine
Chair, Department of Medicine
Indiana University School of Medicine

5/23/2023

IDBR INFECTIOUS DISEASE BOARD REVIEW AUGUST 19-23 2023 LIVE/VIRTUAL

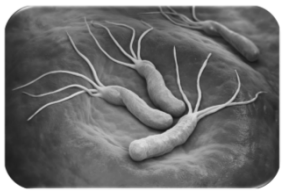
Disclosures of Financial Relationships with Relevant Commercial Interests

- **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 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 only after stopping PPI (2 weeks) & antibiotics (4 weeks)
  - Stool antigen, breath urea, or biopsy used to diagnose Hp
  - NEVER TEST WITH SEROLOGY
- Endoscopy for alarm symptoms

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

19 – Helicobacter and Clostridium Difficile

Speaker: David Aronoff, MD

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

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:

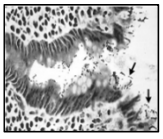
A. Hp organisms, but no gastric or esophageal inflammation.
B. Hp organisms plus gastric inflammation (gastritis).
C. Hp organisms plus esophagitis.
D. Neither Hp organisms, nor inflammation because the urease test is often false positive with a normal endoscopy.

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

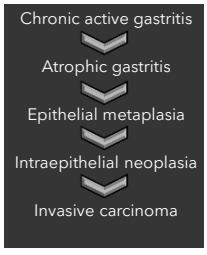
*At greater risk: indigenous Americans, Black/AA, Hispanic, & immigrants from high-cancer-risk countries like Japan, Korea, Taiwan & China

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



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

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 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

IDBR 2023 **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:

- 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
- High-risk 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

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
NO: 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 <u>not</u> 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

IDBR 2023 PREVIEW QUESTION

- 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,[1,2,4] Mark Gilger,[5,6] Frank LoVecchio,[7] Steven F. Moss,[8] Sheila Crowe,[9] Adam Elfant,[10] Thomas Haas,[11] Ronald J. Hapke,[12] and David Y. Graham[13]

- "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** (e.g., 80% or lower).
- 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.

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)

Question #6

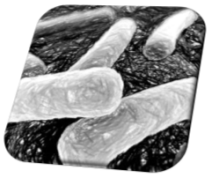
After treatment of this patient for Hp gastritis, the *H. pylori* stool antigen test should be repeated:

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

19 – 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 injury

Clostridioides difficile: Take Home Points

- Fidaxomicin is a favored first-line option, & oral vanco is good (more recurrences)
- 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

The Burden of 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

Antibiotic-Associated Diarrhea (AAD)

- Common, especially after > 3 days of antibiotics
- Remember: not all AAD is due to *C. difficile* (probably <40%)
- Nearly all AA **colitis** is *C. difficile* infection (CDI)
- Disruption of colon microbiome & metabolome, pathogen overgrowth (*S. aureus, K. oxytoca, etc*), & direct drug toxicity may all be at play

Selvaraj V & Alsamman MA. Antibiotic-Associated Diarrhea Beyond *C. Difficile*: A Scoping Review. *Brown Hospital Medicine*. 2022

Pathogenesis of CDI

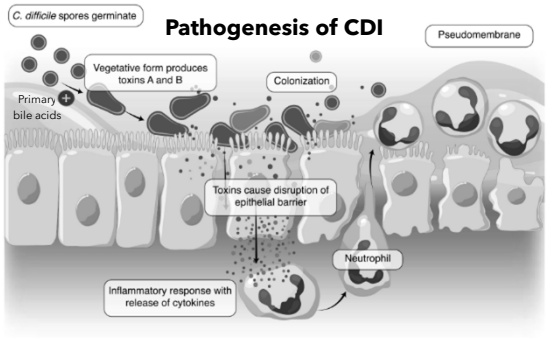


Figure adapted from Seekatz AM, *et al. Therapeutic Advances in Gastroenterology* (2022)

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/

Complications of CDI

- Sepsis ± multiple organ dysfunction
- Megacolon: need for surgical intervention
  - Colectomy
  - Loop iliostomy
- Bowel Perforation
- Lack of treatment response
- Recurrent infection (20%+)
  - Relapse
  - Reinfection

Major Risk Factors for Acquisition of CDI

1. **Antibiotic use**
   - Disruption of microbiome
2. **Recent hospitalization or LTCF**
   - Increased exposure
   - Co-morbidities reduce immunity or alter microbiome
3. **Age > 65 years**
   - Reduced gastric acidity
   - Impaired immunity
   - Altered microbiome

REMEMBER:
Even healthy people in the community without antibiotic exposure can get CDI

Dubberke E, *et al. Infect Control Hosp Epidemiol* 2011;32(4):360-366
Pacheco & Johnson. *Curr Opin Gastroenterol* 2013, 29:42-48
Loo V, *et al. NEJM.* 365;18

Minor Risk Factors for Acquisition of CDI

4. Gastric acid suppression (**proton pump inhibitor**)
   - Reduced biochemical defense
   - Altered microbiome
5. Abdominal surgeries
   - Altered microbiome
6. Immunocompromised host
   - Impaired mucosal immunity
   - Altered microbiome

McFarland LV. *Curr Opin Gastroenterol.* 2009 Jan;25(1):24-35
Dubberke E, *et al. Infect Control Hosp Epidemiol* 2011;32(4):360-366
Pacheco & Johnson. *Curr Opin Gastroenterol* 2013, 29:42-48

CDI Severity

- **Leukocytosis**
- **AKI**
- **Sepsis/shock**
- **Megacolon**

Stool frequency is not part of severity assessment

Clinical Definition	Supportive Clinical Data
Nonsevere	Leukocytosis with a WBC count of ≤15,000 cells/mL and a serum creatinine level <1.5 mg/dL
Severe	Leukocytosis with a WBC count of ≥15,000 cells/mL or a serum creatinine level >1.5 mg/dL
Fulminant	Hypotension or shock, ileus, megacolon

Table from Wilcox M, *IDSE* (2018)
McDonald LC, *et al. Clin Infect Dis.* 2018 Mar 19;66(7):987-994

C. difficile Diagnostic Testing

Whom to test?

- Appropriate epidemiology/ill with diarrhea/endoscopic findings
  - No laxatives within last 48 hrs (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

19 – Helicobacter and Clostridium Difficile

Speaker: David Aronoff, MD

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	Disadvantages
• High sensitivity • Rapid • Relatively inexpensive	• 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	Disadvantages
• High sensitivity • Rapid • Relatively inexpensive	• Does not detect toxin • Detects NON-toxigenic strains • Cannot differentiate colonization from infection

Must be combined to test for toxin (NAAT or EIA)

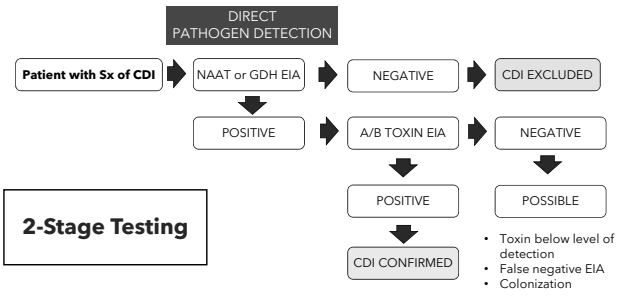
C. difficile Diagnostic Testing

Toxin A/B detection by EIA:

Detects *C. difficile* toxin(s) directly

Advantages	Disadvantages
• Good specificity • Rapid • Relatively inexpensive	• Poor sensitivity • False positives possible

Usually used in a 2-step protocol with NAAT or GDH



Czepiel J, et al. Eur J Clin Micro Infect Dis (2019)

Question #7

- 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

19 – Helicobacter and Clostridium Difficile

Speaker: David Aronoff, MD

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

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.

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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

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

Therapy of CDI

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Recommended Treatment Options for CDI

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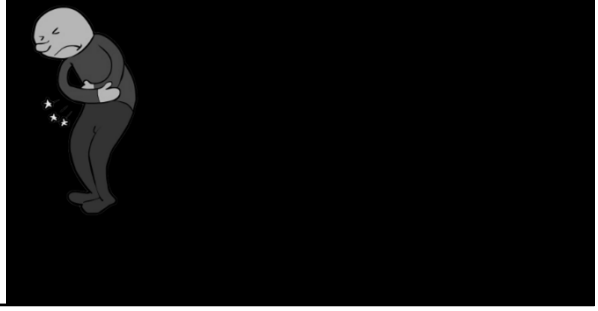
Subsequent recurrences	Preferred: Fidaxomicin, 200 mg twice daily for 10 days or twice daily for five days followed by once every other day for 20 days Alternatives: Vancomycin in a tapered and pulsed regimen Vancomycin, 125 mg four times daily for 10 days, followed by rifaximin (Xifaxan), 400 mg three 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.



19 – Helicobacter and Clostridium Difficile

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*

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

20

Brain Abscess, Cavernous Sinus Thrombosis, and Subdural and Epidural Empyema

Dr. Allen Tunkel

20 – Brain Abscess, Cavernous Sinus Thrombosis, and Subdural and Epidural Empyema

Speaker: Allan Tunkel, MD

Brain Abscess, Cavernous Sinus Thrombosis, Subdural Empyema and Epidural Abscess

Allan R. Tunkel, MD, PhD, MACP
Professor of Medicine and Medical Science
The Warren Alpert Medical School of Brown University

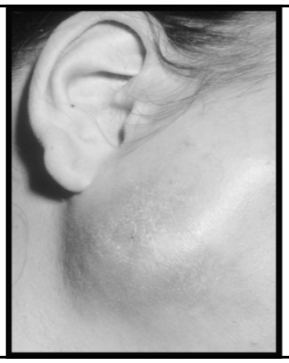
7/2/2023

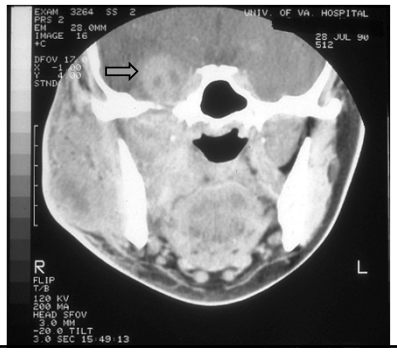
Disclosures of Financial Relationships with Relevant Commercial Interests

- **None**

CASE #1

- 24-year-old female who presented with pain and swelling on the right side of her jaw that had been progressing over the last several weeks. She was unable to open her mouth. She denied fever or headache, and had no past hospitalizations or illnesses. The patient had not been to the dentist within 10 years.
- T 99.8^{o}F, P 88, RR 14, BP 110/80
- Exam revealed swelling and erythema along her right mandible





Question #1 (Case #1)

Which of the following empiric antimicrobial regimens should be initiated?

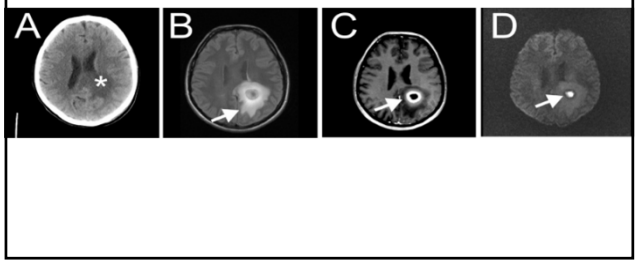
A. Ceftriaxone + metronidazole
B. Vancomycin + cefepime
C. Trimethoprim-sulfamethoxazole
D. Voriconazole
E. Liposomal amphotericin B

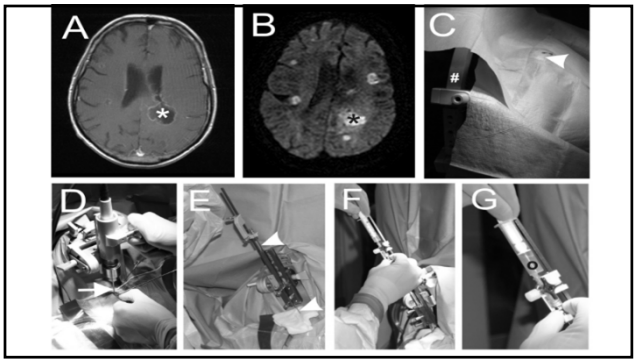
PREDISPOSING CONDITIONS FOR BRAIN ABSCESS

Condition	Relative Frequency (%)
Contiguous focus of infection (otitis media, mastoiditis, sinusitis, face or scalp infection, dental sepsis, osteomyelitis, penetrating head injury)	30-50
Hematogenous spread (lung abscess, empyema, congenital heart disease, bronchiectasis, infective endocarditis, compromised host, hereditary hemorrhagic telangiectasia)	~35
Cryptogenic	10-35

PRINCIPLES OF BRAIN ABSCESS MANAGEMENT

- MR imaging is the diagnostic procedure of choice; diffusion-weighted imaging increases diagnostic accuracy (sensitivity and specificity 96% for differentiation from cancers [PPV 98%; NPV 92%])
- Lumbar puncture is contraindicated
- Biopsy or aspiration (via stereotactic guidance) is needed for microbiologic diagnosis
- Begin empiric antimicrobial therapy based on underlying condition and pathogenesis of spread of infection to brain





EMPIRIC ANTIMICROBIAL THERAPY OF BRAIN ABSCESS

Predisposing Condition	Antimicrobial Regimen
Otitis media or mastoiditis	Metronidazole + a third-generation cephalosporin[a]
Sinusitis	Vancomycin + metronidazole + a third-generation cephalosporin[a]
Dental sepsis	Third-generation cephalosporin[a] + metronidazole
Penetrating trauma or post-neurosurgical	Vancomycin + a third or fourth generation cephalosporin
Lung abscess, empyema, bronchiectasis	Third-generation cephalosporin[a] + metronidazole + trimethoprim-sulfamethoxazole
Bacterial endocarditis	Vancomycin[b]

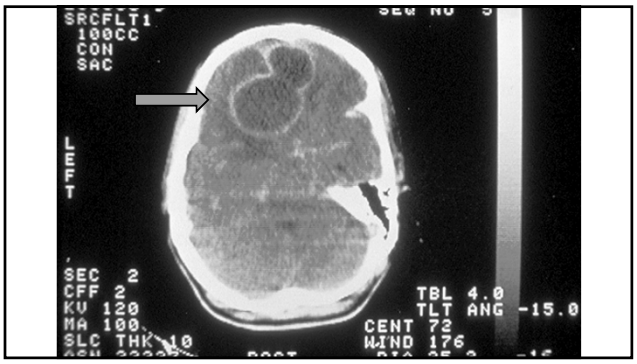
[a]ceftriaxone or cefotaxime
[b]additional agents may be used based on other likely microbial etiologies

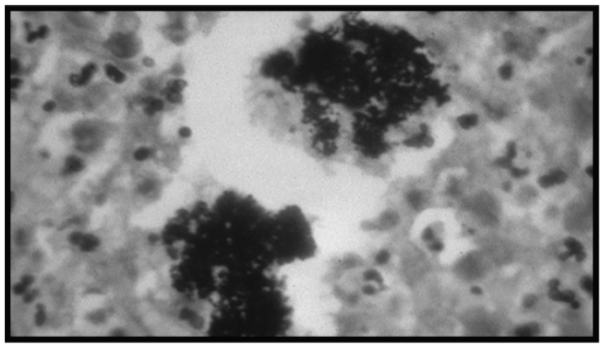
EMPIRIC ANTIMICROBIAL THERAPY OF BRAIN ABSCESS

Predisposing Condition	Antimicrobial Regimen
Unknown	Vancomycin + metronidazole + a third or fourth generation cephalosporin; or vancomycin + meropenem
Transplant recipients	Add voriconazole + trimethoprim-sulfamethoxazole
HIV-infected patients	Add pyrimethamine + sulfadiazine; consider isoniazid, rifampin, pyrazinamide, and ethambutol for possible tuberculosis

CASE #2

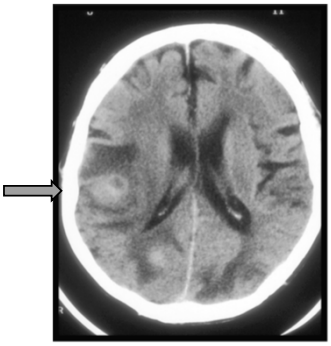
- 21-year-old member of a motorcycle gang thrown from his bike, and suffered a depressed skull fracture
- In the OR, a large subdural hematoma was evacuated
- Discharged in 5 days
- Returned by mother 5 days later because of bizarre behavior
- No headache, afebrile

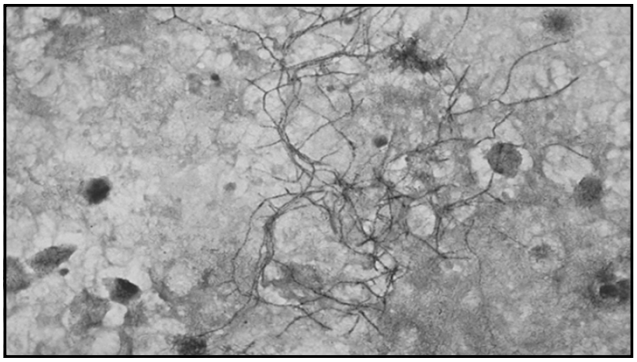




CASE #3

- 78-year-old male with multiple myeloma on chronic prednisone therapy; underwent aortic valve replacement with a bioprosthesis 5 years earlier; presented with new-onset seizures
- T 100.4° F, P 96, RR 18, BP 110/70 mmHg; Exam (-)
- CT scan revealed multiple ring-enhancing lesions
- TEE - no vegetations and normal bioprosthesis
- Empirically placed on vancomycin + ampicillin + gentamicin
- Blood cultures negative

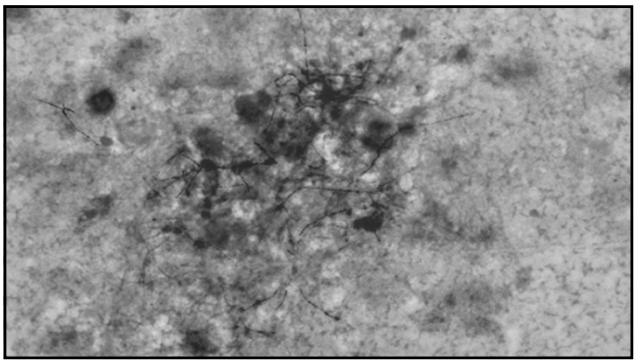




Question #2 (Case #3)

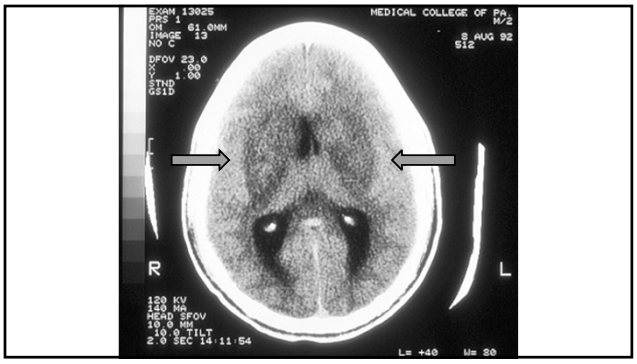
Which of the following antimicrobial regimens should be initiated?

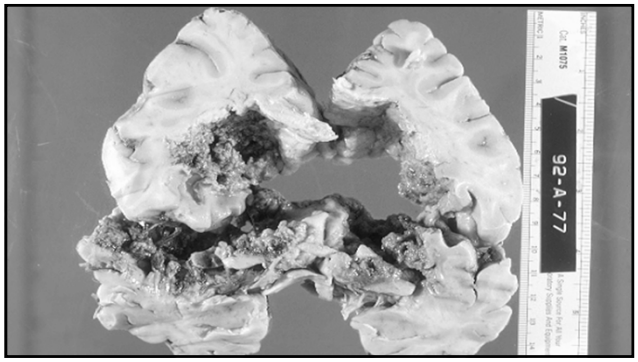
A. Penicillin + metronidazole
B. Trimethoprim-sulfamethoxazole
C. Daptomycin
D. Liposomal amphotericin B + 5-FC
E. Voriconazole

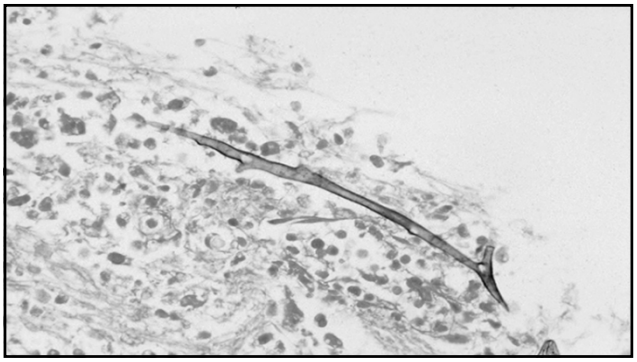


CASE #4

- 24-year-old injection drug user who, while injecting intravenous drugs with his girlfriend, fell out of the second story window of his apartment. When he did not return for 48 hours, she found him unresponsive on the ground and called fire rescue
- T 103°F, P 150, RR 32, BP 110/76 mmHg
- On exam, he was comatose without evidence of head trauma
- WBC 13,000/mm^3, profound metabolic acidosis

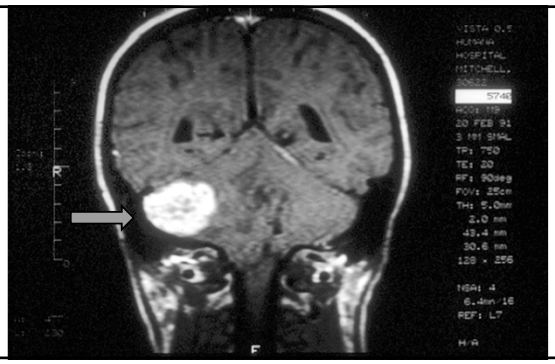


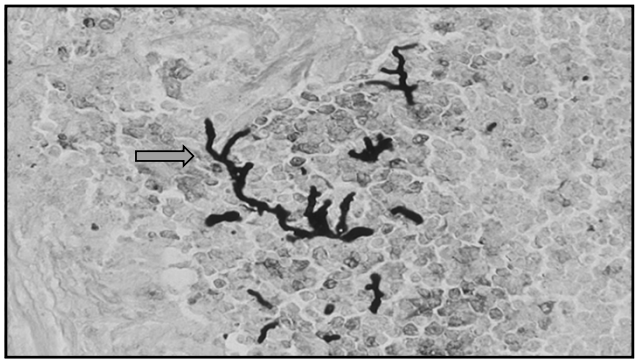




CASE #5

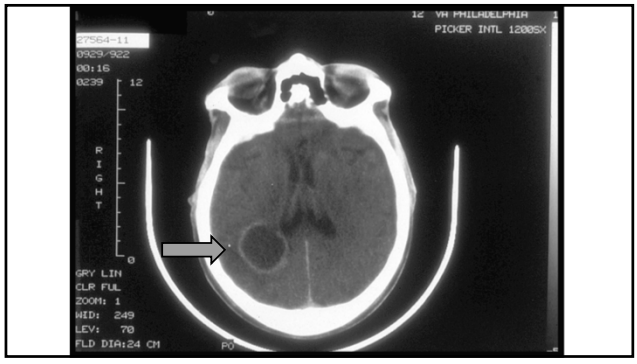
- 11-year-old boy with chronic granulomatous disease on chronic TMP-SMX therapy noted the onset of a mild headache which lasted 10 minutes.
- Two weeks later at a routine physician visit, the patient had no complaints and denied recurrence of the headache
- On examination, the patient had normal vital signs and a normal neurologic examination
- The physician ordered an MR imaging of the head

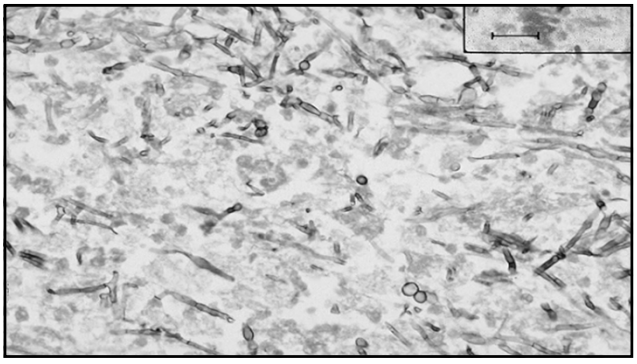




CASE #6

- 80-year-old male with CLL on chronic prednisone therapy presented to the VA Hospital with sepsis and ARDS. Course complicated by VDRF and multiple nosocomial infections, including candidemia for which he received 4 weeks of IV liposomal amphotericin B. After completing the course of therapy, he developed altered mental status
- T 101^0 F, P 100, RR 20, BP 120/76
- Neurologic exam left-sided hyperreflexia and Babinski





PRINCIPLES OF BRAIN ABSCESS MANAGEMENT

- Optimal management usually requires a combined medical and surgical approach (aspirate if >2.5 cm)
- Fungal brain abscess often requires combined medical and surgical therapy
- Initiate corticosteroids with evidence of cerebral edema or mass effect causing increased ICP

ANTIMICROBIAL THERAPY OF BRAIN ABSCESS

Organism	Antimicrobial Therapy
Actinomyces sp.[a]	Penicillin G
Bacteroides fragilis[a]	Metronidazole
Enterobacterales[a]	Third or fourth generation cephalosporin
Fusobacterium sp.[a]	Metronidazole
Pseudomonas aeruginosa	Ceftazidime or cefepime or meropenem
Staphylococcus aureus	Nafcillin, oxacillin, or vancomycin
Strep. milleri;[a] other streptococci[a]	Penicillin G

[a]depending on pathogenesis of infection, may be isolated as part of a mixed infection

ANTIMICROBIAL THERAPY OF BRAIN ABSCESS

Organism	Antimicrobial Therapy
Nocardia asteroides	Trimethoprim-sulfamethoxazole; combination therapy for immunocompromised patients and those failing standard therapy
Mycobacterium tuberculosis	Isoniazid + rifampin + pyrazinamide ± ethambutol

ANTIMICROBIAL THERAPY OF BRAIN ABSCESS

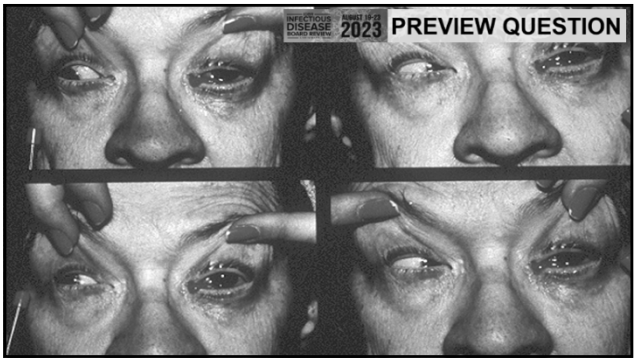
Organism	Antimicrobial Therapy
Aspergillus sp.	Voriconazole
Candida sp.	Lipid formulation of amphotericin B[a]
Mucorales	Lipid formulation of amphotericin B
Scedosporium spp.	Voriconazole

[a]Addition of 5-flucytosine should be considered

CASE #7

INFECTIOUS DISEASE BOARD REVIEW AUGUST 18-23 2023 PREVIEW QUESTION

- 79-year-old female is transferred from a nursing home for failure to thrive as a result of decreased oral intake. A nasogastric tube is placed via the left nares for enteral hyperalimentation
- One week into her hospital course, the patient develops fever to 101.5° F, and left periorbital edema and chemosis
- CT scan of the head without contrast reveals opacification of the sphenoid sinus



Question #3 (CASE #7) PREVIEW QUESTION

Which of the following studies should be performed to establish the diagnosis?

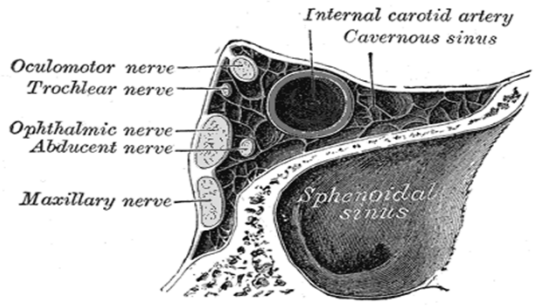
A. CT scan of the head and sinuses with contrast
B. MR imaging with MR venography
C. Cerebral angiography
D. Positron emission tomography of the head
E. Lumbar puncture

EPIDEMIOLOGY AND ETIOLOGY OF SEPTIC CAVERNOUS SINUS THROMBOSIS

Risk Factors	Etiologic Agents
Paranasal sinusitis	Staphylococci (60-70%)
Facial infection	Streptococci (~17%)
Dental infection	Gram-negative bacilli (~5%)
	Pneumococci (~5%)
	Bacteroides sp. (~2%)

CLINICAL FEATURES OF SEPTIC CAVERNOUS SINUS THROMBOSIS

Symptoms	Signs
Headache (52%)	Periorbital edema (73%)
Facial pain	Chemosis
Vision loss	Papillitis
Fever	Oculomotor palsies
Double vision	Proptosis

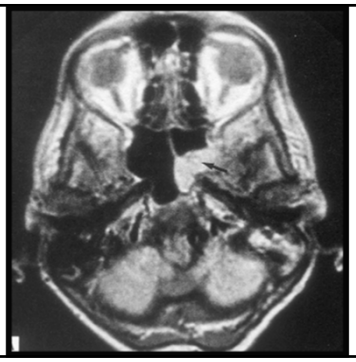


Tunkel AR. Principles and Practice of Infectious Diseases, 8th ed. 2015.

RADIOLOGIC FINDINGS IN SEPTIC CAVERNOUS SINUS THROMBOSIS

MR imaging

- Noninvasive diagnostic procedure of choice
- MRA and MRV can directly visualize cerebral vasculature
- Fullness in cavernous sinus region
- Paranasal sinus fluid

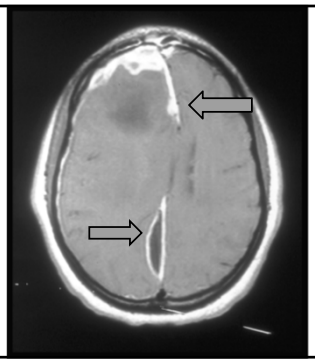


MANAGEMENT OF SEPTIC CAVERNOUS SINUS THROMBOSIS

- Culture and drainage of infected sinuses
- Antimicrobial therapy (vancomycin + metronidazole + 3rd or 4th generation cephalosporin)
- Anticoagulation - Yes
- Corticosteroids - No

CASE #8

- 22-year-old man with a history of paranasal sinusitis presents with fever, severe headache, neck pain, and seizure
- On physical examination, T 102º F and he is lethargic
- Laboratory studies normal



Question #4 (CASE #8)

In addition to appropriate antimicrobial therapy, what other management should be performed?

A. Lumbar puncture
B. External ventricular drain
C. Dexamethasone
D. Burr hole drainage
E. Craniotomy

CRANIAL SUBDURAL EMPYEMA AND CRANIAL EPIDURAL ABSCESS

Risk Factors	Etiologic Agents
Sinusitis (50-80%)	Staphylococci (10-15%)
Otogenic	Streptococci (25-45%)
Head trauma	Gram-negative bacilli (3-10%)
Neurosurgery	Other anaerobes (8%)
Hematogenous	Others (8%)
Meningitis	Unknown (20%)

CRANIAL SUBDURAL EMPYEMA AND CRANIAL EPIDURAL ABSCESS

Subdural Empyema (acute course)

- Fever
- Headache
- Depressed consciousness
- Hemiparesis
- Seizures
- Nuchal rigidity
- Gaze palsies/ataxia

Epidural Abscess (indolent course)

- Headache
- Fever
- Seizures
- Focal neurologic signs
- Altered mental state

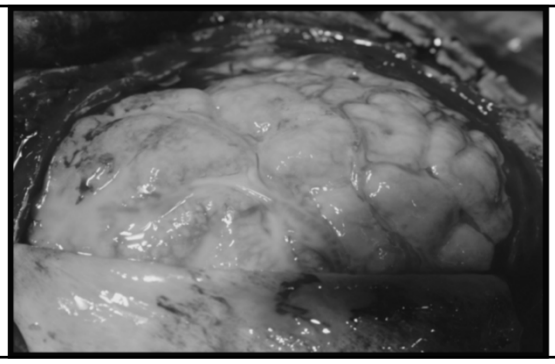
PRINCIPLES OF MANAGEMENT OF CRANIAL SUBDURAL EMPYEMA

- MR imaging (diagnostic procedure of choice) provides better clarity of detail and can differentiate empyema from most sterile effusions and chronic hematomas; diffusion-weighted imaging adds to value of MRI
- Surgical therapy (burr holes or craniotomy) is imperative; better outcome with craniotomy
- Empiric antimicrobial therapy based on pathogenesis of infection

SURGICAL MANAGEMENT OF CRANIAL SUBDURAL EMPYEMA

Surgical Procedure	Mortality Rate
Burr hole(s)	23.3%
Craniectomy	11.5%
Craniotomy	8.4%

Nathoo et al. Neurosurgery 2001;49:872



EPIDEMIOLOGY OF SPINAL EPIDURAL ABSCESS

- Usually occurs secondary to hematogenous dissemination (~50% of cases)
- Contiguous foci (~1/3rd of cases)
- Unidentified source (20-40% of cases)
- Diabetes mellitus identified in up to 50% of patients

ETIOLOGY OF SPINAL EPIDURAL ABSCESS

Organism	Relative Frequency (%)
Staphylococci	50-90
Streptococci	8-17
Gram-negative bacilli	12-17
Other anaerobes	2
Other	2
> 1 organism	5-10
Unknown	6

CLINICAL STAGES OF SPINAL EPIDURAL ABSCESS

I. Back pain and tenderness at the level of infection
II. Radicular pain and paresthesias
III. Impaired spinal cord function; motor paresis and sensory deficits
IV. Complete paralysis

PRINCIPLES OF MANAGEMENT OF SPINAL EPIDURAL ABSCESS

- MR imaging is the diagnostic procedure of choice; can visualize the spinal cord and epidural space, and can identify accompanying osteomyelitis, intramedullary spinal cord lesions, and joint space infection
- Empiric antimicrobial therapy should include an antistaphylococcal agent (i.e., vancomycin) and coverage for gram-negative bacilli

PRINCIPLES OF MANAGEMENT OF SPINAL EPIDURAL ABSCESS

- Surgical therapy imperative in the presence of neurologic dysfunction (best if <24-36 hours of complete paralysis)
- Nonsurgical therapy only for patients with an unacceptably high surgical risk or no neurologic deficits at diagnosis; patient must be followed carefully for clinical deterioration

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QUESTIONS

Allan R. Tunkel, MD, PhD, MACP
Email: allan_tunkel@brown.edu

Agenda Day 3: Monday, August 21, 2023

#	Start		End	Presentation	Faculty
AM Moderator: Paul Auwaerter, MD					
QP3	**8:30 AM EDT**	**-**	**9:00 AM EDT**	**Daily Question Preview Day 3**	**Paul Auwaerter, MD**
21	9:00 AM	-	9:30 AM	Sexually Transmitted Infections: Genital Ulcers Diseases (GUD)	Khalil Ghanem, MD
22	9:30 AM	-	10:15 AM	Infections of Upper and Lower Urinary Tract	Barbara Trautner, MD
FC6	**10:15 AM**	**-**	**10:45 AM**	**Faculty Q&A**	**Drs. Auwaerter (Moderator), Ghanem, and Trautner**
AM Moderator: Richard Whitley, MD					
23	10:45 AM	-	11:15 AM	Sexually Transmitted Infections: Other Diseases and Syndromes	Khalil Ghanem, MD
24	11:15 AM	-	12:00 PM	Encephalitis including West Nile and Rabies	Allan Tunkel, MD
	12:00 PM	-	12:30 PM	Lunch Break	
BR3	**12:30 PM**	**-**	**1:30 PM**	**Board Review Day 3**	**Drs. Auwaerter (Moderator), Bell, Dhanireddy, Ghanem, Klompas, and Trautner**
PM Moderator: Paul Auwaerter MD					
25	1:30 PM	-	2:15 PM	Ticks, Mites, Lice, and the Diseases They Transmit	Paul Auwaerter MD
26	2:15 PM	-	3:00 PM	Immunizations: Domestic, Travel, and Occupational	Shireesha Dhanireddy, MD
27	3:00 PM	-	3:45 PM	Epididymitis, Orchitis, and Prostatitis	Barbara Trautner, MD
FC7	**3:45 PM**	**-**	**4:00 PM**	**Faculty Q&A**	**Drs. Auwaerter (Moderator), Dhanireddy, and Trautner**
28	4:00 PM	-	4:30 PM	Lyme Disease	Paul Auwaerter, MD
29	4:30 PM	-	5:30 PM	Hospital Epidemiology	Michael Klompas, MD
30	5:30 PM	-	6:15 PM	Syndromes in the ICU that ID Physicians Should Know	Taison Bell, MD
31	6:15 PM	-	6:45 PM	Pneumonia	Paul Auwaerter, MD
FC8	**6:45 PM**	**-**	**7:00 PM**	**End of the Day Faculty Q&A**	**Drs. Auwaerter, Bell, Dhanireddy, Ghanem, Klompas, and Trautner**

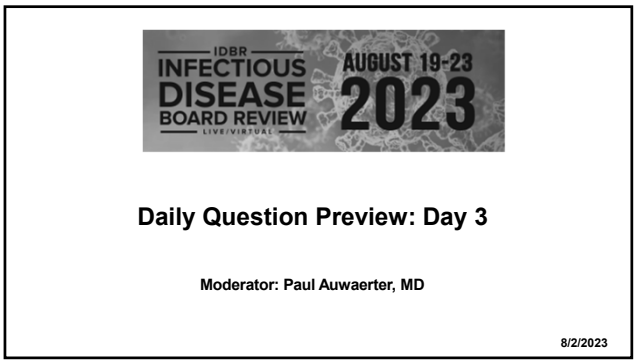
QP3

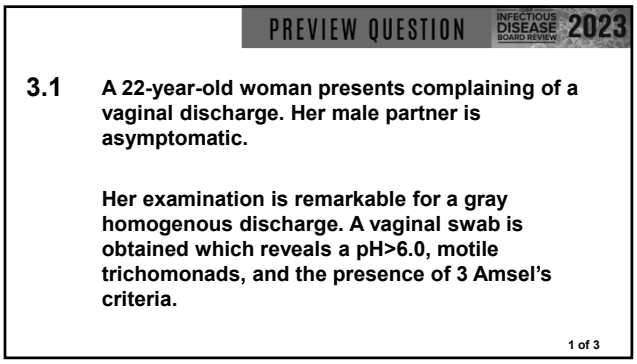
Daily Question Preview 3

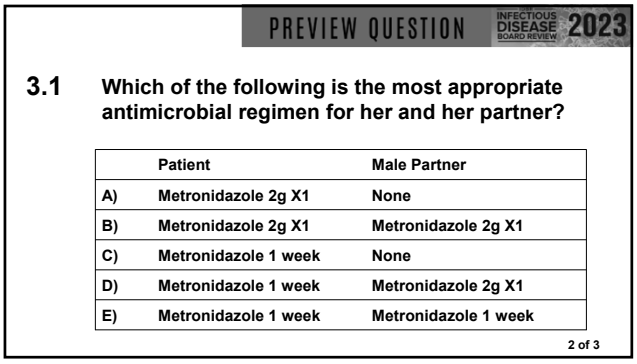
Dr. Paul Auwaerter (Moderator)

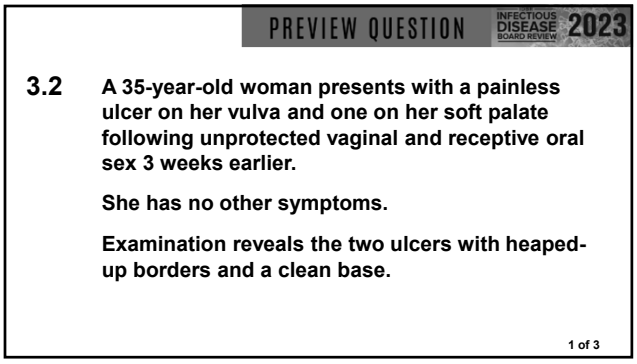
QP3 – Daily Question Preview: Day 3

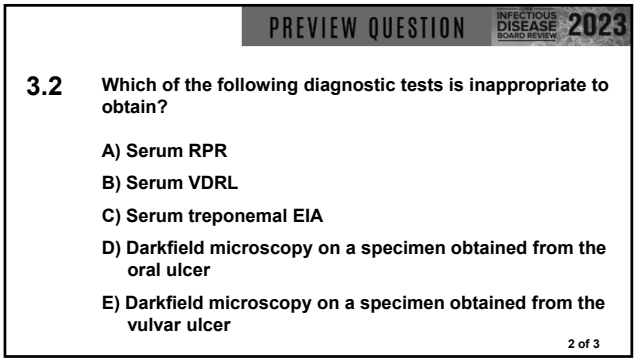
Moderator: Paul Auwaerter, MD

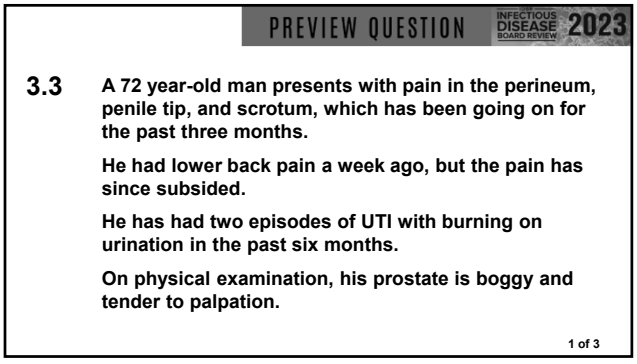












PREVIEW QUESTION INFECTIOUS DISEASE BOARD REVIEW 2023

3.3 **What is the most common cause of a chronic form of this condition?**

A) Herpes

B) Chlamydia

C) *E. coli*

D) Candida

2 of 3

PREVIEW QUESTION INFECTIOUS DISEASE BOARD REVIEW 2023

3.4 **A 35 year-old man who is a member of a religious group that does not support vaccination attended a wedding in Nebraska.**

Two days later he developed pain in his left ear and jaw tenderness.

Eleven days later he had noticeable swelling under both sides of his jaw, fever, and painful swelling of his left testicle.

1 of 3

PREVIEW QUESTION INFECTIOUS DISEASE BOARD REVIEW 2023

3.4 **The likely causative agent is:**

A) Mumps

B) Measles

C) *Escherichia coli*

D) *Neisseria gonorrhea*

2 of 3

PREVIEW QUESTION INFECTIOUS DISEASE BOARD REVIEW 2023

3.5 **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.

1 of 4

PREVIEW QUESTION INFECTIOUS DISEASE BOARD REVIEW 2023

3.5 **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.

2 of 4

PREVIEW QUESTION INFECTIOUS DISEASE BOARD REVIEW 2023

3.5 **Which of the following is the most appropriate management?**

A) Nitrofurantoin

B) Bactrim

C) Fosfomycin

D) Ciprofloxacin

E) Ibuprofen

3 of 4

QP3 – Daily Question Preview: Day 3

Moderator: Paul Auwaerter, MD

PREVIEW QUESTION INFECTIOUS DISEASE BOARD REVIEW 2023

3.6 50-year-old man presents with a several day history of fever, headache, and personality change with progression to confusion.

On exam, temperature is 101°F; he is disoriented and unable to follow commands.

CT scan of the head without contrast is negative.

CSF analysis reveals a WBC of 80/mm3 (95% lymphs), glucose 70 mg/dL (serum 100 mg/dL), protein 120 mg/dL; Gram stain is negative.

1 of 4

PREVIEW QUESTION INFECTIOUS DISEASE BOARD REVIEW 2023

3.6

- Acyclovir is initiated
- MRI with gadolinium reveals enhancement in the left temporal lobe
- Results of initial cerebrospinal fluid (CSF) polymerase chain reaction (PCR) for HSV-1 and HSV-2 return negative
- After 3 days, the patient is now oriented to name and follows simple commands

2 of 4

PREVIEW QUESTION INFECTIOUS DISEASE BOARD REVIEW 2023

3.6 What is the next step in the management of this patient?

A) Perform a brain biopsy of the left temporal lobe

B) Obtain new CSF for HSV PCR testing

C) Send serum for HSV IgG antibodies

D) Repeat brain MRI

E) Discontinue acyclovir

3 of 4

PREVIEW QUESTION INFECTIOUS DISEASE BOARD REVIEW 2023

3.7 72-year-old man presents in late August with complaints of fever, chills, and weakness beginning 1 week earlier; on the day of admission, he becomes confused.

He lives in central New Jersey, where he and his wife have a horse farm; they often noted mosquito and tick bites.

On presentation, he is somnolent and unable to provide a complete history, although denies headache and stiff neck.

1 of 4

PREVIEW QUESTION INFECTIOUS DISEASE BOARD REVIEW 2023

3.7

- T 103.1°F, P 110, RR 16, BP 110/70 mmHg
- No rash or petechiae, neck supple, no adenopathy, lungs clear, heart without murmurs, abdomen normal
- On neurologic exam, he is oriented to person only. Cranial nerves intact. Motor strength 4/5 UE, and 3/5 LLE and 2/5 RLE. Sensation intact. Reflexes diminished in LE

2 of 4

PREVIEW QUESTION INFECTIOUS DISEASE BOARD REVIEW 2023

3.7 Which of the following tests is most likely to establish the etiology of this patient's encephalitis?

A) Serum IgM

B) Serum polymerase chain reaction

C) Cerebrospinal fluid IgM

D) Cerebrospinal fluid polymerase chain reaction

E) Brain MRI

3 of 4

QP3 – Daily Question Preview: Day 3

Moderator: Paul Auwaerter, MD

PREVIEW QUESTION INFECTIOUS DISEASE BOARD REVIEW 2023

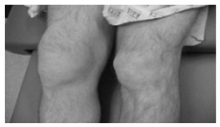
3.8 **56M Long Island, NY with R knee pain and swelling x 3 weeks. Thought this was a wrenched knee from yardwork.**

No fever, rash, tick bite or Lyme disease history

PMH: HTN, hyperlipidemia

PE: afebrile, mildly warm knee, moderate effusion, reduced ROM

Labs: nl CBC



1 of 3

PREVIEW QUESTION INFECTIOUS DISEASE BOARD REVIEW 2023

3.8 **Which of the following is usually true for Lyme arthritis?**

A) If untreated, the knee swelling will not remit

B) *B. burgdorferi* PCR synovial fluid ~ 100% sensitivity

C) Synovial fluid WBCs >50,000 cells/mL

D) Synovial fluid *B. burgdorferi* IgM and IgG immuno(Western)blots ~100% sensitivity

E) Serum *B. burgdorferi* 2-tier testing ~100% sensitivity

2 of 3

PREVIEW QUESTION INFECTIOUS DISEASE BOARD REVIEW 2023

3.9 **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

1 of 4

PREVIEW QUESTION INFECTIOUS DISEASE BOARD REVIEW 2023

3.9 **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

2 of 4

PREVIEW QUESTION INFECTIOUS DISEASE BOARD REVIEW 2023

3.9 **You are aware of a recent *Legionella micdadei* outbreak in the hospital. Which test below, would most help you securing a diagnosis of *L. micdadei* pneumonia?**

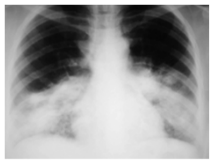
A) Legionella urinary antigen

B) Legionella culture

C) Legionella PCR, respiratory

D) Legionella direct fluorescent antigen (DFA) stain of respiratory sample

E) Paired Legionella acute/convalescent serology



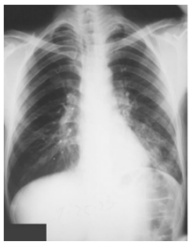
Pre-intubation CXR

3 of 4

PREVIEW QUESTION INFECTIOUS DISEASE BOARD REVIEW 2023

3.10

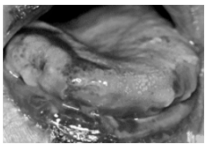
- **18F c/o fever, dry hacking cough, malaise x 3d**
- **Allergy: erythromycin (N/V)**
- **Appears well, T38ºC, RR 16, P 80, BP 110/70**
  - **Oropharynx: normal**
  - **TMs: normal**
  - **Chest: some crackles left lower lobe**

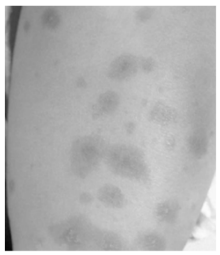


1 of 4

PREVIEW QUESTION INFECTIOUS DISEASE BOARD REVIEW 2023

3.10
- **Azithromycin prescribed**
- **Next day, full body rash and mucosal lesions develop**





2 of 4

PREVIEW QUESTION INFECTIOUS DISEASE BOARD REVIEW 2023

3.10 **What is the most likely etiology?**

A) Mycoplasma pneumoniae

B) Enterovirus D68

C) Measles

D) Lyme disease

E) Drug reaction (azithromycin)

3 of 4

PREVIEW QUESTION INFECTIOUS DISEASE BOARD REVIEW 2023

3.11 **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

1 of 5

PREVIEW QUESTION INFECTIOUS DISEASE BOARD REVIEW 2023

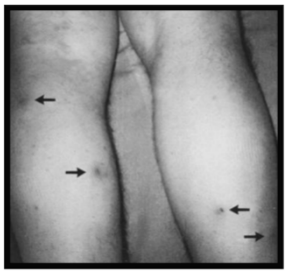
3.11 **Temperature is 38.6º, P76, R14, BP 116/70**
Exam is unremarkable except for four punctuate eschars on the legs and bilateral inguinal lymph node enlargement

Lab:
Thick and thin blood smears (x 2) negative

2 of 5

PREVIEW QUESTION INFECTIOUS DISEASE BOARD REVIEW 2023

3.11 **Four Inoculation Eschars (Arrows)**



3 of 5

PREVIEW QUESTION INFECTIOUS DISEASE BOARD REVIEW 2023

3.11 **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

4 of 5

QP3 – Daily Question Preview: Day 3

Moderator: Paul Auwaerter, MD

PREVIEW QUESTION INFECTIOUS DISEASE BOARD REVIEW 2023

3.12 **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.

1 of 3

PREVIEW QUESTION INFECTIOUS DISEASE BOARD REVIEW 2023

3.12 **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

2 of 3

PREVIEW QUESTION INFECTIOUS DISEASE BOARD REVIEW 2023

3.13 **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.

1 of 3

PREVIEW QUESTION INFECTIOUS DISEASE BOARD REVIEW 2023

3.13 **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

2 of 3

PREVIEW QUESTION INFECTIOUS DISEASE BOARD REVIEW 2023

3.14 **An asymptomatic patient with a new diagnosis of HIV (CD4 = 10 cells/uL and HIV Viral Load 300,000 copies/uL is started on antiretroviral therapy (dolutegravir plus tenofovir alafenamide/emtricitabine).**

His labs are unremarkable as is his chest xray.

1 of 4

PREVIEW QUESTION INFECTIOUS DISEASE BOARD REVIEW 2023

3.14 **His serum toxoplasma IgG is positive.**

He asks whether you want to add prophylaxis for pneumocystis pneumonia but warns you that twice when he has taken sulfonamides he has developed hives and laryngeal edema.

2 of 4

QP3 – Daily Question Preview: Day 3

Moderator: Paul Auwaerter, MD

PREVIEW QUESTION INFECTIOUS DISEASE BOARD REVIEW 2023

3.14 What would you recommend regarding PCP and Toxo prophylaxis?

A) No chemoprophylaxis: his viral load should fall quickly, and his CD4 will rise quickly in response to this first exposure to antiretroviral therapy

B) Trimethoprim sulfamethoxazole plus solu-medrol dose pak

C) Dapsone

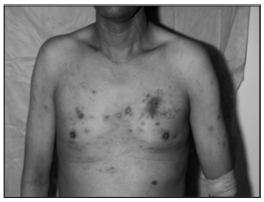
D) Aerosol pentamidine plus pyrimethamine

E) Atovaquone

3 of 4

PREVIEW QUESTION INFECTIOUS DISEASE BOARD REVIEW 2023

3.15 The patient whose photo is shown is HIV positive (CD4=10 cells/uL, VL=2 mil copies) and has noted these lesions developing on his trunk, face and extremities over the past 8 months.



He has had low grade fevers for several months.

1 of 3

PREVIEW QUESTION INFECTIOUS DISEASE BOARD REVIEW 2023

3.15 For your differential diagnosis, what besides Kaposi sarcoma would be the most likely cause of these lesions and their associated fever?

A) HHV-6

B) CMV

C) Cryptococcus neoformans

D) Bartonella

E) Rhodococcus

2 of 3

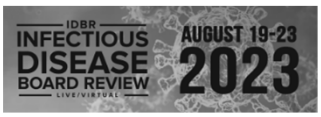
21

Sexually Transmitted Infections: Genital Ulcers Diseases (GUD)

Dr. Khalil Ghanem

21 – Sexually Transmitted Infections: Genital Ulcers Diseases (GUD)

Speaker: Khalil Ghanem, MD



Sexually Transmitted Infections: Genital Ulcer Diseases

Khalil G. Ghanem, MD, PhD
Professor of Medicine
Division of Infectious Diseases
Johns Hopkins University School of Medicine

7/2/2023

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
  - 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

21 – Sexually Transmitted Infections: Genital Ulcers Diseases (GUD)

Speaker: Khalil Ghanem, MD

"KEY WORDS" IN GUD CONTINUED

- **CHANCROID**: painful, indurated, 'ragged' genital ulcers & tender **suppurative inguinal adenopathy** (50%); **kissing lesions** on thigh
- **GI**: **Painless**, progressive (destructive), **"serpiginous"** ulcerative lesions, without regional lymphadenopathy; beefy red with white border & highly vascular
- **LGV**: short-lived **painless** genital ulcer accompanied by **painful suppurative inguinal lymphadenopathy; "groove sign"**

QUESTION #1 PREVIEW QUESTION

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 PREVIEW QUESTION

Which of the following diagnostic tests is **inappropriate** to obtain?

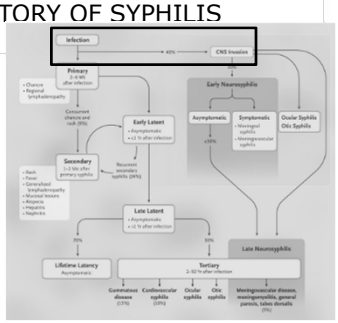
A. Serum RPR
B. Serum VDRL
C. Serum treponemal EIA
D. Darkfield microscopy on a specimen obtained from the oral ulcer
E. Darkfield microscopy on a specimen obtained from the vulvar ulcer

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

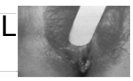
Vertical transmission (may occur during any stage)
- ~80% transmission in the early stages
- ~10% transmission in the late stages

Rarely, transmission may occur through **blood transfusions** and **organ transplantations**

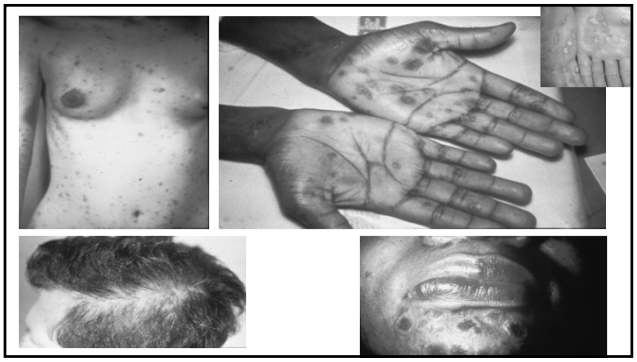


* N Engl J Med 2020;382:845-854

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: evanescent, copper-colored, macular (dry) rash; followed by 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.



21 – Sexually Transmitted Infections: Genital Ulcers Diseases (GUD)

Speaker: Khalil Ghanem, MD

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**

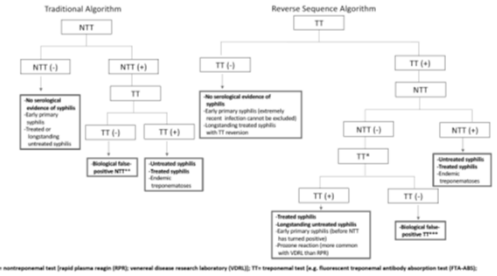
SYPHILIS SEROLOGICAL TESTING

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**



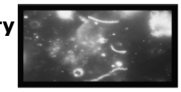
∗ N Engl J Med 2020;382:845-854

21 – Sexually Transmitted Infections: Genital Ulcers Diseases (GUD)

Speaker: Khalil Ghanem, MD

SYPHILIS: DIAGNOSTICS

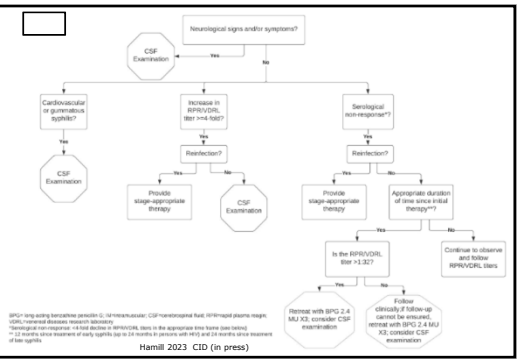
- Darkfield microscopy or PCR for **genital** ulcers of primary syphilis; **sensitivity of serology in primary syphilis only~70%**
- **Sensitivity of serology for secondary or early latent syphilis ~100%**
- Over time, non-treponemal serological titers decline and may become nonreactive even in the absence of therapy while treponemal titers remain reactive for life



NEUROSYPHILIS: DIAGNOSTICS

- No single test can be used to diagnose neurosyphilis
  - 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

Who Should Have a CSF Examination?



Hamill 2023 CID (in press)

*

SYPHILIS THERAPY

- Early stages (primary, secondary, early latent)
  - 2.4 MU of long-acting benzathine penicillin or doxycycline 100mg PO BID X 14 days
- Late latent/unknown duration
  - 2.4 MU of long acting benzathine penicillin G IM X3 (over 2 weeks) [7.2 MU total] or doxycycline 100mg PO BID X 4 weeks

SYPHILIS THERAPY CONTINUED

- Neurosyphilis/Ocular/Otic syphilis
  - Aqueous penicillin 18 to 24 MU IV X 10-14 days
  - Procaine penicillin 2.4 MU IM qd + probenecid 500 mg po QID X 10-14 days (will no longer be available)
  - Ceftriaxone 1-2g IV/IM X 10-14 days (2nd line regimen)
- Jarisch-Herxheimer: within 6 hours (up to 24 hours) after therapy of (usually) early syphilis; antipyretics only; **may induce early labor**

QUESTION #2

A pregnant 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.

21 – Sexually Transmitted Infections: Genital Ulcers Diseases (GUD)

Speaker: Khalil Ghanem, MD

QUESTION #2

Which of the following antibiotics is most appropriate?

A. Azithromycin
B. Benzathine penicillin G
C. Ceftriaxone
D. Doxycycline

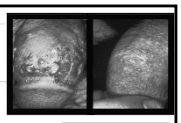
SYPHILIS & HIV

- Clinical manifestations similar but timeline may be compressed
  - PWH more susceptible to early neurosyphilis
- Testing and therapy similar to HIV negative
- Serological failure is more likely among PWH
- Serological response may be slower among PWH
- Follow-up is more frequent (every 3 months)

SYPHILIS & PREGNANCY

- Screen 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)**

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**

21 – Sexually Transmitted Infections: Genital Ulcers Diseases (GUD)

Speaker: Khalil Ghanem, MD

HSV: DIAGNOSTICS IN ASYMPTOMATIC PATIENTS

- Use Glycoprotein G-based type-specific EIA assays
  - If gG2 is reactive, patient has genital herpes
    - 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!**

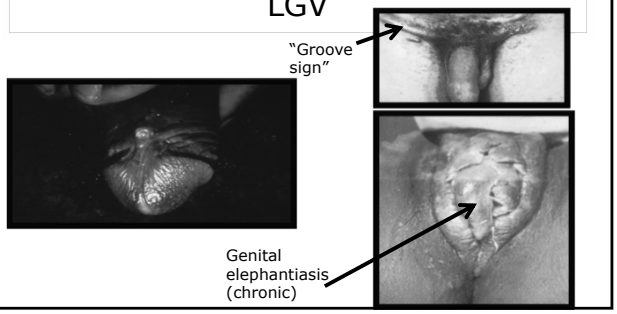
HSV: PREGNANCY

- 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)

LGV

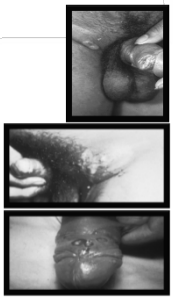


LGV DIAGNOSIS & THERAPY

- **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



21 – Sexually Transmitted Infections: Genital Ulcers Diseases (GUD)

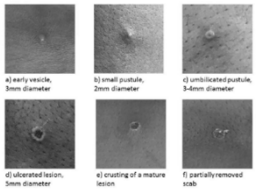
Speaker: Khalil Ghanem, MD

GRANULOMA INGUINALE OR DONOVANOSIS

- *Klebsiella granulomatis (Calymmatobacterium granulomatis)*
- Not endemic in US; common in SE Asia (India), & Southern Africa (recently eradicated in Australia)
- Painless, progressive (destructive), "serpiginous" ulcerative lesions, without regional LAD (pseudobuboes occasionally); beefy red with white border & highly vascular
- Dx: tissue biopsy (no culture test; PCR not FDA cleared); demonstrating the organisms in macrophages, called **Donovan bodies**, using **Wright-Giemsa** stain (NOT Gram's stain)
- Rx: Doxycycline 100mg PO BID X 3 weeks (or until resolution) OR azithromycin 1g PO q week X3 (can also use trimethoprim/sulfa)

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 (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

THANK YOU!

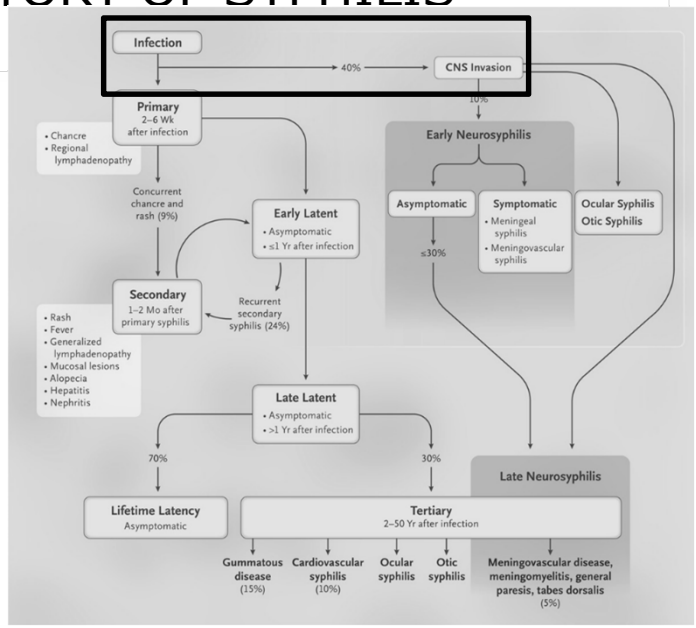
KGHANEM@JHMI.EDU

NATURAL HISTORY OF SYPHILIS

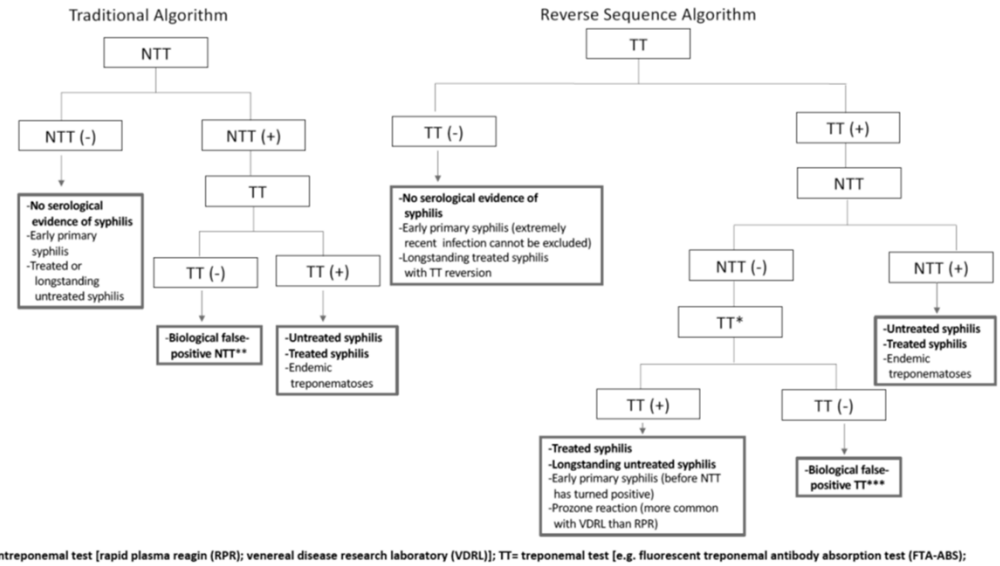
Sexual transmission (only occurs in early stages)
- Risk of infection after 1 exposure: 40%
- Index patient is most contagious during 1º and 2º stage, less so in early latent stage

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**



∗ N Engl J Med 2020;382:845-854



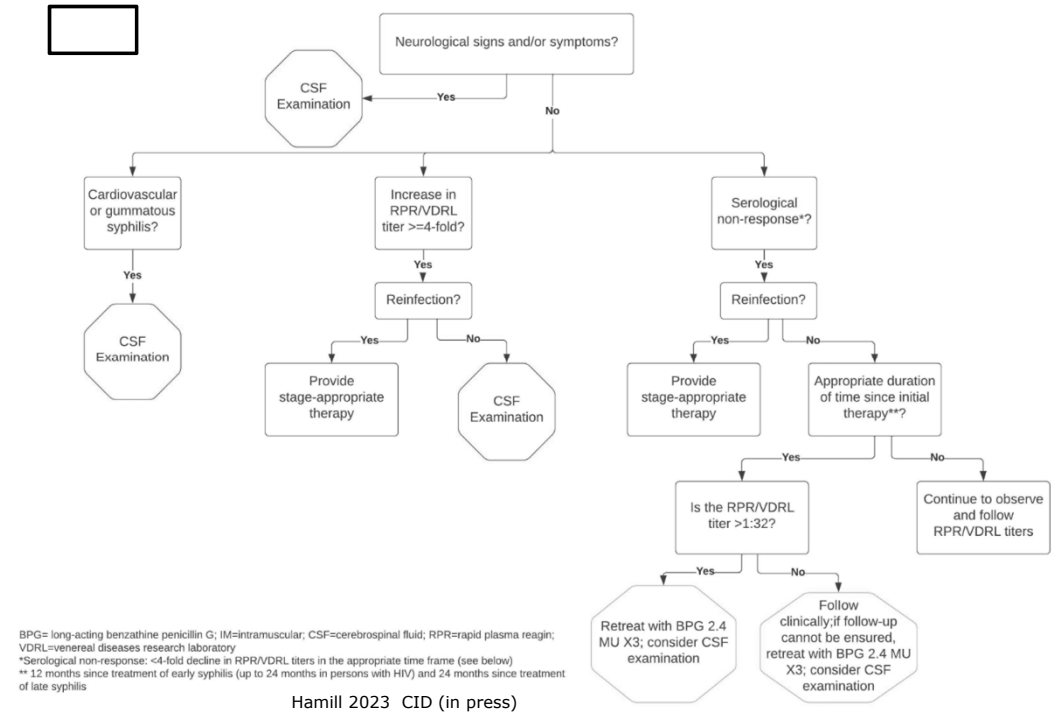
NTT= nontreponemal test [rapid plasma reagin (RPR); venereal disease research laboratory (VDRL)]; TT= treponemal test [e.g. fluorescent treponemal antibody absorption test (FTA-ABS);

∗ N Engl J Med 2020;382:845-854

21 – Sexually Transmitted Infections: Genital Ulcers Diseases (GUD)

Speaker: Khalil Ghanem, MD

Who Should Have a CSF Examination?



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Hamill 2023 CID (in press)

GUD	Pain	Characteristics	Diagnosis	Treatment
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*

22

Infections of Upper and Lower Urinary Tract

Dr. Barbara Trautner

22 – Infections of Upper and Lower Urinary Tract

Speaker: Barbara Trautner, MD

IDBR INFECTIOUS DISEASE BOARD REVIEW AUGUST 19-23 2023 LIVE/VIRTUAL

Urinary Tract Infections

Barbara Trautner, MD, PhD
Professor of Medicine
Baylor College of Medicine

6/25/2023

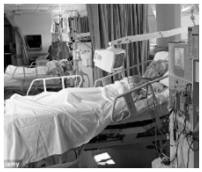
IDBR INFECTIOUS DISEASE BOARD REVIEW AUGUST 19-23 2023

Disclosures of Financial Relationships with Relevant Commercial Interests

- **Consultant:**
  - **Genentech for COVID treatment trial**
  - **Peptilogics for prosthetic joint infection trial**
  - **Shionogi for COVID treatment trial**
- **Research Funding: Genentech**

Topics to cover

- Acute and recurrent cystitis in women
- Asymptomatic bacteriuria
  - Pregnant women
  - Pre-operative screening
- Catheter-associated UTI
- Urosepsis and worse
  - Emphysematous pyelonephritis
  - Emphysematous cystitis
  - Xanthogranulomatous pyelonephritis



UTI differs in different populations

UTI is not the same entity in these different populations

Symptoms and management differ

The Great Divide

My patient populations

- Older adults in long-term care
- Persons who require urinary catheters for bladder drainage
- Persons with neurogenic bladders
- Men

UTI treatment evidence base

- Pre-menopausal women
- Female college students and university staff

IDBR INFECTIOUS DISEASE BOARD REVIEW AUGUST 19-23 2023 **PREVIEW QUESTION**

UTI 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. Bactrim
C. Fosfomycin
D. Ciprofloxacin
E. Ibuprofen

Current IDSA UTI Guidelines*

*update in progress

These guidelines cover:
- Uncomplicated cystitis
- Uncomplicated pyelonephritis
- Premenopausal women
- Primarily outpatients

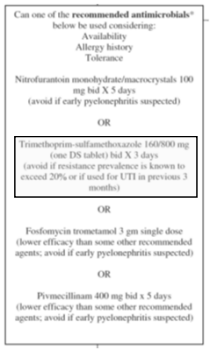
IDSA GUIDELINES

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



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

JAMA Network

From: **Effect of 5-Day Nitrofurantoin vs Single-Dose Fosfomycin on Clinical Resolution of Uncomplicated Lower Urinary Tract Infection in Women: A Randomized Clinical Trial**

JAMA. 2018;319(17):1781-1789. doi:10.1001/jama.2018.3627

Table 3. Clinical and Microbiologic Outcomes

Clinical and Bacteriologic Outcome	No./Total No. (%) Nitrofurantoin (n = 255)	Fosfomycin (n = 258)	Difference, % (95% CI)	P Value[a]
Primary Outcome				
Clinical response at 28 d[b]				
Clinical resolution	171/244 (70)	139/241 (58)	12 (4-21)	.004
Clinical failure	66/244 (27)	94/241 (39)		
Indeterminate	7/244 (3)	8/241 (3)		
Missing[c]	11 (4)	17 (7)		

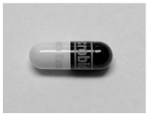
Clinical and microbiological response to 5 days of nitrofurantoin was better than to single dose fosfomycin

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

Cunha et al, Eur J Clin Microbiol Infect Dis 2017; 36(7)
Singh, CMAJ 2015; 187(9)
AGS Beers Criteria 2019

Nitrofurantoin Adverse Events

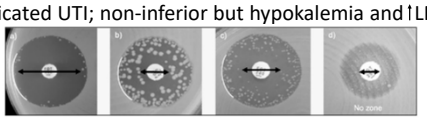


- Pulmonary toxicity--RARE
  - Acute: reversible hypersensitivity reaction
  - Chronic: persistent pulmonary fibrosis
    - Dose dependent?
    - Favors use of lowest possible dose/less frequent dosing for chronic prophylaxis
- Hepatitis—RARE
- Nausea—common
  - Worse with micro- (QID) than macro-crystalline (BID) formulation

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
- ZEUS trial: IV fosfomycin versus piperacillin-tazobactam for complicated UTI; non-inferior but hypokalemia and↑LFTs



Photos from eucast.org; arrows (↔) reflect CLSI recommendations

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.

UTI Question #2

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 12 months
B. Nitrofurantoin one dose after intercourse
C. Ciprofloxacin daily for 6 months
D. Trimethoprim-sulfamethoxazole 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
- Otherwise 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
- Evidence for cranberry products is extremely weak

Recurrent Uncomplicated Urinary Tract Infections in Women: AUA/CUA/SUFU Guideline (2022)

UTI 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 well-controlled hypertension.

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

Prevalence of Asymptomatic Bacteriuria

Population	Prevalence, %
Children	
Boys	<1
Girls	1–2
Healthy women	
Premenopausal	1.0–6.0
Pregnant	1.9–9.5
Postmenopausal (age 50–70 y)	2.6–8.6
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	15–50
Persons with spinal cord injury	
Intermittent catheter use	23–89
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

Nicolle et al, IDSA Guidelines for Asymptomatic Bacteriuria, Clin Inf Dis 2019

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

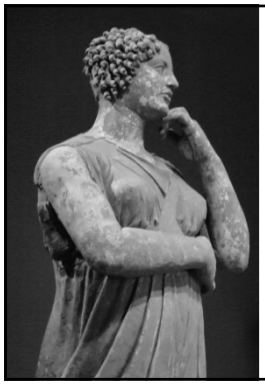
IDSA Guidelines on ASB 2019

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

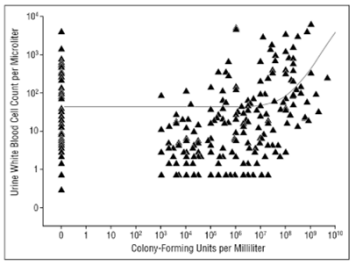
- X Infants and children
- X Non-pregnant women
- X Functionally-impaired older adults
- X Diabetic adults
- X Patients >1 month from kidney transplant
- X Neutropenic patients
- X Patients with solid organ transplant
- X Persons with spinal cord injury
- X Patients with indwelling catheters
- X Prior to non-urologic surgery



Mythbusting: Which of the following is true?

A. A change in urine color is an indication for a urine culture
B. Bad smelling urine is suggestive of a UTI
C. Sediment in the urine means we should change the catheter
D. The level of pyuria helps in diagnosis of catheter-associated UTI
E. Beets can turn urine red

Relationship between pyuria and bacteriuria/candiduria in catheterized patients



Tambyah and Maki, Archives Int Med 2000

UTI 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*.

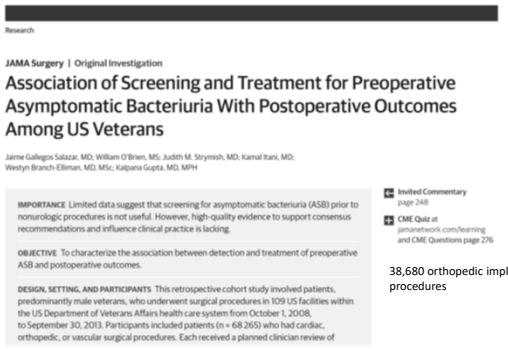
Kidney ultrasonography is unremarkable.

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

Preoperative screening for ASB

New(ish) evidence!



Research

JAMA Surgery | Original Investigation

Association of Screening and Treatment for Preoperative Asymptomatic Bacteriuria With Postoperative Outcomes Among US Veterans

Jaime Gallegos Salazar, MD; William O'Brien, MS; Judith M. Strymish, MD; Kamal Itani, MD; Westyn Branch-Elliman, MD, MSc; Kalpana Gupta, MD, MPH

IMPORTANCE Limited data suggest that screening for asymptomatic bacteriuria (ASB) prior to nonurologic procedures is not useful. However, high-quality evidence to support consensus recommendations and influence clinical practice is lacking.

OBJECTIVE To characterize the association between detection and treatment of preoperative ASB and postoperative outcomes.

DESIGN, SETTING, AND PARTICIPANTS This retrospective cohort study involved patients, predominantly male veterans, who underwent surgical procedures in 109 US facilities within the US Department of Veterans Affairs health care system from October 1, 2008, to September 30, 2013. Participants included patients (n = 68 265) who had cardiac, orthopedic, or vascular surgical procedures. Each received a planned clinician review of

Invited Commentary page 248

CME Quiz at jamanetwork.com/learning and CME Questions page 276

38,680 orthopedic implant procedures

Preoperative Screening for ASB: Key Findings

- Of 17,749 preoperative urine cultures
  - 755 positive
  - 617 were ASB
- ASB did not increase odds of surgical site infection (SSI)
- In 2 cases the urinary organism matched the organism causing SSI (*Staph aureus*)
- ASB was associated with an increased risk of UTI
- Treatment of ASB
  - Not associated with lower risk of surgical site infection
  - Not associated with lower odds of UTI

UTI 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

CAUTI prevention

- Do remove the urinary catheters when possible
  - Only indwelling Foleys count for CAUTI metrics
  - ALL types of urinary catheters are associated with bacteriuria
- Don't culture the urine in asymptomatic patients
- Do follow aseptic insertion
- Do ensure uninterrupted drainage
  - No tugging
  - No kinking
  - No reflux due to elevated drainage bag
- Don't routinely irrigate the bladder, exchange the catheter, or use antimicrobial catheters

https://www.cdc.gov/infectioncontrol/guidelines/cauti/

UTI Question #6

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)

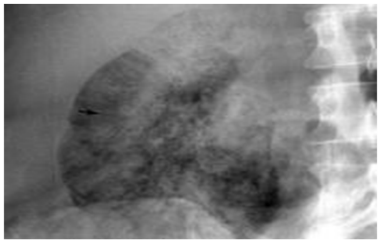
UA: WBC 250, RBC too numerous to count, no bacteria

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.

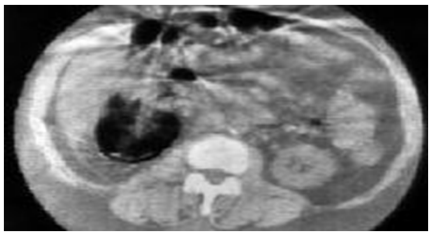
KUB X-Ray of Abdomen



What would you order next?

A. Lateral decubitus chest X-rays
B. Abdominal CT
C. PET scan

Answer: Abdominal CT



Emphysematous pyelonephritis: CT showing gas within the renal parenchyma is definitive

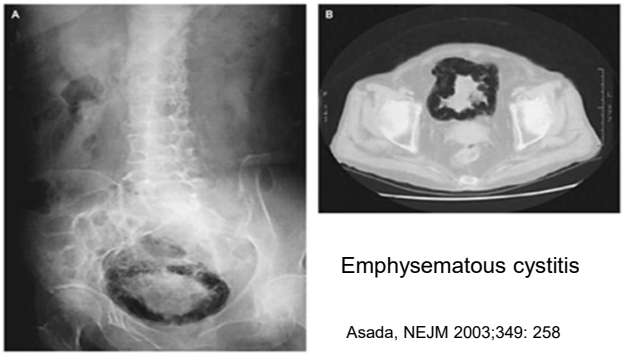
Clinical course of case #6

- 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 CABG

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

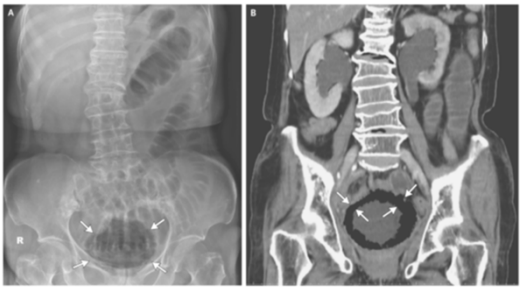
Kamei, J Infection and Chemotherapy 2021



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**

UTI Question #7

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.

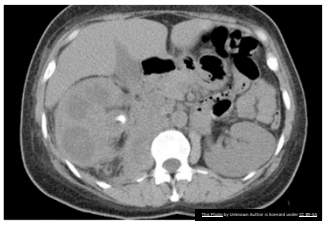
One year prior, he again had a fever, and his blood grew *Serratia, E. coli,* and *Pseudomonas*. Urine grew *Serratia* and *Pseudomonas*.

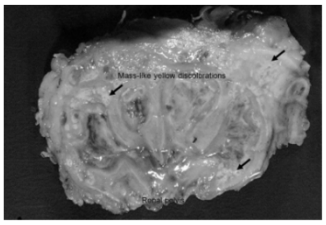
Both times he was treated with appropriate antibiotics, with resolution of fever and stabilization.

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

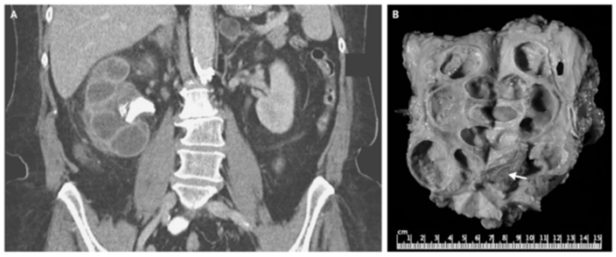




Xanthogranulomatous pyelonephritis

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

To Re-Cap

- Acute and recurrent cystitis in women-nitrofurantoin
- Asymptomatic bacteriuria
  - Pregnant women-screen and treat
  - Pre-operative screening-**not** indicated unless urologic surgery
- Catheter-associated UTI—ensure unobstructed drainage
- Urosepsis and worse
  - Emphysematous pyelonephritis-drainage
  - Emphysematous cystitis-medical management
  - Xanthogranulomatous pyelonephritis-removal

Is everything clear now?

- trautner@bcm.edu
- @bwtrautner

"Treatment" of Cystitis with NSAIDS

- Randomized double-blind trial of diclofenac versus norfloxacin
- 253 women with symptoms of uncomplicated cystitis
  - 73% culture positive
  - 70% of organisms sensitive to norfloxacin
- Norfloxacin was superior to diclofenac for
  - Symptom resolution at 3 days (80% versus 54%)
  - Time to resolution of symptoms (2 versus 4 days)
  - Pyelonephritis prevention (0 cases versus 6, or 5%)

Kronenberg et al, BMJ 2017

LeMaire et al, JAMA Surgery 2018

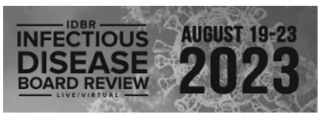
23

Sexually Transmitted Infections: Other Diseases and Syndromes

Dr. Khalil Ghanem

23 – Sexually Transmitted Infections: Other Diseases and Syndromes

Speaker: Khalil Ghanem, MD



Sexually Transmitted Infections: Other Diseases & Syndromes

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7/2/2023

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%

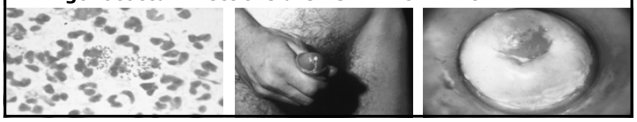
Dombrowski CID 2021; Lau NEJM 2021

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**



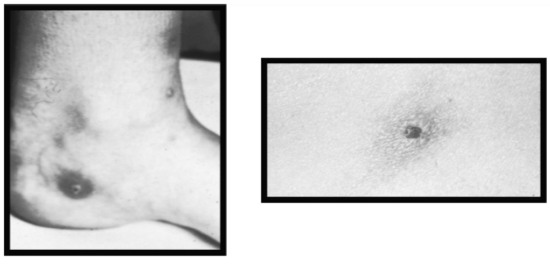
SCREENING FOR GONORRHEA

- 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
- 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 sensitive) OR
    - Moxifloxacin 400mg POX 7 days (if macrolide resistant or if macrolide resistance is unknown)
  - Emerging resistance to fluoroquinolones (13.6% moxifloxacin resistance)

    Emerg Infect Dis. 2017;23(5):809-812
- **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 PREVIEW QUESTION

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 PREVIEW QUESTION

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

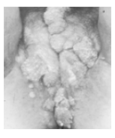
- Campylobacter
- Shigella
- Entamoeba
- CMV
- *Giardia lamblia** (mainly enteritis; especially among MSM)

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

23 – 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)

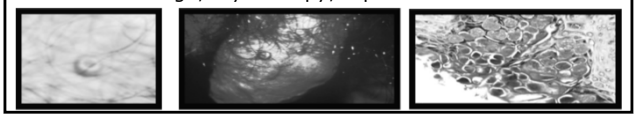
*FDA approved a supplemental biologics licensure application in 6/2020: prevention of oropharyngeal and other head and neck cancers caused by HPV types targeted by the vaccine

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

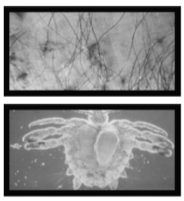
MOLLUSCUM CONTAGIOSUM

- Poxvirus
- 1 to 5mm lesions; painless papules; CENTRAL UMBILICATION
- Not necessarily sexually transmitted
- Molluscum bodies: intracytoplasmic inclusions
- Rx: curettage; cryotherapy; topical cidofovir

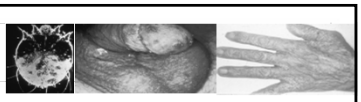


PEDICULOSIS PUBIS

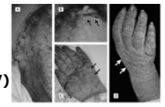
- Pediculosis pubis= pubic lice= crabs (*Pthirus pubis*)
  - Nits confined to upper shaft=old infection (no need for retreatment)
  - Maculae ceruleae (blue gray macules)
  - Permethrin 1% cream OR Pyrethrins with piperonyl butoxide (topical)
  - Resistance increasing; consider malathion 0.5% lotion 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

24

Encephalitis including West Nile and Rabies

Dr. Allan Tunkel

24 – Encephalitis including West Nile and Rabies

Speaker: Allan Tunkel, MD

Encephalitis Including West Nile and Rabies

Allan R. Tunkel, MD, PhD, MACP
Professor of Medicine and Medical Science
The Warren Alpert Medical School of Brown University

7/22/2023

Disclosures of Financial Relationships with Relevant Commercial Interests

- **None**

ENCEPHALITIS Definitions

3

- Encephalitis
  - Inflammation of brain parenchyma with neurologic dysfunction
  - Gold standard is pathologic examination and testing of brain tissue
  - Usually based on clinical, laboratory, and imaging
- Encephalopathy
  - Altered consciousness (confusion, disorientation, behavioral changes, cognitive impairment) ± inflammation
  - Usually metabolic or toxic conditions

ENCEPHALITIS Epidemiology

4

- ~5 cases/100,000 population annually in US from 1990-2017
- >1 million cases annually worldwide
  - Rabies
  - Measles
  - Japanese encephalitis virus

ENCEPHALITIS Etiology

5

- California Encephalitis Project (CEP) reviewed 1,570 cases over 7-year period (CID 2006;43:1565)
- Confirmed or probable etiology in 16%
  - 69% viral
  - 20% bacterial
  - 7% prion
  - 3% parasitic
  - 1% fungal
- Possible etiology in 13%

ENCEPHALITIS Etiology

6

- Australian Childhood Encephalitis Study (CID 2020;70:2517)
- 287 children with confirmed encephalitis
- 57% infectious (confirmed/probable)
- 25% immune-mediated
- 17% unknown

Reasons Etiology not Identified

- Undiscovered pathogens
- Uncommon presentation by common pathogens
- Common presentation by uncommon pathogens
- Wrong test
- Wrong sample
- Wrong timing
- Not an infection

General Approach

- Can't test for everything
- Epidemiologic and clinical clues
- General diagnostic studies
- Neuroimaging clues
- Consider noninfectious etiologies

Tunkel et al. Clin Infect Dis 2008;47:303
Venkatesan et al. Clin Infect Dis 2013;57:1114

CASE #1

PREVIEW QUESTION

- 50-year-old man presents with a several day history of fever, headache, and personality change with progression to confusion
- On exam, temperature is 101ºF; he is disoriented and unable to follow commands
- CT scan of the head without contrast is negative
- CSF analysis reveals a WBC of 80/mm^3 (95% lymphs), glucose 70 mg/dL (serum 100 mg/dL), protein 120 mg/dL; Gram stain is negative

CASE #1

PREVIEW QUESTION

- Acyclovir is initiated
- MRI with gadolinium reveals enhancement in the left temporal lobe
- Results of initial cerebrospinal fluid (CSF) polymerase chain reaction (PCR) for HSV-1 and HSV-2 return negative
- After 3 days, the patient is now oriented to name and follows simple commands

QUESTION #1

PREVIEW QUESTION

What is the next step in the management of this patient?

A. Perform a brain biopsy of the left temporal lobe
B. Obtain new CSF for HSV PCR testing
C. Send serum for HSV IgG antibodies
D. Repeat brain MRI
E. Discontinue acyclovir

CASE #1 (Continued)

- Repeat CSF analysis on day #4 reveals that the PCR is now positive for HSV-1
- The patient continues to improve and completes a 14-day course of acyclovir
- One month later, he presents again with fever and confusion
- CSF analysis reveals a WBC count of 30/mm^3 (all lymphocytes) with normal glucose and mildly elevated protein; CSF PCR tests for HSV-1 and HSV-2 are negative

QUESTION #2

13

Which of the following is the most likely reason for his second presentation of encephalitis?

A. Relapse of herpes simplex encephalitis
B. Development of acyclovir-resistant herpes simplex encephalitis
C. Development of autoimmune encephalitis
D. Acyclovir neurotoxicity

Herpes Simplex Encephalitis

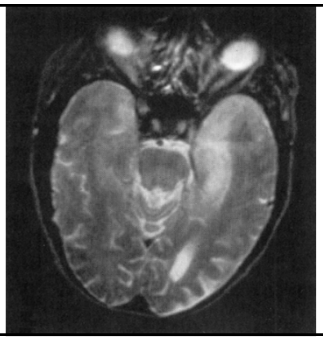
14

- Epidemiology
  - Among the most severe of all human viral infections of brain; >70% mortality with no or ineffective therapy
  - Accounts for 10-20% of encephalitis viral infections
  - Occurs throughout the year and in patients of all ages
  - Described following whole brain irradiation or following a neurosurgical procedure
  - Majority in adults caused by HSV-1
- Clinical features
  - Fever, personality change, dysphasia, autonomic dysfunction

Herpes Simplex Encephalitis

15

- Electroencephalography
  - Sensitivity of ~84%
  - Periodic lateralizing epileptiform discharges (PLEDs)
- Neuroimaging
  - Computed tomography (lesions in 50-75% of patients)
  - Magnetic resonance imaging (>90% of cases)
- Brain biopsy
  - Inflammation with widespread hemorrhagic necrosis
  - Intranuclear inclusions (50% of patients)
  - Reserve for patients not responding to acyclovir therapy



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Herpes Simplex Encephalitis

17

- Cerebrospinal fluid (CSF) findings
  - Lymphocytic pleocytosis (mean of 100 cells/mm^3)
  - Presence of red blood cells (25% never have RBCs)
  - Elevated protein
  - Normal in 5-10% of patients on first evaluation
- CSF Polymerase Chain Reaction
  - Sensitivity 98%
  - Specificity 94%
  - Positive predictive value 95%
  - Negative predictive value 98%
  - If negative, may need new CSF sample in 3-7 days

Herpes Simplex Encephalitis

18

- Acyclovir is the antiviral agent of choice
  - Mortality of 19% at 6 months
  - Mortality of 28% at 18 months
  - Morbidity ~50%
- Dosage in adults is 30 mg/kg/day in 3 divided dosages (in those with normal renal function) for 14-21 days
- No added benefit on oral valacyclovir (3-month course) after standard course of acyclovir

24 – Encephalitis including West Nile and Rabies

Speaker: Allan Tunkel, MD

Other Herpesviruses

- Varicella-zoster virus
  - Can occur without rash (zoster sine herpete)
  - Focal neurologic deficits and seizures
  - CSF PCR; lower sensitivity in those with vasculopathy so also check CSF antibodies
  - MRI/MRA large vessel vasculitis and ischemia
  - Acyclovir (however, no controlled studies) + ?corticosteroids (if vasculopathy)
- Epstein-Barr virus
  - Encephalitis and/or transverse myelitis
  - Serologic testing; CSF PCR (may have false-positives)
  - Corticosteroids?

Other Herpesviruses

- Human herpesvirus 6
  - Immunocompromised patients, but seen in children
  - CSF PCR (sensitivity >95%); high rate of detection in healthy adults (PPV only 30%)
  - Ganciclovir or foscarnet
- B virus
  - Bite or scratch from old world primates (macaques)
  - Vesicular eruption at site; neurologic disease in 3-7 days
  - Culture and PCR at site of bite; CSF PCR
  - Prophylactic valacyclovir
  - Therapy: acyclovir, valacyclovir, or ganciclovir

Other Herpesviruses

- Cytomegalovirus
  - Immunocompromised (especially HIV)
  - Evidence of widespread disease
  - CSF PCR (sensitivity 82-100%; specificity 86-100%)
  - MRI may reveal subependymal gadolinium enhancement and non-specific white matter changes
  - Ganciclovir + foscarnet

CASE #2

PREVIEW QUESTION

- 72-year-old man presents in late August with complaints of fever, chills, and weakness beginning 1 week earlier; on the day of admission, he becomes confused
- He lives in central New Jersey, where he and his wife have a horse farm; they often noted mosquito and tick bites
- On presentation, he is somnolent and unable to provide a complete history, although denies headache and stiff neck

CASE #2

PREVIEW QUESTION

- T 103.1°F, P 110, RR 16, BP 110/70 mmHg
- No rash or petechiae, neck supple, no adenopathy, lungs clear, heart without murmurs, abdomen normal
- On neurologic exam, he is oriented to person only. Cranial nerves intact. Motor strength 4/5 UE, and 3/5 LLE and 2/5 RLE. Sensation intact. Reflexes diminished in LE

QUESTION #3

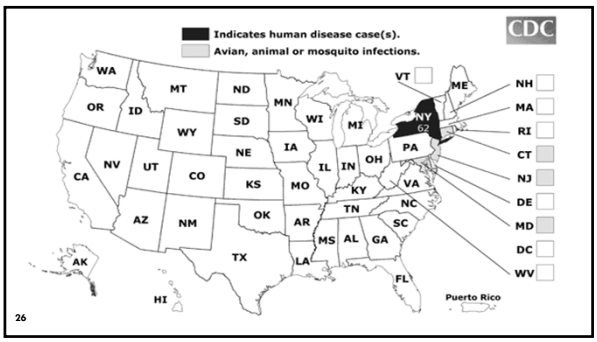
PREVIEW QUESTION

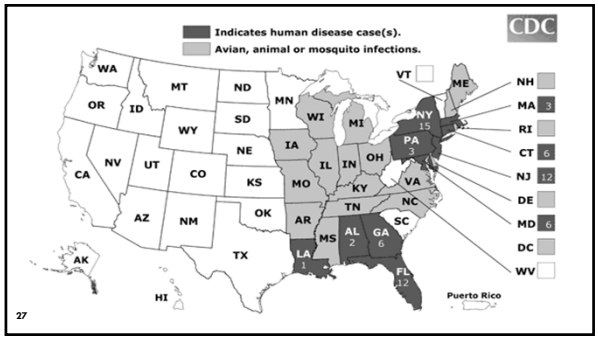
Which of the following tests is most likely to establish the etiology of this patient's encephalitis?

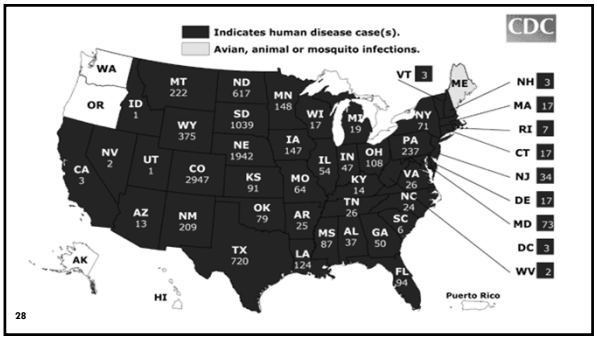
A. Serum IgM
B. Serum polymerase chain reaction
C. Cerebrospinal fluid IgM
D. Cerebrospinal fluid polymerase chain reaction
E. Brain MRI

West Nile Virus (WNV) Encephalitis

- First US cases reported in 1999 in New York City
- Birds are main reservoirs
- Mosquito vector
- Other modes of transmission
  - Transplanted organs
  - Blood transfusions
  - Breast milk
  - Transplacental
  - Occupational







WNV Human Cases Reported To CDC

Year	Total Human Cases	Neuroinvasive	Deaths
2007	3630	1227	124
2009	720	386	32
2011	712	486	43
2012	5674	2873	286
2014	2122	1283	85
2018	2544	1594	137
2019	971	633	60
2021	2911	2008	227
2022	1126	816	90

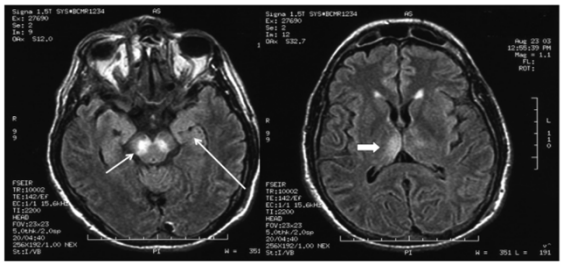
West Nile Virus Clinical Syndromes

- No clinical illness or symptoms (~80%)
- West Nile Fever (~20%)
- Severe WNV Disease (1 in 150)
  - Meningitis (37%)
  - Encephalitis/Meningoencephalitis (53%)
  - Poliomyelitis-like flaccid paralysis (7%)

West Nile Virus Encephalitis

31

- Diagnosis
  - Serum IgM antibody (8-14 days of illness onset)
  - CSF reveals lymphocytic pleocytosis and elevated protein; glucose is normal
  - CSF IgM (positive in >90%)
  - CSF PCR (<60% sensitivity)
  - Neuroimaging



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West Nile Virus Encephalitis

33

- Therapy
  - Supportive
  - Ribavirin, interferon alpha, and IVIG don't work

Other Arboviruses

34

- St. Louis encephalitis virus
  - Mosquito vector; bird reservoir
  - Endemic in western US; periodic outbreaks in eastern US
  - Urinary symptoms early; SIADH (one-third of cases)
  - Serology; CSF IgM
- Japanese encephalitis virus
  - Most common cause of mosquito-borne encephalitis worldwide (SE Asia, China, India, Nepal, Korea, Japan)
  - Mainly children; rice fields where vectors breed
  - Seizures and parkinsonian features; poliomyelitis-like flaccid paralysis
  - Serology; CSF IgM

Other Arboviruses

35

- Powassan virus
  - Tick vector (Ixodes scapularis in NE); rodent reservoir; New England
  - Prevalence among animal hosts and vectors increasing
  - Parkinsonism, involvement of basal ganglia and thalamus common
  - Serology; CSF IgM; metagenomic sequencing
- Tickborne encephalitis virus
  - Tick vector, rodent reservoir; drinking unpasteurized milk or cheese; solid organ transplantation; rituximab
  - Eastern Russia, central Europe
  - Poliomyelitis-like paralysis
  - Serology; CSF IgM
  - Anti-TBE immune globulin for post-exposure prophylaxis

Other Arboviruses

36

- La Crosse virus
  - Mosquito vector; chipmunk and squirrel reservoir
  - Midwest and eastern US; woodlands
  - 2nd most common arbovirus in US
  - Serology; CSF IgM; SIADH (~20%)
- Eastern equine encephalitis virus
  - Mosquito vector; bird reservoir in North America; organ transplantation
  - Primarily Atlantic and Gulf coast states
  - Abrupt onset with fulminant course; seizures common
  - High case-fatality rate (50-70%)
  - Serologic testing
  - High CSF WBC count (>1000 cells/mm^3)

Measles Virus

37

- Acute disseminated encephalomyelitis
  - Usually 1-2 weeks after exposure; incidence 1 per 1,000 infections
  - Fever, fatigue, headache, nausea, vomiting
- Inclusion body encephalitis
  - Unvaccinated children and adults; immunocompromised
  - Symptoms 1-6 months after exposure; decreased consciousness, focal signs, seizures
- Subacute sclerosing panencephalitis
  - 6-10 years after infection (range 3-35 years)
  - Behavioral changes, cognitive impairment at presentation
  - Myoclonus, seizures, neurologic deterioration (coma and death) later

BioFire FilmArray

38

Bacteria	Viruses	Fungi
Escherichia coli K1	Cytomegalovirus	*Cryptococcus neoformans/gatti*
Haemophilus influenzae	Enterovirus	
Listeria monocytogenes	Herpes simplex virus 1	
Neisseria meningitidis	Herpes simplex virus 2	
Streptococcus agalactiae	Human herpesvirus 6	
Streptococcus pneumoniae	Human parechovirus	
	Varicella zoster virus	

Metagenomic Next-Generation Sequencing

- Consider for encephalitis cases in which no cause identified
- Allows unbiased or agnostic pan-species molecular diagnostics
- In one study of 204 patients (58 with meningitis or encephalitis), NGS identified an infectious cause in 22% not identified by clinical testing (Wilson et al. NEJM 2019;380:2327).
- Possible role in testing of enigmatic cases

CASE #3

40

- 36-year-old man is on a hiking trip in northern California and is bitten on his lower leg by a skunk
- Upon presentation, he is afebrile and has several puncture wounds on his right lower extremity
- You irrigate with wounds with soap and povidone iodine, and administer a tetanus booster
- He has never been vaccinated against rabies

QUESTION #4

41

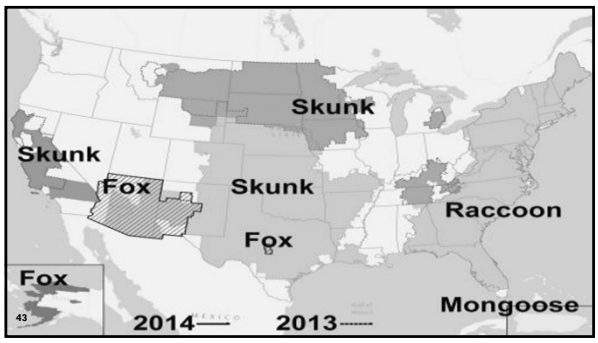
In addition to administration of rabies vaccine, what is the most appropriate management?

A. Rabies immune globulin at the bite sites
B. Rabies immune globulin in the deltoid muscle
C. Rabies immune globulin in the buttocks
D. Rabies immune globulin intraperitoneally
E. Nothing further is indicated

Rabies

42

- Transmitted by bite of infected animal
  - Dogs are principal vector (98% of cases) worldwide
  - May be transmitted after unrecognized bites by bats
- Rare and sporadic in US – 125 cases from 1960-2018
  - 36 (28%) attributed to dog bite during international travel
  - 89 acquired in US; 62 (70%) attributed to bats
- Worldwide in distribution (50,000-100,000 annual deaths)
- Incubation period 20-90 days



Rabies

- Encephalitic (furious) form (80%)
  - Agitation alternating with lucidity
  - Hypersalivation
  - Hydrophobia
  - Bizarre behavior
  - Disorientation, stupor, coma, death
- Paralytic (dumb) form
  - Ascending paralysis; early muscle weakness
  - Later cerebral involvement

Rabies

- Diagnosis
  - Culture and RT-PCR of saliva
  - Immunofluorescent detection of viral antigens and RT-PCR in nuchal biopsy
  - CSF antibodies and RT-PCR
  - Brain biopsy (antigen detection/Negri bodies)
- Therapy
  - Supportive
  - Milwaukee Protocol has failed in 26 cases
  - Post-exposure prophylaxis (rabies immune globulin at bite site and vaccine)

CASE #4

- 22-year-old woman with no significant past medical or psychiatric history develops headache and low-grade fever followed by confusion and hallucinations
- On presentation, she is afebrile and disoriented; she has evidence of abnormal movements of her mouth and face
- CSF analysis reveals a WBC count of 20/mm^3, with normal glucose and protein
- Brain MRI is normal

CASE #4

- EEG reveals diffuse slowing
- CSF Gram stain and cultures, and PCR for HSV are negative
- A diagnosis of autoimmune encephalitis is considered, and appropriate studies sent
- CSF returns positive for antibodies to the NR1 subunit of the N-methyl-D-aspartate receptor
- Corticosteroids and IV immune globulin are initiated

QUESTION #5

Which of the following studies should now be performed?

A. CT scan of the chest
B. CT scan of the abdomen
C. Carotid ultrasound
D. Renal ultrasound
E. Transvaginal ultrasound

ENCEPHALITIS
Noninfectious Etiologies

- Acute disseminated encephalomyelitis (ADEM)
  - 10-15% of encephalitis cases in US
  - Post-infectious
  - Symptoms 2-4 weeks after trigger
  - MRI bilateral asymmetric T2 hyperintensity in subcortical and deep white matter
  - Corticosteroids
- Anti-N-methyl-D-aspartate receptor (Anti-NMDAR) encephalitis

Anti-NMDAR Encephalitis

- Neuronal antibody-associated encephalitis
- In California Encephalitis Project, this entity exceeded that of any single viral entity in children and was also seen in adults
- Female to male ratio of about 8:2
- 37% of patients younger than 18 years at presentation

Anti-NMDAR Encephalitis

- Abnormal behavior (psychiatric symptoms)
- Cognitive dysfunction
- Seizures
- Movement disorders (orofacial dyskinesias)
- Decreased level of consciousness
- Autonomic instability
- May be associated with ovarian teratoma (in ~50% of patients older than 18 years)

Anti-NMDAR Encephalitis

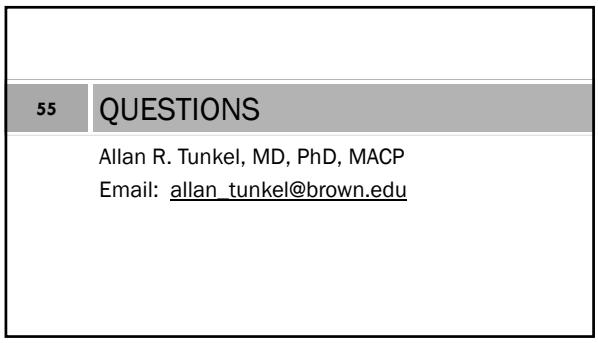
- CSF analysis
  - Mild pleocytosis (median WBC 23/mm^3); normal glucose and protein
  - Specific IgG antibodies to GluN1 subunit of the NMDAR in CSF and serum
  - Viral causes of encephalitis (e.g., HSV) are associated with development of NMDAR antibodies

Anti-NMDAR Encephalitis

- Neuroimaging
  - Abnormal in 50%, but nonspecific
  - T2 and FLAIR hyperintensity (hippocampi, cerebellar or cerebral cortex, frontobasal and insular regions, basal ganglia, brainstem)
- EEG
  - Diffuse or focal slowing
  - Occasional superimposed epileptic activity

Anti-NMDAR Encephalitis

- Therapy
  - First-line
    - Corticosteroids
    - Intravenous immunoglobulin
    - Plasma exchange
  - Second-line
    - Rituximab or cyclophosphamide
  - Female patients should be evaluated for ovarian teratoma; if present, remove
- 75% of patients have mild sequelae or fully recover; relapse in up to 24%



BR3

Board Review Session 3

Drs. Auwaerter (Moderator), Bell, Dhanireddy, Ghanem, Klompas, and Trautner

BR3 – Board Review: Day 3

Moderator: Paul Auwaerter, MD

Board Review: Day 3

Moderator: Paul Auwaerter, MD
Faculty: Drs. Bell, Dhanireddy, Ghanem, Klompas, and Trautner

8/2/2023

BOARD REVIEW DAY 3

#31 A 58-year-old male presents with a four-month history of migratory polyarthralgia and then develops intermittent low-grade fevers, weight loss (15 lb), fatigue and chronic diarrhea with greasy and foul-smelling stools.

He lacks risk factors for HIV infection.

He was born and resides in a farming community in central California and is employed as an accountant.

1 of 4

BOARD REVIEW DAY 3

#31 His history is only notable for hypertension and hyperlipidemia, for which he has received medications since his mid-40s.

On physical examination, he has diffuse abdominal tenderness, mild peripheral lymphadenopathy, and a skin exam wherein he appears tanned but has no recent sun exposure.

Laboratory testing reveals anemia, hypoalbuminemia, and elevated acute-phase reactants.

2 of 4

BOARD REVIEW DAY 3

#31 Which of the following tests would most likely lead to a diagnosis?

A) Small bowel biopsy

B) Serological testing for tissue transglutaminase (tTG) and deamidated gliadin peptide (DGP) antibodies

C) FDA-approved multiplex panel for enteric pathogens

D) Stool ova and parasite collections x 3, including trichrome staining

E) Large bowel biopsy

3 of 4

BOARD REVIEW DAY 3

#31 Which of the following tests would most likely lead to a diagnosis?

A) Small bowel biopsy***

B) Serological testing for tissue transglutaminase (tTG) and deamidated gliadin peptide (DGP) antibodies

C) FDA-approved multiplex panel for enteric pathogens

D) Stool ova and parasite collections x 3, including trichrome staining

E) Large bowel biopsy

4 of 4

BOARD REVIEW DAY 3

#32 An 18-year-old cis-gender woman presents to her primary care physician's office complaining of lower abdominal pain with low-grade fevers and chills.

She denies any other symptoms.

Her last menstrual period was two weeks earlier, and it was normal. She is in a monogamous relationship with a male partner.

1 of 4

BOARD REVIEW DAY 3 INFECTIOUS DISEASE BOARD REVIEW 2023

#32 **On examination, her temperature was 38.3°C, and she has mild abdominal tenderness on deep palpation, and cervical motion tenderness on bimanual examination.**

Her urine pregnancy test was negative, and a wet mount of vaginal secretions was unremarkable.

2 of 4

BOARD REVIEW DAY 3 INFECTIOUS DISEASE BOARD REVIEW 2023

#32 **In addition to doxycycline and metronidazole, which of the following antibiotics is most appropriate to treat her infection as an outpatient?**

A) Ertapenem IM

B) Cefotetan IV

C) Azithromycin PO

D) Levofloxacin PO

E) Ceftriaxone IM

3 of 4

BOARD REVIEW DAY 3 INFECTIOUS DISEASE BOARD REVIEW 2023

#32 **In addition to doxycycline and metronidazole, which of the following antibiotics is most appropriate to treat her infection as an outpatient?**

A) Ertapenem IM

B) Cefotetan IV

C) Azithromycin PO

D) Levofloxacin PO

E) Ceftriaxone IM***

4 of 4

BOARD REVIEW DAY 3 INFECTIOUS DISEASE BOARD REVIEW 2023

#33 **An 80-year-old resident of a nursing home has severe dementia, type 2 diabetes mellitus and a chronic indwelling Foley catheter which is in place to manage his persistent incontinence.**

He has no remarkable medical history and is quite healthy except for his dementia.

He has received antibiotics for presumed urinary tract infection twice in the last year.

1 of 4

BOARD REVIEW DAY 3 INFECTIOUS DISEASE BOARD REVIEW 2023

#33 **The nursing home staff decided to obtain a urinalysis and urine culture: they call you because the urine culture is growing Candida albicans with a colony count of 100,000 cfu/ml.**

His UA shows 30-40 WBC and 10-20 RBC per HPF, with a 1+ leukocyte esterase.

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

2 of 4

BOARD REVIEW DAY 3 INFECTIOUS DISEASE BOARD REVIEW 2023

#33 **What would you recommend?**

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

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

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

D) Change Foley catheter and IV caspofungin for 1 week

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

3 of 4

BOARD REVIEW DAY 3 | INFECTIOUS DISEASE BOARD REVIEW 2023

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

4 of 4

BOARD REVIEW DAY 3 | INFECTIOUS DISEASE BOARD REVIEW 2023

#34 A 64-year-old healthy man with benign prostatic hypertrophy and Type 2 diabetes mellitus who had a hemorrhagic stroke one month ago presented to the emergency room with high fever, chills, and difficulty urinating.

His temperature was 40.2° C, blood pressure 80/50 mm Hg, pulse 124/min.

The remainder of the exam was normal except for mild confusion and a tender distended urinary bladder to palpation.

1 of 4

BOARD REVIEW DAY 3 | INFECTIOUS DISEASE BOARD REVIEW 2023

#34 Laboratory Tests:

- WBC: 22,000/mm^3 (94% PMN's, 6% lymphs)
- Hgb:12.4, platelets 164,000/mm3
- Creatinine: 4 mg/dL
- Glucose 140 mg/dL
- Liver function tests: normal
- Urinalysis: 100-200 WBCs

The patient is volume resuscitated, but requires levophed to maintain an adequate blood pressure.

2 of 4

BOARD REVIEW DAY 3 | INFECTIOUS DISEASE BOARD REVIEW 2023

#34 Which of the following treatments on admission has been most clearly shown to improve survival for this febrile, hypotensive syndrome?

A) Timing of initial effective antimicrobial therapy

B) Low-dose dopamine

C) Corticosteroids

D) Central venous catheter to measure venous oxygen saturation

E) Tight glucose control

3 of 4

BOARD REVIEW DAY 3 | INFECTIOUS DISEASE BOARD REVIEW 2023

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A) Timing of initial effective antimicrobial therapy***

B) Low-dose dopamine

C) Corticosteroids

D) Central venous catheter to measure venous oxygen saturation

E) Tight glucose control

4 of 4

BOARD REVIEW DAY 3 | INFECTIOUS DISEASE BOARD REVIEW 2023

#35 A 65-year-old woman with long-standing diabetes mellitus and congestive heart failure due to ischemic cardiomyopathy received the 23-valent pneumococcal polysaccharide vaccine at the age of 45.

1 of 3

BOARD REVIEW DAY 3 | INFECTIOUS DISEASE BOARD REVIEW 2023

#35 What is the most appropriate next step?

A) No additional pneumococcal vaccines

B) 13-valent pneumococcal conjugate vaccine now

C) 20-valent pneumococcal conjugate vaccine now

D) 23-valent pneumococcal polysaccharide vaccine now and again in 5 years

E) 23-valent pneumococcal polysaccharide vaccine now

2 of 3

BOARD REVIEW DAY 3 | INFECTIOUS DISEASE BOARD REVIEW 2023

#35 What is the most appropriate next step?

A) No additional pneumococcal vaccines

B) 13-valent pneumococcal conjugate vaccine now

C) 20-valent pneumococcal conjugate vaccine now***

D) 23-valent pneumococcal polysaccharide vaccine now and again in 5 years

E) 23-valent pneumococcal polysaccharide vaccine now

3 of 3

BOARD REVIEW DAY 3 | INFECTIOUS DISEASE BOARD REVIEW 2023

#36 You are charged with leading an initiative to decrease nosocomial infections in non-ICU patients.

It is standard practice in your hospital to bathe ICU patients daily with chlorhexidine.

You wonder if this practice ought to be extended to include non-ICU patients.

1 of 3

BOARD REVIEW DAY 3 | INFECTIOUS DISEASE BOARD REVIEW 2023

#36 This intervention is likely to be most effective in what population?

A) All non-ICU inpatients

B) All inpatients on oncology wards

C) All inpatients with central lines

D) All obstetric inpatients

E) All inpatients with prosthetic material in situ (e.g., joint replacements, mechanical valves, pacemakers, etc. placed at any time)

2 of 3

BOARD REVIEW DAY 3 | INFECTIOUS DISEASE BOARD REVIEW 2023

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3 of 3

BOARD REVIEW DAY 3 | INFECTIOUS DISEASE BOARD REVIEW 2023

#37 A 55-year-old woman from rural Connecticut seeks your advice on what to do about a tiny tick she removed from her abdomen five days previously.

She does not know how long the tick had been there because she had been on a camping trip and not bathing regularly.

She takes prednisone and methotrexate for her rheumatoid arthritis.

She feels well and has no skin lesions.

1 of 3

BOARD REVIEW DAY 3 | INFECTIOUS DISEASE BOARD REVIEW 2023

#37 **Assuming that the tick was likely Ixodes scapularis, you would:**

A) Prescribe a single 200 mg dose of doxycycline.

B) Prescribe a 10-day course of doxycycline, 100 mg BID.

C) Prescribe a single 500 mg dose of amoxicillin.

D) Prescribe a 10-day course of amoxicillin 500 mg TID.

E) Prescribe nothing unless compatible manifestations develop.

2 of 3

BOARD REVIEW DAY 3 | INFECTIOUS DISEASE BOARD REVIEW 2023

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C) Prescribe a single 500 mg dose of amoxicillin.

D) Prescribe a 10-day course of amoxicillin 500 mg TID.

E) Prescribe nothing unless compatible manifestations develop.***

3 of 3

BOARD REVIEW DAY 3 | INFECTIOUS DISEASE BOARD REVIEW 2023

#38 **A young cis-gender woman is diagnosed with pharyngeal gonorrhea.**

Which of the following antimicrobials has the highest efficacy when treating this infection?

A) Cefixime

B) Ceftriaxone

C) Doxycycline

D) Spectinomycin

E) Ciprofloxacin

1 of 2

BOARD REVIEW DAY 3 | INFECTIOUS DISEASE BOARD REVIEW 2023

#38 **A young cis-gender woman is diagnosed with pharyngeal gonorrhea.**

Which of the following antimicrobials has the highest efficacy when treating this infection?

A) Cefixime

B) Ceftriaxone***

C) Doxycycline

D) Spectinomycin

E) Ciprofloxacin

2 of 2

BOARD REVIEW DAY 3 | INFECTIOUS DISEASE BOARD REVIEW 2023

#39 **You are given the task of developing a set of initial targets for preventing inappropriate antibiotic use by your hospital's new Antibiotic Stewardship team.**

Eliminating inappropriate uses of antibiotics is your mandate.

1 of 3

BOARD REVIEW DAY 3 | INFECTIOUS DISEASE BOARD REVIEW 2023

#39 **Of the following, which of the following should you recommend for elimination?**

A) Treatment of asymptomatic bacteriuria in pregnancy

B) Treatment of asymptomatic bacteriuria in patients undergoing joint arthroplasty

C) Treatment of asymptomatic bacteriuria in patients undergoing urologic procedures where mucosal bleeding is expected

D) Treatment of asymptomatic bacteriuria within 1 month of renal transplantation

2 of 3

BOARD REVIEW DAY 3 | INFECTIOUS DISEASE BOARD REVIEW 2023

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D) Treatment of asymptomatic bacteriuria within 1 month of renal transplantation

3 of 3

BOARD REVIEW DAY 3 | INFECTIOUS DISEASE BOARD REVIEW 2023

#40 **A 24-year-old woman had completed her fifth course of cytotoxic chemotherapy for a poorly differentiated osteosarcoma.**

She had an absolute neutrophil count of 5/cu mm and platelet count of 7,000/cu mm when she developed the sudden onset of fever to 40°C but was otherwise stable.

1 of 5

BOARD REVIEW DAY 3 | INFECTIOUS DISEASE BOARD REVIEW 2023

#40 **The percutaneously inserter central catheter (PICC) exit site in her right upper arm and proximal skin were non-tender. There is no exit site inflammation or exudate.**

Two blood cultures were drawn through the PICC line and one culture was drawn peripherally.

The laboratory reports the next morning that the 2 blood cultures drawn through the line are positive for an organism.

2 of 5

BOARD REVIEW DAY 3 | INFECTIOUS DISEASE BOARD REVIEW 2023

#40 **The peripheral culture is negative at 24 hours.**

Lack of another source of infection has raised the likelihood that the patient has catheter-acquired sepsis.

The patient and the oncologist are hopeful that the catheter might be salvaged, particularly while the patient is thrombocytopenic.

3 of 5

BOARD REVIEW DAY 3 | INFECTIOUS DISEASE BOARD REVIEW 2023

#40 **Which of the following organisms would make removal of the catheter mandatory?**

A) Candida albicans sensitive to fluconazole

B) Enterococcus faecalis sensitive to ampicillin

C) E. coli sensitive to cephalosporins

D) Streptococcus mitis sensitive to penicillin

E) Staphylococcus epidermidis sensitive to vancomycin

4 of 5

BOARD REVIEW DAY 3 | INFECTIOUS DISEASE BOARD REVIEW 2023

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5 of 5

BR3 – Board Review: Day 3

Moderator: Paul Auwaerter, MD

BOARD REVIEW DAY 3 — INFECTIOUS DISEASE BOARD REVIEW 2023

#41 A 31-year-old male first grade school teacher developed fever, rhinorrhea, and malaise for several days, followed by a progressively worsening dry cough.

He has now been sick for 12 days.

His chest x-ray was normal.

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

1 of 4

BOARD REVIEW DAY 3 — INFECTIOUS DISEASE BOARD REVIEW 2023

#41 A nasopharyngeal swab, sent for Bordetella pertussis PCR, was positive.

He was previously in excellent health.

He received all of his childhood immunizations but nothing subsequently.

2 of 4

BOARD REVIEW DAY 3 — INFECTIOUS DISEASE BOARD REVIEW 2023

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

A) His clinical syndrome is not due to pertussis if his chest x-ray is normal
B) He should not return to the classroom until his PCR is negative
C) His students should be offered macrolide chemoprophylaxis. Students who refuse a macrolide should be excused from school for 21 days
D) If the teacher was immunized as a child, this is likely a false positive PCR
E) All his household contacts, regardless of age and vaccine status, should receive prophylaxis

3 of 4

BOARD REVIEW DAY 3 — INFECTIOUS DISEASE BOARD REVIEW 2023

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

A) His clinical syndrome is not due to pertussis if his chest x-ray is normal
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D) If the teacher was immunized as a child, this is likely a false positive PCR
E) All his household contacts, regardless of age and vaccine status, should receive prophylaxis***

4 of 4

BOARD REVIEW DAY 3 — INFECTIOUS DISEASE BOARD REVIEW 2023

#42 A 67-year-old woman from Guatemala is admitted to the hospital with fever, sweats, weight loss, and swelling of the right neck.

She has no headache, no tooth pain, no shortness of breath, and no cough.

Exam is notable for a cachectic, chronically ill looking woman with a plum sized protuberance on the right posterior cervical triangle of the neck. Dentition is normal.

1 of 4

BOARD REVIEW DAY 3 — INFECTIOUS DISEASE BOARD REVIEW 2023

#42 There is no drainage from the lesion. She has no splenomegaly or swollen glands in the rest of the body.

Radiograph of the chest is clear. She denies contact with animals.

An interferon gamma release assay is positive. An HIV test is negative.

2 of 4

BOARD REVIEW DAY 3 | INFECTIOUS DISEASE BOARD REVIEW 2023

#42 What kind of room will you place the patient in?

A) Standard pressure single patient room
B) Standard pressure multiple patient room
C) Negative pressure single patient room
D) Negative pressure multiple patient room
E) Positive pressure single patient room

3 of 4

BOARD REVIEW DAY 3 | INFECTIOUS DISEASE BOARD REVIEW 2023

#42 What kind of room will you place the patient in?

A) Standard pressure single patient room
B) Standard pressure multiple patient room
C) Negative pressure single patient room***
D) Negative pressure multiple patient room
E) Positive pressure single patient room

4 of 4

BOARD REVIEW DAY 3 | INFECTIOUS DISEASE BOARD REVIEW 2023

#43 In otherwise excellent health, a 66-year-old physician in Maryland has a syncopal episode during a coffee break at a large medical meeting.

His pulse is found to be 28 bpm, which speeds up over the next few minutes as he regains consciousness.

In the Emergency Room, he is in complete heart block. A temporary transvenous pacemaker is inserted to increase his heart rate to 60 bpm.

1 of 5

BOARD REVIEW DAY 3 | INFECTIOUS DISEASE BOARD REVIEW 2023

#43 The ER physician astutely elicits the history that the physician likes to garden in a Maryland suburban town of Bethesda and pulls ticks off from time to time.

Over the past few weeks, he has been feeling fatigued with muscle aches. He is started on oral doxycycline 2 days earlier.

The Borrelia burgdorferi ELISA is positive, and the subsequently triggered Western blots returned positive for both IgM and IgG antibodies.

2 of 5

BOARD REVIEW DAY 3 | INFECTIOUS DISEASE BOARD REVIEW 2023

#43 You are called for Infectious Disease advice as part of the pre-op evaluation the evening before a permanent pacemaker is scheduled to be inserted.

He is still in complete heart block, and his non-paced ventricular rate is still 40 on day 2 of hospitalization.

The patient is alert and oriented and making urine.

He feels fine. You find nothing remarkable on his exam or in his routine pre-op labs.

3 of 5

BOARD REVIEW DAY 3 | INFECTIOUS DISEASE BOARD REVIEW 2023

#43 You would recommend which of the following:

A) Continue doxycycline, and perform the permanent pacemaker insertion as scheduled
B) Change to ceftriaxone, and perform the permanent pacemaker insertion as scheduled
C) Change to ceftriaxone; cancel the pacemaker insertion
D) Continue doxycycline, add prednisone 40 mg daily and cancel the pacemaker insertion

4 of 5

BOARD REVIEW DAY 3 | INFECTIOUS DISEASE BOARD REVIEW 2023

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A) Continue doxycycline, and perform the permanent pacemaker insertion as scheduled

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C) Change to ceftriaxone; cancel the pacemaker insertion***

D) Continue doxycycline, add prednisone 40 mg daily and cancel the pacemaker insertion

5 of 5

BOARD REVIEW DAY 3 | INFECTIOUS DISEASE BOARD REVIEW 2023

#44 A 40-year-old cis-gender man from India was visiting New York City and was advised by a commercial sex worker to seek medical attention for a lesion she saw on the shaft of his penis.

The lesion had been present for several months and was painless.

He had otherwise been well.

1 of 4

BOARD REVIEW DAY 3 | INFECTIOUS DISEASE BOARD REVIEW 2023

#44 On examination, a 2x3-cm ulcerated lesion with a cobblestone base and rolled margin was seen on the penile shaft near the coronal sulcus.

There was no inguinal adenopathy or fever.

Punch biopsy was done because of concern about squamous carcinoma and revealed macrophages with numerous intracellular safety pin-like structures on Wright-Giemsa stain.

Bacterial culture grew Staphylococcus epidermidis.

2 of 4

BOARD REVIEW DAY 3 | INFECTIOUS DISEASE BOARD REVIEW 2023

#44 Which of the following is the most likely etiologic agent?

A) Chlamydia trachomatis L1, L2 or L3

B) Klebsiella granulomatis (Calymmatobacterium granulomatis)

C) Haemophilus ducreyi

D) Histoplasma capsulatum

E) Treponema carateum

3 of 4

BOARD REVIEW DAY 3 | INFECTIOUS DISEASE BOARD REVIEW 2023

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E) Treponema carateum

4 of 4

BOARD REVIEW DAY 3 | INFECTIOUS DISEASE BOARD REVIEW 2023

#45 A 52-year-old man has been in the ICU following a cocaine related stroke.

He was intubated following his stroke, developed Staph epidermidis bacteremia from a PICC line (peripherally inserted central catheter), and is now off antibiotics (7 day course of daptomycin has been completed) ready to move to the rehabilitation floor.

He has a Foley catheter and a peripheral IV line.

The patient is alert and oriented and has no new complaints.

1 of 5

BOARD REVIEW DAY 3 INFECTIOUS DISEASE BOARD REVIEW 2023

#45 **The resident preparing to transfer the patient calls an ID consult because the urine in the Foley bag is cloudy.**

The patient is afebrile with normal vital signs, no new physical findings, and he does not have pain over his bladder and no flank pain.

The medical resident has obtained a urinalysis on fresh urine from the Foley catheter.

There are 50-75 WBCs per high power field and 5-10 RBCs with 2+ bacteria. Culture is sent.

2 of 5

BOARD REVIEW DAY 3 INFECTIOUS DISEASE BOARD REVIEW 2023

#45 **There are 50-75 WBCs per high power field and 5-10 RBCs with 2+ bacteria. Culture is sent.**

There are no changes in his complete blood count or chemistry profile.

The patient has no known antibiotic allergies.

3 of 5

BOARD REVIEW DAY 3 INFECTIOUS DISEASE BOARD REVIEW 2023

#45 **What would you suggest?**

A) No change in regimen: follow for 48 hours with Foley in place, pending urine culture result and treat with antibiotic according to culture

B) Leave Foley in place; do not treat bacilluria

C) Replace the Foley and treat empirically with ciprofloxacin

D) Remove the Foley and do a voiding test to determine if Foley is necessary; no antibiotic therapy

E) Remove the Foley and do a voiding test to determine if Foley is necessary; treat empirically with ciprofloxacin

4 of 5

BOARD REVIEW DAY 3 INFECTIOUS DISEASE BOARD REVIEW 2023

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5 of 5

25

Ticks, Mites, Lice, and the Diseases They Transmit

Dr. Paul Auwaerter

25 – Ticks, Mites, Lice and The Diseases They Transmit

Speaker: Paul Auwaerter, MD

IDBR INFECTIOUS DISEASE BOARD REVIEW LIVE/VIRTUAL AUGUST 19-23 2023

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

7/11/2023

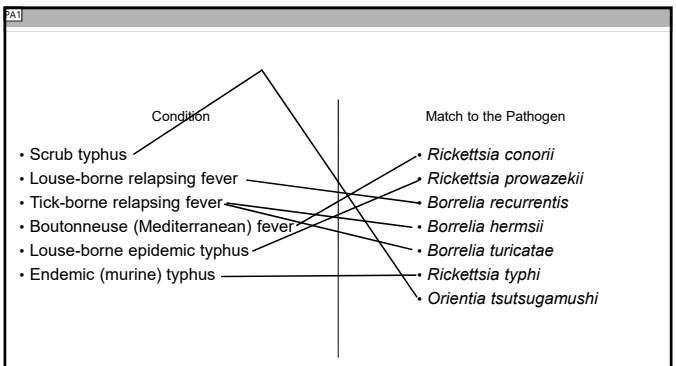
IDBR INFECTIOUS DISEASE BOARD REVIEW LIVE/VIRTUAL AUGUST 19-23 2023

Disclosures of Financial Relationships with Relevant Commercial Interests

- **Consultant: Gilead, Shionogi**
- **Research: Pfizer**
- **Ownership Interest: Johnson & Johnson, Wellstat**

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

25 – Ticks, Mites, Lice and The Diseases They Transmit

Speaker: Paul Auwaerter, MD

The Major Tick-borne Diseases of North America

- Lyme disease (separate talk)
- Rocky Mountain spotted fever (RMSF)
- Ehrlichioses
- Anaplasmosis
- Relapsing fever (*Borrelia* spp.)
- Babesia spp.

Other Tick-borne Diseases of North America

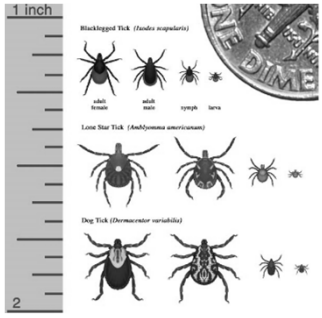
- Tick paralysis
- Southern tick associated rash illness (STARI)
- Viruses:
  - Powassan (Deer Tick Virus Lineage II, flavivirus)
  - Colorado tick fever (coltivirus)
  - Heartland virus (phlebovirus)
  - Bourbon virus (thogotovirus)
- Spotted Fever Group Rickettsia (partial)
  - R. parkeri
  - Rickettsia 364D aka R. philippii (Pacific Coast tick fever)
- Coxiella 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

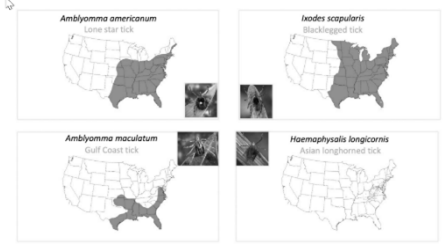
Top Ticks in North American That Transmit Human Pathogens (Ixodidae)



#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

Expanding Range and Ticks New to the US



I. scapularis
-Ticks that carry B. burgdorferi and bite humans mostly northern tick populations

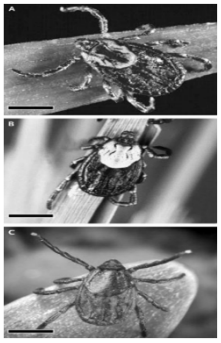
H. longicornis
May carry multiple pathogens, participation in transmitting to Humans occurs but uncertain to what degree

* Molaei, JID 2022;226(3):370-373

Common North American Hard Ticks (Ixodidae) 3

Dog ticks

Most important ticks for transmission of RMSF

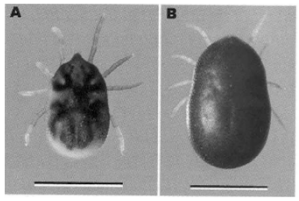


D. variabilis
American dog tick

D. andersoni
(Rocky Mt. wood tick)

R. sanguineous
(Brown dog tick)

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

Tickborne Disease Surveillance Data Summary

Total Reported Cases by Tickborne Disease, 2016-2019

Reported Tickborne Disease	2016	2017	2018	2019
Lyme disease	36,429	42,743	33,666	34,945
Anaplasmosis	4,151	5,762	4,008	5,655
Spotted Fever Rickettsiosis	4,269	6,248	5,544	5,207
Babesiosis	1,910	2,368	2,160	2,420
Ehrlichia chaffeensis ehrlichiosis	1,377	1,642	1,799	2,093
Tularemia	230	239	229	274
Undetermined ehrlichiosis/anaplasmosis	200	269	283	185
Ehrlichia ewingii ehrlichiosis	22	45	33	43
Powassan virus disease	22	34	21	43
Total	**48,610**	**59,350**	**47,743**	**50,865**

CDC, https://www.cdc.gov/ticks/data-summary/index.html (accessed 7/6/23)

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:

62M living in an exurb of Phoenix, Arizona presents in early September with a three day history of fever, myalgia, headache and rash.

He works as a lineman for a utility company. He lives with his family in an older adobe home with dogs. He has beginnings of petechial features on the wrists and ankles.

Which of the following is the most likely diagnosis?

A. Human Monocytic Ehrlichiosis (HME)
B. Human Granulocytic Anaplasmosis (HGA)
C. Babesiosis
D. Rocky Mountain Spotted Fever (RMSF)
E. Tularemia

Rickettsial species: two major groups
(not a comprehensive pathogen list)

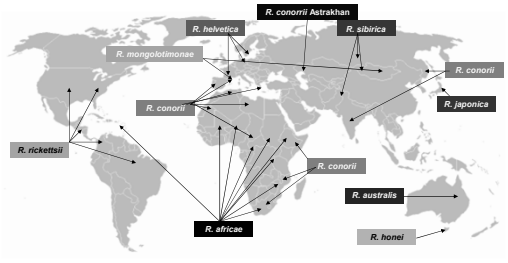
Spotted Fever Group (SFG)

- RMSF (R. rickettsii)
- R. parkeri
- Rickettsia sp. 364D
- Rickettsialpox (R. akari)
- R. conorii
- R. africae
- R. japonica
- R. australis
- …many more

Typhus Group

- Epidemic typhus
  - R. prowazekii
    - Body louse
    - Worldwide
- Murine/endemic typhus
  - R. typhi
    - Rat flea
    - Temperate--tropical, usually

Tick-borne Rickettsia World Wide: many species



- 24 species causing human disease. List continues to grow.

Parola, Clin Microbiol Rev 2013;26(4):657-702

Approximate Geographic Distribution of R. rickettsii in the American Continents

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

Figure 1–Number of reported cases of spotted fever rickettsiosis – United States, 2000–2019

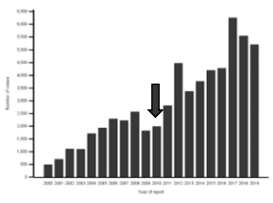
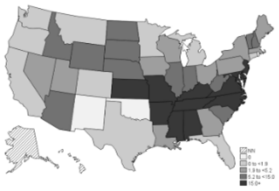


Figure 4–Annual incidence (per million population) of reported spotted fever rickettsiosis–United States, 2019. (NN= Not notifiable)



Source: CDC (accessed 7/6/23)
Change in category from RMSF to "spotted fever rickettsioses" 2010
Includes RMSF, *R. parkeri*, Pacific Coast tick fever, and Rickettsialpox.

RMSF in the United States

Incidence/Case Fatality 1920-2015

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

CDC, https://www.cdc.gov/rmsf/stats/index.html (accessed 6/21/23)

Am J Trop Med Hyg 2012;86:713-9

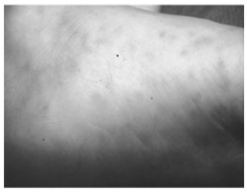
Rocky Mountain Spotted Fever Signs and Symptoms

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%

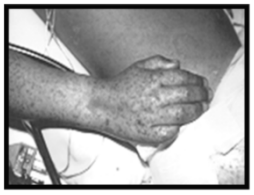
Adapted from Helnick CG et al. *J Infect Dis* 150:480, 1984

Rocky Mountain Spotted Fever

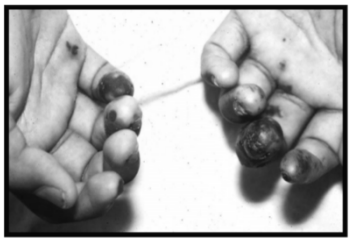
Early: rash absent or maculopapular
Starts on extremities



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.
    - Caveats: DON'T USE AS SCREENING TEST
      - False positives (especially IgM) common
        - Georgia blood donor study 11.1% IgG > 1:64, but of these only 28% fit case definition for Spotted Fever Group rickettsiosis [Straily A, JID 2020;221:1371]
        - Single IgG titer insufficient for reliable diagnosis
      - Background seroprevalence up to 20% in some regions, e.g., Carolinas
        - Asx infection likely common
      - Both RMSF IgM & IGG can persist
        - May mislead diagnosis, cause necessary treatment

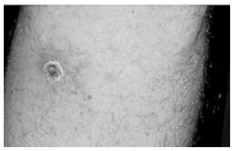
Question #2:

31M from Tidewater region of Virginia presents in June with three days of fever and rash.

Exam: unremarkable but T39.2°C, discrete black eschar on leg, scattered maculopapular rash elsewhere

Which of the following is the most likely etiologic agent?

A. Rickettsia rickettsii
B. Ehrlichia chaffeensis
C. Rickettsia parkeri
D. Anaplasma phagocytophilum
E. Rickettsia akari

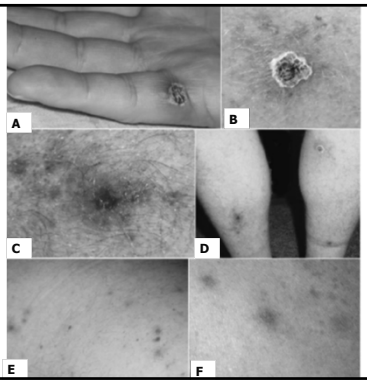


"American Boutonneuse Fever" Rickettsia parkeri

- Transmission: Lone Star or Gulf Coast ticks (*A. maculatum*)
  - Southeastern US, Gulf Coast
- AKA "Maculatum fever"
  - Also seen in 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
CID 2008; 47:1188-96

Green: Lone star tick range; Yellow: A. maculatum tick found; Red dots: R. parkeri
Note: Overlap of Lone star and Gulf coast tick range

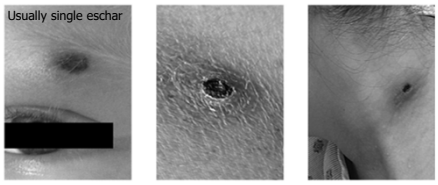
Pacific Coast Tick Fever

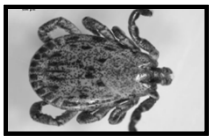
Rickettsia philippii (Rickettsia 364D)
Described in 2008

Transmitted by Pacific Coast tick (*Dermacentor occidentalis*)

Northern Baja → Southern Oregon, Most cases

Common symptoms:
Eschar
Fever
Headache





Dermacentor occidentalis

Pladgett K
PLOS Neg Trop Dis 2016

Question #6

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

Clinical Characteristics

Almost All Neuroinvasive Disease
Tick-borne flavivirus infection

- Mostly present in Spring
  - 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%, all > 50 years)

POWV in 12 States (2006-2016): 99 cases

Krow-Lucal ER. Vect Borne Zoo Dis 2018; 18(6):286-290

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 3

PREVIEW QUESTION

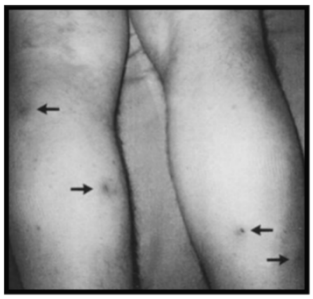
28F presents 8d after from a safari in Tanzania

Fever, mild headache, fatigue x 5d
Prior to travel, immunized against yellow fever
Took malaria prophylaxis: atovaquone/proguanil

Temperature is 38.6º, P76, R14, BP 116/70
Exam is unremarkable except for four punctuate eschars on the legs and bilateral inguinal lymph node enlargement

Lab:
Thick and thin blood smears (x 2) negative

Four Inoculation Eschars (Arrows)



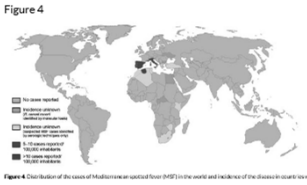
Question #3 Continued: PREVIEW QUESTION

Which Of The Following Is The Most Likely Etiologic Agent?

A. Rickettsia conorii
B. Rickettsia africae
C. Rickettsia rickettsii
D. Anaplasma phagocytophilum
E. Ehrlichia chaffeensis

Range of R. africae
African Tick Bite Fever
(green)

Range of R. conorii
Mediterranean Spotted Fever



Rovery, EID 2008;14(9)

Clinical Characteristics of R. africae Infection

	%
fever ≥ 38.5º	88
neck muscle myalgia	81
inoculation eschars	95
multiple eschars	54
lymphadenopathy	43
rash (vesicular)	46(45)
death	0

Raoult D, et al. N Engl J Med 2001; 344:1504-10

African Tick Bite Fever

- Seroprevalence:
  - High in residents, R. africae, 30-56%
- Amblyomma ticks (cattle, ungulates)
  - Clusters of cases, multiple eschars
- Incubation period 6-7d
- Dx:
  - Biopsy or swab: PCR or MIFA
  - Serology
- Rx: doxycycline
- Complications unusual

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%)

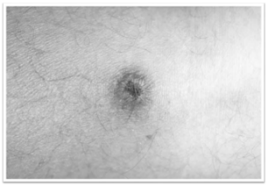
Jensenius M, EID 2009;15(11)

Question #4:

48M presents in October with fever and rash

Supervisor for apartment bldg in Queens, NY. Lives in cellar apt.

Exam: T 39^{0}C
brown-black 8mm eschar on RLE
~30 papulovesicular lesions on trunk



Question #4:

Which of the following Is the most likely etiologic agent?

A. R. rickettsii
B. R. parkeri
C. R. akari
D. R. conorii
E. Borrelia recurrentis

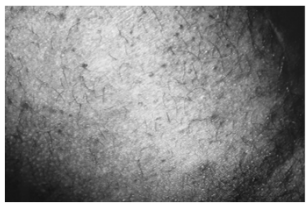
Rickettsialpox

Organism
- R. akari

Reservoir
- House mouse

Vector
- Mouse mites

Clinical
- Single eschar
- Rash: papulovesicular (20-40) or maculopapular
- Diagnosis
  - PCR swab eschar/vesicle
- Treatment: doxycycline



Maculopapular rash due to R. akari (CDC)

Partial DDx of Vesicular Rash

HSV
VZV
Pox viruses
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

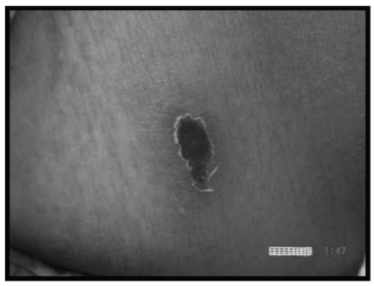
Scrub Typhus

Organism
- O. tsutsugamushi (> 70 strains)

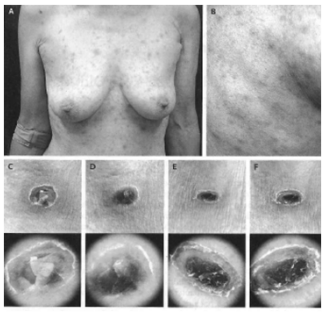
Vector
- Trombiculid mite (chiggers)

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%

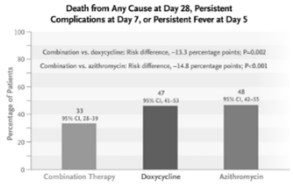


Eschar is often associated with regional lymphadenitis



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 #5:

31M presents in January with 3d fever, HA, malaise, and myalgia.

Works as counselor at wilderness camp in Pennsylvania.

Flying squirrels common at camp including residing in the walls of his cabin.

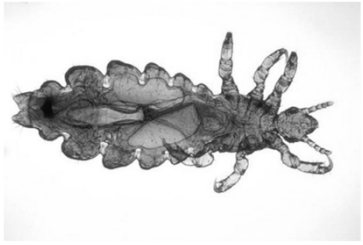
Exam is notable only for fever (39.6^0; no rash), tachycardia (P110)

A diagnostic test for which of the following is most likely to be positive

A. Murine typhus
B. Epidemic typhus
C. RMSF
D. Tularemia
E. Relapsing fever

If 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

55

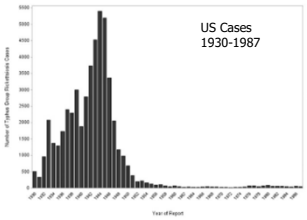
Typhus: Two Forms

	Epidemic	Endemic
Organism	***R. prowazekii***	***R. typhi***
Vector	Louse (body, head)	Flea (rat, cat)
Who	War refugees, crowded conditions/poor hygiene	Worldwide (U.S. Southern California, Texas, Hawaii)
Severity	Lethal	Mild
Treatment	Tetracycline Doxycycline Chloramphenicol	Tetracycline Doxycycline Chloramphenicol
Prevention	Boil clothes, delouse (lindane, malathion, permethrin, DDT)	Flea prevention (cats, domestic animals) Reduce rodent population
Recrudesce	Brill-Zinsser Disease (years-decades)	None known

Murine (or endemic) typhus

- In US, mostly seen in California, Hawaii, and Texas
- Infected flea feces → skin
- Most don't recall fleabite
- Usually non-specific febrile infection
  - Likely quite underdiagnosed
  - ~50% with rash
  - Occasional severe disease:
    - Meningoencephalitis
    - Pneumonitis
    - Shock

Historically, decline w/ better sanitation
No longer reportable since 1987 (Outbreak LA County 2018)



Dittrich, Lancet Global Health 2015;3:e104; Blanton Am J Trop Med 2017;96(1):53

CDC, accessed 7/6/2023 https://www.cdc.gov/typhus/murine/history.html

Murine (or endemic) typhus

- Dx:
  - Serology *R. typhi* (IFA)
    - Acute/convalescent, 4x rise
    - Cross-reacts with R. prowazekii and SFG rickettsia
  - PCR
    - Blood, often negative
- Treatment: No RCTs
  - Doxycycline (preferred)
    - Azithromycin: recent open label trial found azithromycin inferior to doxy
  - Alternatives: limited data
    - Chloramphenicol
    - Levofloxacin
    - Ciprofloxacin

Dittrich, Lancet Global Health 2015;3:e104; Blanton Am J Trop Med 2017;96(1):53

Newton, CID 2019;68(1 March):739

Other location-specific tick-borne Rickettsioses: partial

- Queensland tick typhus, *R. australis*
  - Australia-Queensland, New South Wales, Tasmania, coastal areas of eastern Victoria
- North Asian tick fever, *R. sibeirica*
  - North China; Mongolia; Asiatic areas of Russia
- Tick-borne lymphadenopathy (TIBOLA) or *Dermacentor*-borne necrosis erythema and lymphadenopathy (DEBONEL), ascribed to *R. slovaca* or *R. raoulti:*
  - Europe and Asia.
- Far-Eastern tick-borne rickettsiosis, *R. beilongjiangensis:*
  - Far East Russia and northern China.
- Oriental spotted fever, *R. japonica:*
  - Japan.
- Thai tick typhus, *R. bonei:*
  - Thailand, Australia, Tasmania, Flinders Island
- Australian spotted fever:
  - *R. marmionii*, Australia.

Question #6:

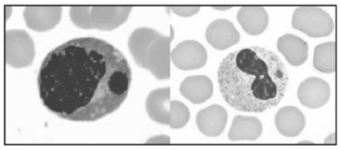
- 43F visited southern Missouri on vacation, returns 7d later with fever, headache and diffuse myalgia x 3d
- Physical examination: no findings
- Laboratory evaluation :
  - WBC: 2.1/mm³ (80% PMNs, 10% lymphocytes, 8% monocytes
  - Hemoglobin: 7.0 g/dL, hematocrit: 24%
  - Platelets: 105,000/mm³
  - AST: 364 U/L, ALT: 289 U/L
  - renal function: normal

Question #6

Which of the following is the most likely etiologic agent?

A. Anaplasma phagocytophilum
B. Ehrlichia chaffeensis
C. Borrelia hermsii
D. Babesia divergens
E. Borrelia burgdorferi

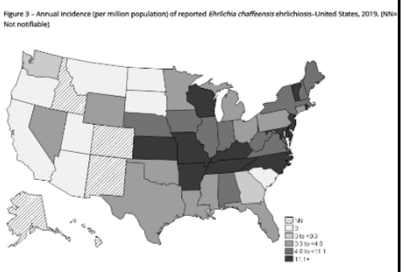
Morulae



HME HGA

Human Monocytic Ehrlichiosis (HME)

- E. chaffeensis
- Vector: Lone star tick
- Rash: ~30%
  - Maculopapular or petechial
- Labs: LFTs ↑, leukopenia, thrombocytopenia
- Mortality 2.7%
- Diagnosis
  - PCR
  - Morulae (2-38%)
  - Serology: acute/convalescent
  - Treatment: doxycycline



Source: CDC (accessed 7/7/23)

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 (accessed 7/7/23)

Other Ehrlichia (less common)

Organism	Vector	Geography	Risk	Mortality
E. ewingii (a canine ehrlichia)	Lone star	Most cases in Southcentral US	Immune compromised	Low
E. muris	*Ixodes persulcatus* *H. flava*	Europe, Russia, Japan, West Coast US	Older patients	Low
Ehrlichia muris eauclairensis (former Ehrlichia muris-like [EML] agent)	Deer tick	Wisconsin, Minnesota	Elderly, immune compromised	Low

Question #7:

- 48F c/o headache and fatigue worsening over 2 months since May tick bite
  - PMH: negative
  - SH: Married, works from home, has a dog, resides in suburban eastern PA
  - Treated with doxycycline for Lyme disease, no benefit
- Physical examination: afebrile, normal vital signs, no findings

- Laboratory evaluation :
  - WBC: 7.0 cells/mm³ (70% PMNs, 18% lymphocytes, 12% monocytes
  - Hemoglobin: 11.8 g/dL, hematocrit: 35%
  - Platelets: 145,000/mm³
  - ALT: 22 U/L
  - Babesia IgG 1:128 (positive ≥ 1:64)
  - Blood smear: no parasites

Question #7:

- The best recommended next step:

A. Check Babesia 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
- 1500-2000 cases/ yr

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
- Reservoir, vector
  - White-footed mouse;
  - Tick transmission: Ixodes scapularis
- Severe disease risks:
  - asplenic, HIV, chemotherapy, age >55, transplant

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)

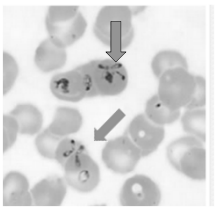
- Labs
  - increased LTFs,
  - thrombocytopenia
  - anemia (Hb<10),
  - parasitemia (>10%)

Immunocompromised mortality
- > 20%

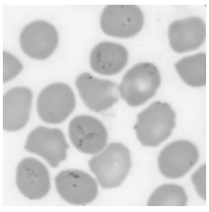
Hatcher JC, et al. Clin Infect Dis 2001; 32:1117-25

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

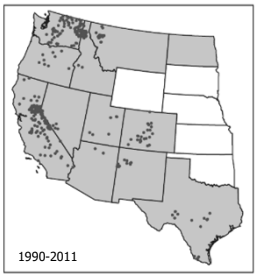
Krause, et al CID 2021; 72 (2) e49-65

Tickborne Relapsing Fever US

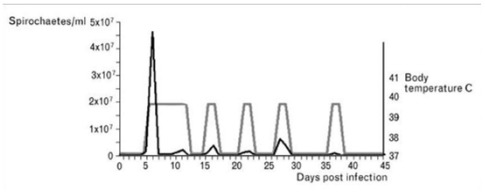
Borrelia spp. (mainly B. hermsii)
- Ornithodorus soft ticks (brief, painless)

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,
- **Rx: PCN, doxycycline**
  - Jarisch Herxheimer reaction in 54%

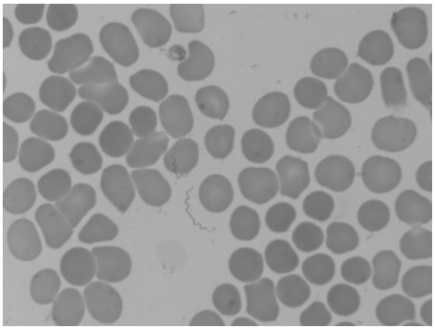


MMWR 2012;61:174-6



Relapsing Fever: recurrent bacteremia (black line) correlates with sudden fever (grey).

After initial bacteremia, relapses are lower and fever duration somewhat shorter.



Diagnosis: observation of spirochetes in blood film, PCR

Colorado Tick Fever

- Transmission D. andersoni
  - 4,000-10,000 feet
- 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

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 or antibody production is delayed until 14-21 days after onset of symptoms.

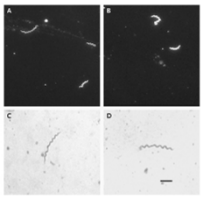
Timing of specimen collection	Specimens	Preferred Test
<14 days after symptom onset	Serum (CSF if suspected CNS involvement)	RT-PCR for viral RNA
≥14 days after symptom onset	Serum (CSF if suspected CNS involvement)	Antibody testing*; consider RT-PCR for samples from days 14-21

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

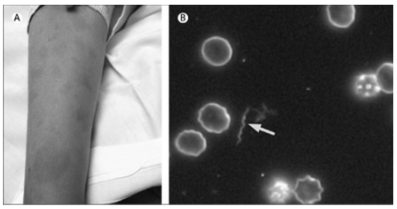


Spirochetes in CSF

Gugliotta, NEJM 2013

Telford, Clin Microbiol Infect 2015

Borrelia mayonii



5 of 6: acute febrile illness with rash (macular)
1 of 6: 1 months knee pain/swelling
To date: only see in in Minnesota and Wisconsin

Pritt et al. Lancet ID 2016;16(5):556

Cluster of Tick Paralysis Cases

- Four cases within 20 miles of each other
  - Ages 6, 58, 78, 86 years
- Ticks on neck or back
  - Usually dog ticks or Rocky Mt wood ticks
- Ascending motor paralysis without sensory loss
- Treatment: remove tick = cure
- Pathogenesis: neurotoxin in tick saliva

MMWR 2006; 55: 933-5

Question #8:

A 59 y.o. man from Missouri presents with fever (39^0), headache, myalgia, anorexia, nausea, one week after removing an engorged tick from his groin. No travel.

Exam: unremarkable except ill appearing, no rash.
Lab: wbc 2300 plt 42,000 ALT 111

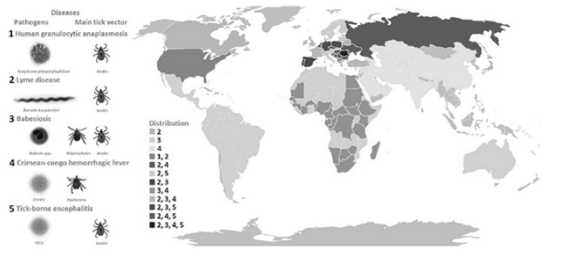
Suspect ehrlichiosis (but no morulae on blood smear)

Question #8:

After sending appropriate diagnostic tests the patient has not improved after three days of doxycycline. Which of the following is the most likely etiologic agent?

A. R. rickettsii
B. B. burgdorferi
C. R. parkeri
D. Heartland virus
E. Severe fever with thrombocytopenia syndrome virus

But wait: There's More (#4) and More (#5)



Front Cell Infect Microbiol, 2017;7:114

25 – Ticks, Mites, Lice and The Diseases They Transmit

Speaker: Paul Auwaerter, MD

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?

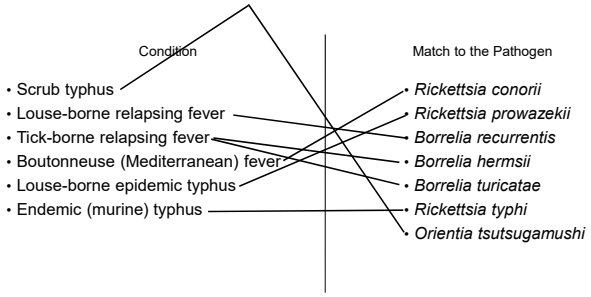
- Babesia:
  - Cause of blood transfusion infection in US
  - Splenectomy or immunocompromise = risk severe infection risk
- Co-infections in the US: may complicate some infections especially after black-legged tick (*I. scapularis)* bite
  - Lyme disease + Babesia OR Lyme disease + HGA mostly
- Flying 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

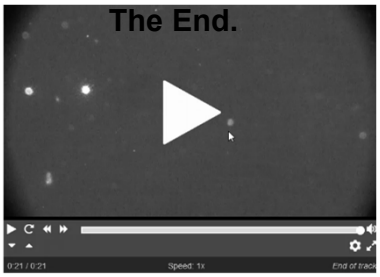
Disease	Usual Organism	Geography	Eschar	Rash	High fever	Comment
TICK-BORNE						
RMSF	R. rickettsii	N,C,S ,America	No	Yes	Yes	Serious
STARI	Unknown	S, SC, MA	No	Yes (EM)	No	Mild
R. parkeri	R. parkeri	Gulf, South, Atlantic	Yes (>1)	Yes	No	
African tick bite fever	R. africae	Sub-Saharan Africa	Yes (>1)	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



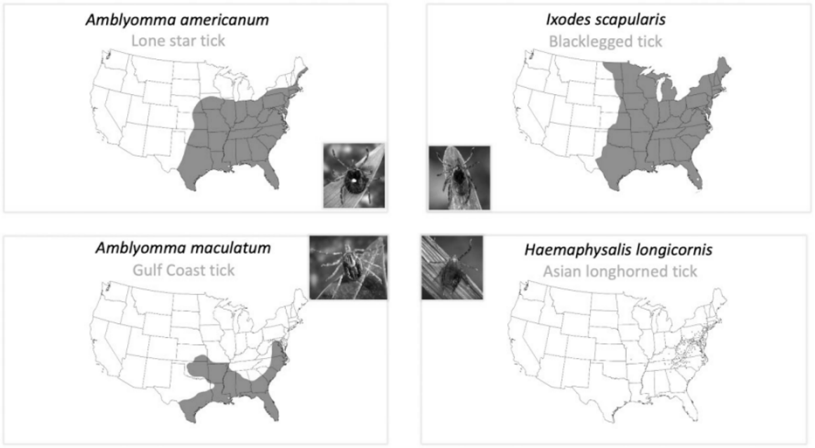
Thank You! and The End.



B. mayonii Spirochete in Culture

Pritt, Clin Micro and Inf 2022

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

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**

*

26

Immunizations: Domestic, Travel, and Occupational

Dr. Shireesha Dhanireddy

26 – Immunizations: Domestic, Travel, and Occupational

Speaker: Shireesha Dhanireddy, MD

IDBR INFECTIOUS DISEASE BOARD REVIEW AUGUST 19-23 2023 LIVE/VIRTUAL

Immunizations: Domestic, Travel, and Occupational

Shireesha Dhanireddy, MD
Professor, Allergy & Infectious Diseases
University of Washington

7/11/2023

IDBR INFECTIOUS DISEASE BOARD REVIEW AUGUST 19-23 2023

Disclosures of Financial Relationships with Relevant Commercial Interests

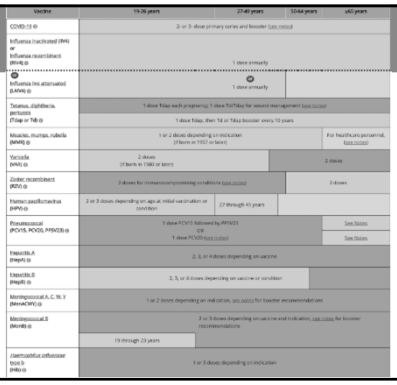
- **None**

Objectives

- Review vaccine guideline resources
- Review ACIP recommendations for routine immunizations
- Discuss travel immunizations
- Review vaccines in special populations

Key Sources

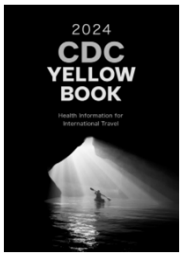
Only ACIP guidance for routine immunizations will be tested



* *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

IDBR INFECTIOUS DISEASE BOARD REVIEW AUGUST 19-23 2023 **PREVIEW QUESTION**

22 year old man with h/o egg allergy and no prior influenza vaccine presents for routine visit. He states he has had hives after eating eggs. No h/o anaphylaxis. **Which of the following is recommended?**

A. Defer vaccination and refer to an allergist for testing
B. Vaccinate with any inactivated influenza vaccine without monitoring
C. Vaccinate and monitor for 30 minutes after receiving any inactivated influenza vaccine
D. Vaccinate with only live attenuated influenza vaccine

Egg Allergy – ACIP Recommendations

- Egg allergy
  - 1.3% of children
  - 0.2% of adults
- Ok to get influenza vaccine if the following:
  - No reaction with cooked eggs
  - Only hives after exposure
- If have anaphylaxis, angioedema, respiratory distress or required epinephrine
  - CAN STILL RECEIVE VACCINE – but should be given by a provider who can recognize allergic reactions
  - 33 cases of anaphylaxis out of 25.1 million doses
  - 8/33 had symptoms within 30 min

Question: Measles Vaccine

PREVIEW QUESTION

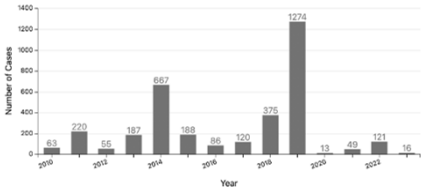
71 year old man underwent unrelated HSCT for MDS AML 12 years ago which was relatively uncomplicated without GVHD and he has been off immunosuppression for 2 years. His primary care provider checks a rubeola serology as there is an outbreak in the community and patient is concerned regarding risk. The serology is negative.

Which of the following do you recommend?

A. Vaccine is not recommended as it is live and there is risk of vaccine related disease
B. One dose of MMR vaccine recommended
C. Two doses of MMR vaccine recommended

Measles Vaccine

- 90% of cases in unvaccinated or unknown states individuals
- As of early 6/8/23,16 confirmed cases of measles in US this year
- Vaccine very effective!
  - 93% effective after 1 dose
  - 97% effective after 2 doses
  - Immunity is felt to be lifelong*



Measles Vaccine

Evidence of presumptive immunity
- Written documentation of adequate vaccination
  - 1+ doses of vaccine at ≥12mos
    - Pre-school age
    - Adults not at high risk
  - 2 doses
    - School age children
    - College students
    - Healthcare personnel
    - International travelers
- Lab evidence of immunity
- Lab confirmation of measles disease
- Birth prior to 1957

Measles Vaccine

Who doesn't need vaccine:
- Adults born before 1957 (except HCW – should receive during an outbreak)
- Those with laboratory evidence of immunity

Who needs 1 dose:
- Adults born after 1957 considered low risk without documented vaccine and no lab evidence of immunity or prior infection

Who needs 2 doses:
- Healthcare workers
- International travelers born in 1957 or later
- Persons attending colleges or post-high school educational institutions

Measles Vaccine

Measles vaccine may be administered post-transplant if:

- 2 years post transplant
- No active GVHD
- At least 1 year off immunosuppressive medications

Question: 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.

Question: Pneumococcal Vaccine

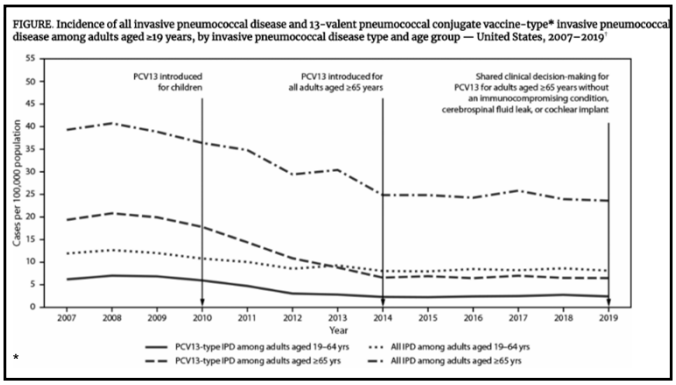
A 37 year-old man recently diagnosed with HIV presents to clinic for routine care after starting antiretroviral therapy 3 months ago. He has not received pneumococcal vaccination. Which of the following is most accurate?

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



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 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

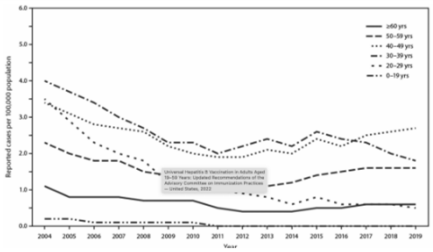
Question: Hepatitis B Vaccine

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

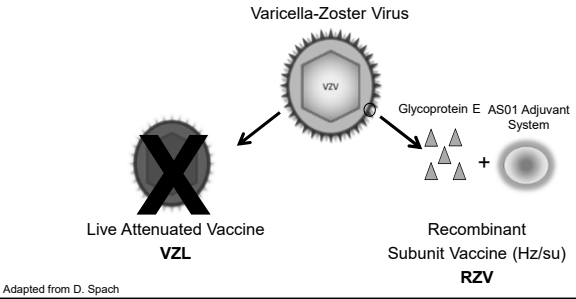
- Sexual exposure
  - Partners with Hep B
  - More than 1 sex partner in last 6 months
  - Getting STI testing or treatment
  - MSM
- Percutaneous exposure (IDU, household contacts, healthcare, public safety, patients on HD or those working with HD patients)
- International travelers
- People with HIV
- 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?

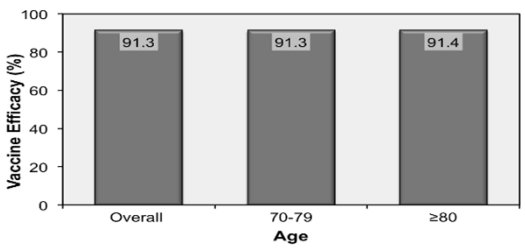
A. Vaccine not indicated given her history of zoster
B. Check VZV titer to confirm history. If negative, proceed with vaccination
C. Recommend recombinant zoster vaccine

Zoster Vaccines



Adapted from D. Spach

RZV Efficacy Against First Episode of Zoster in Immunocompetent Patients ≥50



Cunningham AL, et al. N Eng J Med. 2016;375:1019-32.

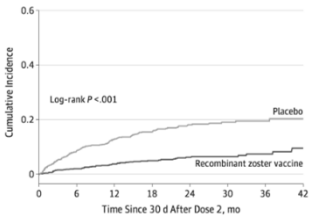
ACIP Recommendations for Zoster Vaccine

- ZVL is no longer available
- RZV is preferred over ZVL
- Healthy adults ≥ 50 years
  - Regardless of prior h/o HZ
  - No need to wait any specific period of time after HZ to give RZV (just not during acute episode)
- 2 doses, 2-6 months apart
- Wait a minimum of 8 weeks after giving ZVL to give RZV

ACIP Recommendations for Zoster Vaccine in Immunocompromised Persons

- RZV recommended for all IC adults 18+
- 2 doses 8 weeks apart

Efficacy of RZV in Preventing Incident Herpes Zoster in Patients Who Had Undergone HSCT



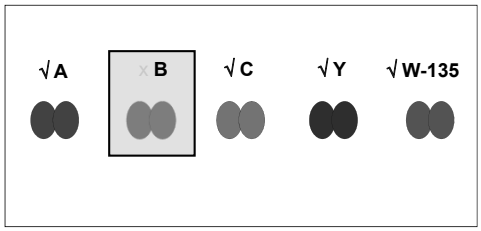
Source: Bastidas et al. JAMA 2019.

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

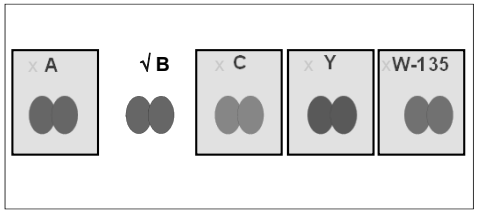
Meningococcal Quadrivalent Vaccines
Serogroups Included in Vaccine: A, C, Y, W-135



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

ACIP Meningococcal B Vaccine Recommendation Adolescents and Young Adults

- Recommended fo
  increased risk, pr
  - Meningococcal
  - Asplenia
  - Complement d
  - On eculizumab
  - Microbiologist
    Neisseria meni


Meningococcus returns to OSU: Student being treated for disease

- Same vaccine should be used for all doses

CDC. MMWR. 2015;64:1171-6.

Eculizumab

- Soliris (eculizumab) 1000-2000x increased risk of meningococcal meningitis
- CDC recommendations –
  - Immunize with both quadrivalent and B vaccines at least 2 weeks prior to giving eculizumab if possible
  - Repeat immunization every 5 years while on eculizumab
- Risk remains increased despite vaccination

Question: Tdap

A 27 year-old pregnant woman presents for her routine obstetrics visit at her 32 week gestation visit. She is G2P1. She has a healthy 2 year old daughter at home. Which statement is correct regarding Tdap in pregnancy?

A. She should receive a Tdap today only if she has not received in the past 5 years.
B. She should receive Tdap only if she did not receive during her prior pregnancy
C. She should receive Tdap today

Tdap Recommendations

WHO
- All adolescents aged 11 through 18 years (age 11-12 preferred)
- All adults aged 19 through 64 who have not received a dose
- All adults aged ≥ 65 years (2/2012)
- All pregnant women during each pregnancy

WHAT
- Boostrix preferred for adults ≥ 65 years (but either okay)

WHEN
- Regardless of interval between last Td if has not received Tdap
- During each pregnancy for pregnant women – optimum timing is 3rd trimester (27-34 weeks)

MMWR 2013;62:131-135

Question: Hepatitis A

A couple in their 30's plans to adopt a 2 year-old girl from Ethiopia. They have a regular babysitter and another 7 year-old child.

Who should receive the Hepatitis A vaccine?

A. Both parents
B. Mother only
C. Both parents and 7 year-old child
D. Both parents, 7 year-old child, and babysitter

26 – Immunizations: Domestic, Travel, and Occupational

Speaker: Shireesha Dhanireddy, MD

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

- 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 …

Speaker: Shireesha Dhanireddy, MD

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

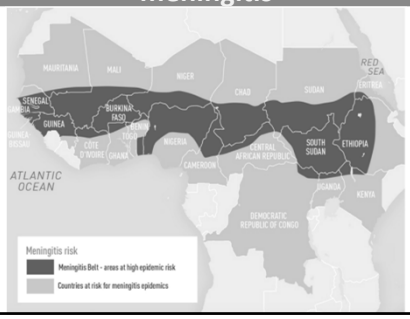
- Recommended for ≥ 9 months traveling to or living in areas of risk or countries requiring vaccine for entry
- In 2014, WHO concluded that single dose fellow fever vaccine provides lifelong protection and no booster needed
  - Exceptions if ongoing risk and the following
    - pregnant when initially 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

STAMARIL® (through Expanded Access Program) no longer being shipped to US as of May 6, 2021

Areas of frequent epidemics of meningococcal meningitis



Meningococcal Vaccine and Travel

- Quadrivalent meningococcal vaccine recommended for travelers to the meningitis belt during dry season (Dec-June)
  - For ages 2 months – 55 years --> MenACWY (conjugate vaccine) recommended
  - For ≥ 56 years, Men ACWY recommended (polysaccharide vaccine not available)
- Meningitis B vaccine not recommended for travel
- Approx 7-10 days after vaccine for the development of protective antibody levels

26 – Immunizations: Domestic, Travel, and Occupational

Speaker: Shireesha Dhanireddy, MD

Meningococcal Vaccine and Travel for Umrah or Hajj

- Travelers to Saudi Arabia for Umrah or Hajj are required to provide documentation of meningococcal vaccination at least 10 days before arrival
  - No more than 3 years before for polysaccharide vaccine
  - No more than 9 years before for conjugate

Typhoid Vaccine

- Highest risk for travelers to South Asia (6-30 x more than other destinations)
- Increased risk in West Africa, particularly in rural areas
- 2 vaccines available in US
  - Oral, live attenuated (given at least 1 wk before travel); age 6 and above, q 5 years if ongoing risk or travel
  - IM, polysaccharide (given at least 2 wks before travel); age 2 and above, q 2 years if ongoing risk or travel
  - Both 50-80% effective
- Indicated in travelers
- Delay vaccine >72 hrs after antibacterial medications

Japanese Encephalitis

JEV

- 35,000-50,000 cases/year
- 20-30% mortality
- 30-50% with neurologic sequelae
- Very low risk in travelers *(< 1 case per million travelers)*
- Risks are extended travel > 1 month, rural areas, irrigated areas (rice paddies), or going to an outbreak area
- Vaccine 2 doses, 28 days apart. 2nd dose should be given at least a week prior to travel
- 2 months or older
  - Smaller dose for children under 3
  - ? Booster dose for ≥ 17 years if risk and > 1 year since prior vaccine

Cholera Vaccine

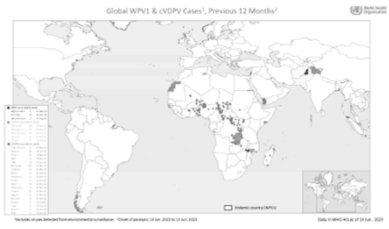
- Approved in 2016
- Single-dose vaccine recommended for adults 18-64 years travelling to an area of active transmission (where cases have been reported in the past year)
- Cholera in travelers is extremely rare
- Risk factors: aid workers in outbreak settings
- Vaccine 90% effective in preventing severe diarrhea (declined to 80% after 3 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*.

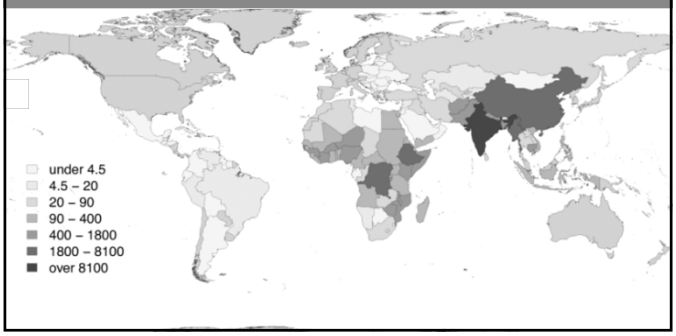
What do you recommend?

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, 2017



Rabies Vaccine

- Pre-exposure prophylaxis – updated February 2021
  - Vaccination on day 0, 7, ~~and 21 OR 28 days~~

May also give booster dose between 21 days and 3 years of completing 2-dose series

Risk Category	Nature of Risk	Typical Population	Preexposure Recommendations
Continuous	Virus present continuously, often in high concentrations. Specific exposures likely to go unrecognized. Bite, nonbite, or aerosol exposure.	Rabies research laboratory workers; rabies biologics production workers.	Primary course. Serologic testing every 6 months; booster vaccination if antibody titer is below acceptable level.
Frequent	Exposure usually episodic, with source recognized, but exposure also might be unrecognized. Bite, nonbite, or aerosol exposure.	Rabies diagnostic lab workers, spelunkers, veterinarians and staff, and animal-control and wildlife workers in rabies-enzootic areas. All persons who frequently handle bats.	Primary course. Serologic testing every 2 years; booster vaccination if antibody titer is below acceptable level.
Infrequent	Exposure nearly always episodic with source recognized. Bite or nonbite exposure.	Veterinarians and terrestrial animal-control workers in areas where rabies is uncommon to rare. Veterinary students. Travelers visiting areas where rabies is enzootic and immediate access to appropriate medical care including biologics is limited.	Primary course. No serologic testing or booster vaccination.
Rare (population at large)	Exposure always episodic with source recognized. Bite or nonbite exposure.	U.S. population at large, including persons in rabies-epizootic areas.	No vaccination necessary.

*

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

26 – Immunizations: Domestic, Travel, and Occupational

Speaker: Shireesha Dhanireddy, MD

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

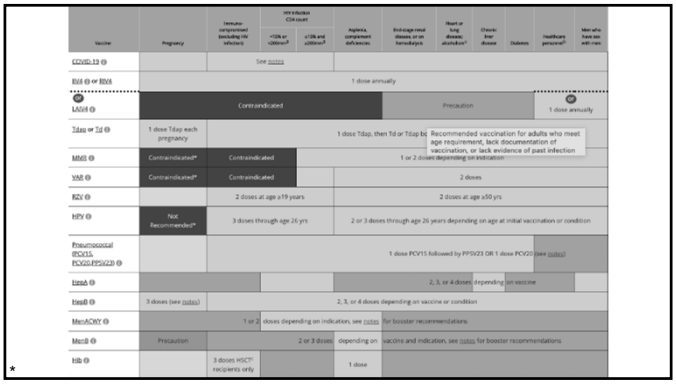
- ***Varicella exposure***
  - If no evidence of immunity and no contraindications (ie not severely immunocompromised) → Give vaccine ideally 3-5 days after exposure
  - For non-immune immunocompromised hosts and pregnant women, passive immunization with VariZIG is recommended
- ***Hepatitis B exposure***
  - 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

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



26 – Immunizations: Domestic, Travel, and Occupational

Speaker: Shireesha Dhanireddy, MD

Vaccinations for Immunocompromised Hosts: Levels of Immunosuppression

- ***High-level Immunosuppression***
  - Combined primary immunodeficiency disorder
  - Receiving cancer chemotherapy
  - Within 2 months after SOT
  - HIV with CD4 count < 200 in adolescents/adults and < 15% in children
  - Daily steroid therapy ≥ 20mg (or > 2mg/kg/day for pts < 10kg) of prednisone or equivalent for ≥ 14 days
  - Certain biologic immune modulators or rituximab
  - HSCT (duration of high level immunosuppression variable)
- ***Low-level immunosuppression***
  - Asymptomatic HIV with CD4 count 200-499 for adolescents/adults and 15-24% in children
  - Lower doses of steroids
  - MTX ≤ 0.4mg/kg/week, azathioprine ≤ 3mg/kg/day, 6-mercaptopurine ≤ 1.5mg/kg/day

Vaccinations for Persons with HIV

If CD4 count > 200	**If CD4 count < 200**
Inactivated influenza	Inactivated influenza
Tdap	Tdap
Pneumococcal	Pneumococcal
Meningococcal	Meningococcal
HBV	HBV
HPV	HPV
MMR	~~MMR~~
Varicella	~~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

Vaccinations for Healthcare Workers

25 year old nursing student is being seen in student health clinic for routine visit. She brings medical records indicating that she received her first dose of hepatitis B vaccine 18 months ago and the second vaccine 1 month thereafter. She asks today if she requires additional doses. No other medical problems and she is not on any other medications.

Which of the following is most appropriate?

A. No additional doses of HBV vaccination needed
B. Restart HBV vaccine series
C. Check hepatitis B surface Ab titer to assess immunity
D. Give 3rd dose of HBV vaccine series today

Vaccines for Healthcare Workers

- Hepatitis B
  - Pre-vaccine serologies not indicated unless born in geographic regions with prevalence ≥ 2%, MSM, PWID, immunosuppressed, liver disease NOS
  - All HCP should be vaccinated with at least 3 doses
  - Should have post-vaccination anti-HBs ≥ 10 mIU/mL (drawn 1-2 months after last dose of vaccine)

Post-Vaccine HBV serologies

- Serologic testing not necessary after routine vaccination of infants, children, or adults
- Anti-HBs recommended for the following:
  - Infants born to HBsAg–positive or unknown mothers (check HBsAb and sAg)
  - Health care personnel and public safety workers
  - Hemodialysis patients
  - Persons with HIV
  - Other immunocompromised persons (e.g., hematopoietic stem-cell transplant recipients or persons receiving chemotherapy)
  - Sex partners of HBsAg-positive persons

Vaccines for Healthcare Workers

Hepatitis B	If you don't have documented evidence of a complete hepB vaccine series, or if you don't have an up-to-date blood test that shows you are immune to hepatitis B (i.e., no serologic evidence of immunity or prior vaccination) then you should • Get the 3-dose series (dose #1 now, #2 in 1 month, #3 approximately 5 months after #2). • Get anti-HBs serologic tested 1–2 months after dose #3.
Flu (Influenza)	Get 1 dose of influenza vaccine annually.
MMR (Measles, Mumps, & Rubella)	If you were born in 1957 or later and have not had the MMR vaccine, or if you don't have an up-to-date blood test that shows you are immune to measles or mumps (i.e., no serologic evidence of immunity or prior vaccination), get 2 doses of MMR (1 dose now and the 2nd dose at least 28 days later). If you were born in 1957 or later and have not had the MMR vaccine, or if you don't have an up-to-date blood test that shows you are immune to rubella, only 1 dose of MMR is recommended. However, you may end up receiving 2 doses, because the rubella component is in the combination vaccine with measles and mumps. For HCWs born before 1957, see the MMR ACIP vaccine recommendations.
Varicella (Chickenpox)	If you have not had chickenpox (varicella), if you haven't had varicella vaccine, or if you don't have an up-to-date blood test that shows you are immune to varicella (i.e., no serologic evidence of immunity or prior vaccination) get 2 doses of varicella vaccine, 4 weeks apart.
Tdap (Tetanus, Diphtheria, Pertussis)	Get a one-time dose of Tdap as soon as possible if you have not received Tdap previously (regardless of when previous dose of Td was received). Get Td boosters every 10 years thereafter. Pregnant HCWs need to get a dose of Tdap during each pregnancy.
* Meningococcal	Those who are routinely exposed to isolates of *N. meningitidis* should get one dose.

Resources

- www.cdc.gov/vaccines/recs/ACIP/default.htm
- www.immunize.org/acip

THANK YOU

sdhanir@uw.edu

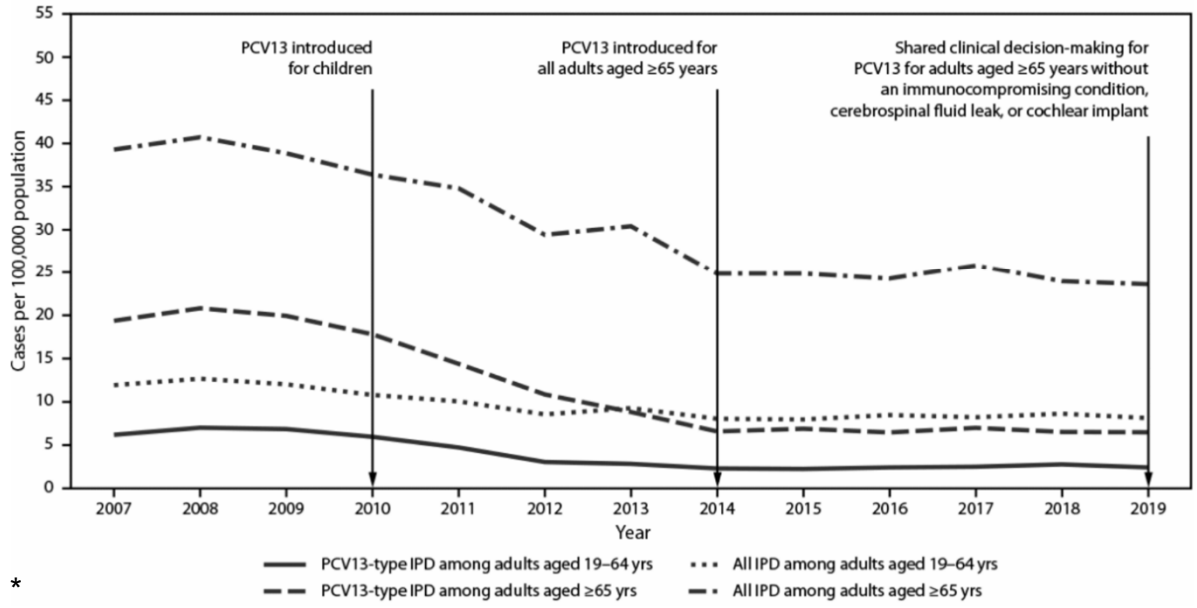
Key Sources

Only ACIP guidance for routine immunizations will be tested

* *https://www.cdc.gov/vaccines/schedules/hcp/adult.html*

Vaccine	19-26 years	27-49 years	50-64 years	≥65 years
COVID-19	2- or 3- dose primary series and booster (see notes)			
Influenza inactivated (IIV4) or Influenza recombinant (RIV4)	1 dose annually			
Influenza live attenuated (LAIV4)	Or 1 dose annually			
Tetanus, diphtheria, pertussis (Tdap or Td)	1 dose Tdap each pregnancy; 1 dose Td/Tdap for wound management (see notes)			
	1 dose Tdap, then Td or Tdap booster every 10 years			
Measles, mumps, rubella (MMR)	1 or 2 doses depending on indication (if born in 1957 or later)			For healthcare personnel, (see notes)
Varicella (VAR)	2 doses (if born in 1980 or later)		2 doses	
Zoster recombinant (RZV)	2 doses for immunocompromising conditions (see notes)		2 doses	
Human papillomavirus (HPV)	2 or 3 doses depending on age at initial vaccination or condition	27 through 45 years		
Pneumococcal (PCV15, PCV20, PPSV23)	1 dose PCV15 followed by PPSV23 OR 1 dose PCV20 (see notes)			See Notes
				See Notes
Hepatitis A (HepA)	2, 3, or 4 doses depending on vaccine			
Hepatitis B (HepB)	2, 3, or 4 doses depending on vaccine or condition			
Meningococcal A, C, W, Y (MenACWY)	1 or 2 doses depending on indication, see notes for booster recommendations			
Meningococcal B (MenB)	2 or 3 doses depending on vaccine and indication, see notes for booster recommendations			
	19 through 23 years			
Haemophilus influenzae type b (Hib)	1 or 3 doses depending on indication			

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†



*

Rabies Vaccine

May also give booster dose between 21 days and 3 years of completing 2-dose series

- Pre-exposure prophylaxis – updated February 2021
  - Vaccination on day 0, 7, ~~and 21 OR 28 days~~

Risk Category	Nature of Risk	Typical Population	Preexposure Recommendations
Continuous	Virus present continuously, often in high concentrations. Specific exposures likely to go unrecognized. Bite, nonbite, or aerosol exposure.	Rabies research laboratory workers; rabies biologics production workers.	Primary course. Serologic testing every 6 months; booster vaccination if antibody titer is below acceptable level.
Frequent	Exposure usually episodic, with source recognized, but exposure also might be unrecognized. Bite, nonbite, or aerosol exposure.	Rabies diagnostic lab workers, spelunkers, veterinarians and staff, and animal-control and wildlife workers in rabies-enzootic areas. All persons who frequently handle bats.	Primary course. Serologic testing every 2 years; booster vaccination if antibody titer is below acceptable level.
Infrequent	Exposure nearly always episodic with source recognized. Bite or nonbite exposure.	Veterinarians and terrestrial animal-control workers in areas where rabies is uncommon to rare. Veterinary students. Travelers visiting areas where rabies is enzootic and immediate access to appropriate medical care including biologics is limited.	Primary course. No serologic testing or booster vaccination.
Rare (population at large)	Exposure always episodic with source recognized. Bite or nonbite exposure.	U.S. population at large, including persons in rabies-epizootic areas.	No vaccination necessary.

*

Vaccine	Pregnancy	Immuno-compromised (excluding HIV infection)	HIV infection CD4 count <15% or <200mm³	HIV infection CD4 count ≥15% and ≥200mm³	Asplenia, complement deficiencies	End-stage renal disease, or on hemodialysis	Heart or lung disease; alcoholism[B]	Chronic liver disease	Diabetes	Healthcare personnel[D]	Men who have sex with men
COVID-19		See notes									
IIV4 or RIV4	1 dose annually										
or LAIV4	Contraindicated					Precaution				or 1 dose annually	
Tdap or Td	1 dose Tdap each pregnancy	1 dose Tdap, then Td or Tdap bc									
MMR	Contraindicated*	Contraindicated	1 or 2 doses depending on indication								
VAR	Contraindicated*	Contraindicated		2 doses							
RZV		2 doses at age ≥19 years		2 doses at age ≥50 yrs							
HPV	Not Recommended*	3 doses through age 26 yrs		2 or 3 doses through age 26 years depending on age at initial vaccination or condition							
Pneumococcal (PCV15, PCV20,PPSV23)		1 dose PCV15 followed by PPSV23 OR 1 dose PCV20 (see notes)									
HepA				2, 3, or 4 doses depending on vaccine							
HepB	3 doses (see notes)	2, 3, or 4 doses depending on vaccine or condition									
MenACWY	1 or 2 doses depending on indication, see notes for booster recommendations										
MenB	Precaution	2 or 3 doses depending on vaccine and indication, see notes for booster recommendations									
Hib		3 doses HSCT[C] recipients only		1 dose							

Recommended vaccination for adults who meet age requirement, lack documentation of vaccination, or lack evidence of past infection

*

Vaccines for Healthcare Workers

	Hepatitis B	If you don't have documented evidence of a complete hepB vaccine series, or if you don't have an up-to-date blood test that shows you are immune to hepatitis B (i.e., no serologic evidence of immunity or prior vaccination) then you should • Get the 3-dose series (dose #1 now, #2 in 1 month, #3 approximately 5 months after #2). • Get anti-HBs serologic tested 1–2 months after dose #3.
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*	Meningococcal	Those who are routinely exposed to isolates of *N. meningitidis* should get one dose.

27

Epididymitis, Orchitis, and Prostatitis

Dr. Barbara Trautner

27 – Epididymitis, Orchitis, and Prostatitis

Speaker: Barbara Trautner, MD

IDBR INFECTIOUS DISEASE BOARD REVIEW AUGUST 19-23 2023 LIVE/VIRTUAL

Prostatitis, Epididymitis, and Orchitis

Barbara Trautner, MD, PhD
Professor of Medicine
Baylor College of Medicine

6/25/2023

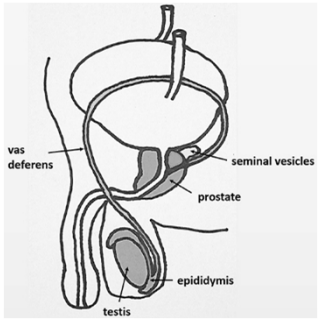
IDBR INFECTIOUS DISEASE BOARD REVIEW AUGUST 19-23 2023

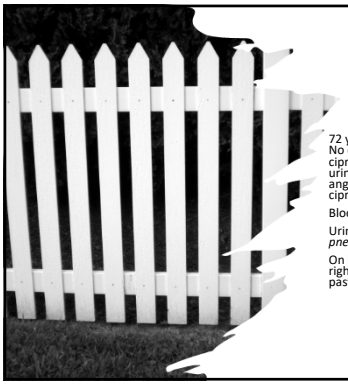
Disclosures of Financial Relationships with Relevant Commercial Interests

- **Consultant:**
  - **Genentech for COVID treatment trial**
  - **Peptilogics for prosthetic joint infection trial**
  - **Shionogi for COVID treatment trial**
- **Research Funding: Genentech**

Overview

- Epididymitis
- Prostatitis
  - Acute
  - Chronic
- Prostate biopsy
- Orchitis





Case #1

72 year-old man presented to ER with fever, urinary retention. No culture sent. Sent home with transurethral catheter and ciprofloxacin. Walks into ID clinic one month later with the urinary catheter is still in place. Temp 102.5, costovertebral angle tenderness present on exam. Admitted and started on ciprofloxacin.

Blood cultures: *Serratia marcescens (sensitive to cipro)*

Urine cultures: *Serratia marcescens and Klebsiella pneumoniae (both sensitive to cipro)*

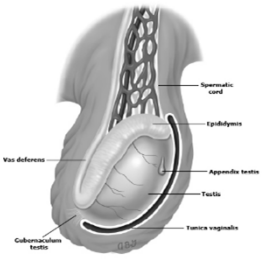
On hospital day 2, he is still febrile to 102.3, and he reports right testicular pain/swelling. He says this was present for the past 7 days but is more obvious now.

Case #1 continued

Given his fevers on 2 days of ciprofloxacin, and the new awareness of right testicular pain and swelling, your next step is to:

A. Add vancomycin to cover enterococci
B. Order a scrotal ultrasound
C. Add doxycycline for coverage of sexually transmitted infections
D. Consult urology emergently for testicular torsion

Normal testicular anatomy



The testicle is vertical and its anterior portion is surrounded by the tunica vaginalis.

UpToDate

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27 – Epididymitis, Orchitis, and Prostatitis

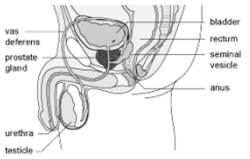
Speaker: Barbara Trautner, MD

Epididymitis: Clinical Presentation

- Testicular pain, swelling, and tenderness
- Scrotal erythema
- Fever
- Dysuria or other urinary irritative symptoms
- Urethral discharge
- Reactive hydrocele can occur
- Epididymo-orchitis if testes also inflamed
- Gradual onset (if sudden, consider testicular torsion)
- Cremasteric reflex is preserved

Risk factors for epididymitis

- Insertive anal intercourse
- Urinary outlet obstruction
- Prostate biopsy
- Urinary tract instrumentation
- Immunosuppression



Workowski et al, Sexually Transmitted Infections Treatment Guidelines, 2021
Recommendations and Reports / Vol. 70 / No. 4
UpToDate Acute Scrotal Pain in Adults

Etiologic agents of epididymitis

>14 and < 35 years of age: typically sexually transmitted

- *Neisseria gonorrheae*
- *Chlamydia trachomatis*
- *Mycoplasma genitalium*

Chronic or atypical

- *Mycobacterium tuberculosis*
- *Brucellosis*
- *Nocardia*
- *Blastomycosis*

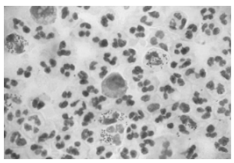
> 35 years of age: enteric flora or spread from urine

- *Escherichia coli*
- *Klebsiella*
- *Proteus*
- *Pseudomonas*
- Enterococci

McGowan, Chapter 110, in Mandell, Douglas, and Bennett's Principles and Practice of Infectious Diseases, 9th edition

Workup of epididymitis

- Physical exam
  - Intact cremasteric reflex
  - Testes in normal location
  - No draining sinus
- Gram stain of urethral secretions
- Urinalysis and urine culture
- Nucleic acid amplification test (NAAT) of urine
  - *N. gonorrhoeae*
  - *C. trachomatis*
- Consider blood cultures
- Failure to improve within 48-72 hours
  - Scrotal ultrasound
- Call urology if concern for torsion



https://en.wikipedia.org/wiki/Neisseria_gonorrhoeae

Gram stain of urethral discharge

Differentiating epididymitis from torsion

Table 1. Selected Differential Diagnosis of Acute Scrotum

Condition	*Typical presentation*	*Examination findings*	*Ultrasound findings*
Epididymitis	Gradual onset of pain that occasionally radiates to the lower abdomen; symptoms of lower urinary tract infection	Localized epididymal tenderness that progresses to testicular swelling and tenderness; normal cremasteric reflex; pain relief with testicular elevation (Prehn sign)	Enlarged, thickened epididymis with increased blood flow on color Doppler
Orchitis	Abrupt onset of testicular pain	Testicular swelling and tenderness; normal cremasteric reflex	Testicular masses or swollen testicles with hypoechoic and hypervascular areas
Testicular torsion	Acute onset of pain, usually severe	High-riding transversely oriented testis; abnormal cremasteric reflex; pain with testicular elevation	Normal-appearing testis with decreased blood flow on color Doppler

Trojian, American Family Physician, 2009

Treatment of epididymitis

- If patient is low risk for sexually transmitted infection
  - Levofloxacin or trimethoprim-sulfamethoxazole—for enterics
- If risk for sexually transmitted infection
  - And NO insertive anal intercourse
    - Ceftriaxone—for *N. gonorrhoeae*
    - Doxycycline (azithro as alternative)—for *C. trachomatis*
  - And YES insertive anal intercourse
    - Ceftriaxone—for *N. gonorrhoeae*
    - Fluoroquinolone (can cover for chlamydia)—for enterics
- For all: scrotal elevation and cold packs

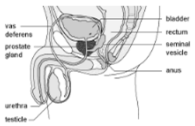
UpToDate Acute Scrotal Pain in Adults
MMWR Vol. 70, No. 4,2021
Trojian, American Family Physician, 2009

27 – Epididymitis, Orchitis, and Prostatitis

Speaker: Barbara Trautner, MD

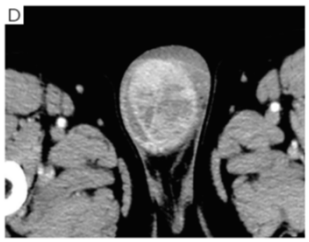
Epididymitis: Management and Complications

- Medical management
  - Antibiotics
  - NSAIDS
  - Scrotal elevation and ice packs
- Complications
  - Testicular infarction
  - Scrotal abscess
  - Epididymo-orchitis



Case #2

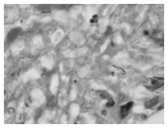
- 63 year-old man currently living homeless in Houston presented with a gradually enlarging, painful right testicle over the past 4 months
- Afebrile and he has thickened right scrotal skin but no fistula on exam
- WBC 15,000; negative HIV, AFP, RPR, and beta-HCG
- CT with contrast shows uneven enhancement of right testes and epididymis; the left epididymis was also enlarged with diffuse enhancement
- What test would you NOT do next?
  - A. TB spot
  - B. Urine culture for AFB
  - C. Testicular biopsy
  - D. Urine PCR for TB



Li, Chen, Fang et al, Quant Imaging Med Surg 2021; 11(6)

Tuberculous epididymo-orchitis

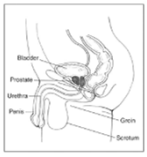
- Genitourinary TB typically starts in the epididymis
- Hematogenous or contiguous spread (direct from sexual contact)
- Presents as painful scrotal mass
- Imaging may reveal bilateral involvement
- TB testing often positive
- Diagnosis: AFB stain, culture, and PCR of urine
  - Consider also prostatic secretions
- Avoid fine needle biopsy if any concern for germ cell tumor
- Fistulas, abscesses, and infertility can result if untreated



Yadav et al, Transl Androl Urol 2017
Liu et al, Surgical Infections 2021
Li et al, Quant Imaging Med Surg 2021

Prostatitis NIH Consensus Categories

- I Acute bacterial* prostatitis
- II Chronic bacterial* prostatitis
- III Chronic prostatitis/chronic pelvic pain syndrome
  - IIIA Inflammatory
  - IIIB non-inflammatory
- IV Asymptomatic inflammatory prostatitis
  - Incidental finding, no need to treat



*includes non-bacterial pathogens, such as fungal organisms

Understanding the Prostatitis NIH Consensus Categories

Condition	Bacteriuria	Localized to Prostate	Abnormal Rectal Exam	Systemic Illness
I Acute Bacterial Prostatitis	+	+	+	+
II Chronic Bacterial Prostatitis	+	+	–	–
III Chronic Pelvic Pain Syndrome	–	–	–	–
IV Asymptomatic Inflammatory Prostatitis	–	–	+/–	–

McGowan, Chapter 110, in Mandell, Douglas, and Bennett's Principles and Practice of Infectious Diseases, 9th edition

Understanding the Prostatitis NIH Consensus Categories

Condition	Bacteriuria	Localized to Prostate	Abnormal Rectal Exam	Systemic Illness
I Acute Bacterial Prostatitis	+	+	+	+
II Chronic Bacterial Prostatitis	+	+	–	–
III Chronic Pelvic Pain Syndrome	–	–	–	–
IV Asymptomatic Inflammatory Prostatitis	–	–	+/–	–

McGowan, Chapter 110, in Mandell, Douglas, and Bennett's Principles and Practice of Infectious Diseases, 9th edition

27 – Epididymitis, Orchitis, and Prostatitis

Speaker: Barbara Trautner, MD

Case #3

A 69 year-old man presents with pain in the lower abdomen, rectum, and perineum for the past 48 hours. He has chills and nausea in addition to urinary urgency, frequency, and dysuria. Gentle digital rectal examination finds a painful and swollen prostate. He has not been able to pass urine for the past 10 hours.

Management should include:

A. Nitrofurantoin
B. Urology consultation for catheterization
C. Culture of expressed prostatic secretions
D. PSA (prostate specific antigen) levels

Acute bacterial prostatitis: clinical presentation

- Acutely ill patient
- Prostatic tenderness is the distinguishing feature
- Fever, chills, irritative urinary symptoms
- Lower abdominal, rectal, or perineal pain
- Voiding difficulties
- Pathogenesis: from infection in the urinary tract, prostate biopsy, or hematogenous spread
- Risk factors: urinary catheters, urinary stasis, urinary instrumentation

UpToDate Acute Bacterial Prostatitis
Brede and Shoskes, Nat Rev Urol 2011

Infectious prostatitis: Causative agents

Acute **> 60% caused by**

- *Escherichia coli*
- *Proteus*
- Other Enterobacterales
- *Pseudomonas*
- Staph, strep, enterococci
- *Salmonella typhi* (HIV)
- Burkholderia (traveler to SE Asia or N. Australia)
- STI: gonorrhea or chlamydia

Chronic or immunocompromised

- Mycobacteria
- Fungal
  - Cryptococcus
  - Histoplasma
  - Aspergillus
  - Coccidioidomycosis
  - Candida
  - Blastomycosis

Diagnostic workup of prostatitis

- Physical exam
  - Painful prostate
- Urinalysis and urine culture
- Consider blood cultures
- Failure to improve within 48-72 hours
  - Prostate ultrasound, computed tomography (CT) scan, MRI
- Call urology if unable to void

Antibiotic treatment of acute bacterial prostatitis

- Most common pathogens are *E. coli* and other Enterobacterales
  - Microbiologic causes are very diverse
- Acute prostatitis
  - Start broad—cephalosporins, carbapenems, +/-aminoglycoside
  - Treatment duration 2-6 weeks
- Oral options: fluoroquinolones, sulfonamides, tetracyclines, macrolides, fosfomycin all penetrate the prostate
- Chronic prostatitis
  - Duration unclear—4, 6, 12 weeks all reported

Lipsky et al, Clinical Infect Dis 2010
Schaeffer and Nicolle, NEJM 2016
Chou et al, Drugs 2022
Brehm, ID Clin North America 2023
UpToDate Chronic Bacterial Prostatitis

Case #4

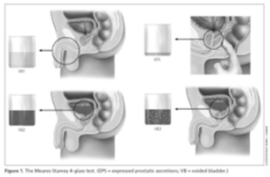
A 72 year-old man presents with pain in the perineum, penile tip, and scrotum, which has been going on for the past three months. He had lower back pain a week ago, but the pain has since subsided. He has had two episodes of UTI with burning on urination in the past six months. On physical examination, his prostate is boggy and tender to palpation.

What is the most common cause of a chronic form of this condition?

A. Herpes
B. Chlamydia
C. *E. coli*
D. Candida

Chronic bacterial prostatitis

- Patients not acutely ill
- Recurrent UTI with same organism is common
- The four-glass Mears-Stamey test is cited often
- In practice urologists more often do the two-glass test
  - Urine samples pre/post prostatic massage



Sharp et al, Am Fam Physician 2010

Case #5

A 58-year-old man presents with fever and shaking chills the day after undergoing transrectal prostate biopsy for possible prostate cancer. Prior to the biopsy, he had received one dose of oral ciprofloxacin.

In the emergency department, his temperature is 101.5, and he has rigors. He reports rectal pain and difficulty voiding. His creatinine is normal. Blood and urine cultures are sent. Which of the following antibiotics would be **an appropriate choice**?

A. Amikacin
B. Fosfomycin
C. Ciprofloxacin
D. Trimethoprim-sulfamethoxazole

Antibiotic prophylaxis for prostate biopsy

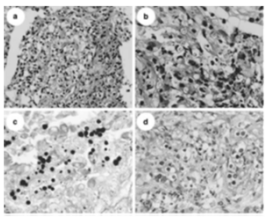
- Strongly recommended
- Pre-procedure antibiotics reduce the risk of bacteriuria, symptomatic UTI, bacteremia, fever, acute prostatitis, hospitalization
- No one best choice
- Options include fluoroquinolones, TMP/SMX, gentamicin, and ceftriaxone
- One dose, one hour to the procedure
- No benefit seen for enemas prior to procedure
- Infection after biopsy often caused by fluoroquinolone-resistant *E. coli*

Zani et al, Cochrane Review, 2011

Case #6

A 55-year-old man with HIV/AIDS (CD4 32) was referred to urology for obstructive voiding symptoms. Prostate exam revealed asymmetric enlargement. Urinalysis and urine culture unremarkable. Ultrasound showed bilateral nodules consistent with malignancy. Biopsy revealed:

A. Candida
B. E. coli
C. Cryptococcus
D. Aspergillus
E. Nocardia



Wada et al, Prostate Cancer and Prostatic Dis 2008
Adams et al, Urology 1992
Wise and Shteynshlyuger, Curr Urology Rep 2006

Case #7

INFECTIOUS DISEASE BOARD REVIEW AUGUST 10-13 2023 PREVIEW QUESTION

A 35 year-old man who is a member of a religious group that does not support vaccination attended a wedding in Nebraska. Two days later he developed pain in his left ear and jaw tenderness. Eleven days later he had noticeable swelling under both sides of his jaw, fever, and painful swelling of his left testicle. The likely causative agent is:

A. Mumps
B. Measles
C. Escherichia coli
D. Neisseria gonorrhea

Orchitis (isolated involvement of testes)

- Viral infections are common
  - Mumps
  - Coxsackie B
  - Lymphocytic choriomeningitis
- Bacterial
  - Contiguous spread from epididymis
  - Same organisms as epididymitis
    - *E. coli* and other enterics
    - Also same rare organisms (TB, fungal)

https://www.environmentandsociety.org/arcadia/mumps-post-secondary-environment-targeted-advertising-2007-2008-alberta-mumps-vaccination

27 – Epididymitis, Orchitis, and Prostatitis

Speaker: Barbara Trautner, MD

To Wrap Up:

- Epididymitis
  - Consider sexually transmitted infection versus *E. coli* and other enteric flora
- Prostatitis
  - Consider acute bacterial prostatitis in men with febrile UTI—detected by physical exam
  - Consider chronic bacterial prostatitis in men with recurrent or relapsing UTI
- Fungal, TB, and other indolent organisms (Brucella) can invade and infect the male genitourinary tract
- Isolated orchitis is rare in adults—consider viral etiology

Is everything clear now?

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- @bwtrautner

28

Lyme Disease

Dr. Paul Auwaerter

28 – Lyme Disease

Speaker: Paul Auwaerter, MD

IDBR INFECTIOUS DISEASE BOARD REVIEW LIVE/VIRTUAL AUGUST 19-23 2023

Lyme Disease

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7/11/2023

IDBR INFECTIOUS DISEASE BOARD REVIEW LIVE/VIRTUAL AUGUST 19-23 2023

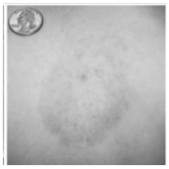
Disclosures of Financial Relationships with Relevant Commercial Interests

- **Consulting –Pfizer, medical-legal**
- **Research –Pfizer**

Question # 1

A 56 y.o man from southern Missouri
Onset in July:
Myalgia and malaise
Rash of two days duration
Tick bite 1 week ago

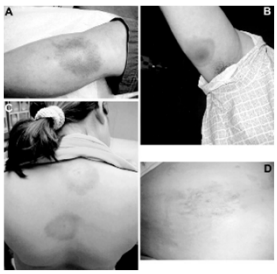
Exam: T 37.0°C
Annular "bulls-eye" ~6 cm
(same area that engorged tick was removed earlier in the week)



Question # 1

Which of the following is the most likely diagnosis?

A. Lyme disease (*Borrelia burgdorferi* infection)
B. Human Monocytic Ehrlichiosis (*Ehrlichia chaffeensis)*
C. *Borrelia mayonii*
D. Southern tick-associated rash illness (STARI)
E. B. lonestarii infection



STARI

Rash variable

Usually single lesion

Multiple described

Maybe Bull's eye-like

Expanding range of Lone Star Tick
(name may be obsolete?)

STARI

No infection yet convincingly documented *B. lonestarii* (single case)

Appears to occur after bite of Lone star tick

B. burgdorferi tests including serology negative

Likely accounts for some reported Lyme disease cases in non-endemic states

Unclear if doxycycline needed, typically given

No sequelae

James AM, J Infect Dis 2001;183:1810

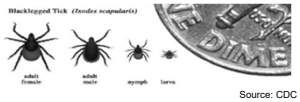
CDC, https://www.cdc.gov/stari/geo/index.html (accessed 7/18/22, last updated 11/19/18)

28 – Lyme Disease

Speaker: Paul Auwaerter, MD

B. burgdorferi: Vector-borne Infection

- Spirochetal infection due to *Borrelia burgdorferi* (Bb)
- Tick-borne disease
  - *Ixodes* species
  - In North America
    - *Ixodes scapularis* (mostly)
      - Black legged tick
    - *Ixodes pacificus*
      - Western black legged tick
- Not known as STD or blood-borne infection



Source: CDC

Commonly called the "deer tick"

Small-sized tick, unengorged

Adults: sesame seed

Nymphs: poppy seed

Bacterial reservoir:

Mice, other small mammals

Not: deer, humans

Most common vector-borne infection in US: A mostly regional disease

Reported Cases of Lyme Disease — United States, 2019

Source: CDC accessed 7/11/23

Lyme Borreliosis

USA

- *Borrelia burgdorferi*
  - Geographically localized
    - ~30,000 cases reported annually in US
      - Actual >10x more than reported
    - 95% cases in 14 states
    - Coastal, lake and river environs
      - New England
      - Mid-Atlantic
      - Upper Midwest

Europe (+ other genospecies)

- *Borrelia afzelii & Borrelia garinii >> Borrelia burgdorferi*
- Occasionally others
- Genus name: changing to *Borreliella?*

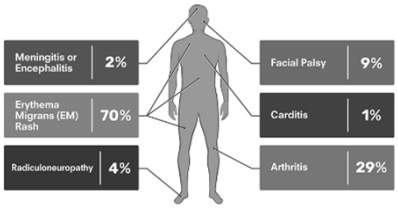
(to distinguish from relapsing fever *Borrelia spp.)*

Lyme Disease Presentations

- Early, localized
  - Rash: erythema migrans
- Early, disseminated
  - Rash: multiple erythema migrans
  - Cardiac
  - Neurologic
- Late
  - Lyme arthritis
  - Neurologic (rare)
  - Dermatologic (Europe)
- Overlapping presentations possible

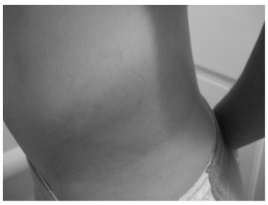
LYME DISEASE

Relative frequency of clinical features among confirmed cases – United States, 2008–2019



(based on 62% of 311,561 confirmed cases reported--probably favoring later presentations, Source CDC)
http://www.cdc.gov/lyme/stats/chartstables/casesbysymptom.html

Question # 2



July, 18M living in suburban Maryland, with this rash growing to ~12 cm, first noted 4d, ago, asymptomatic. Landscaper, had tick bite 10d ago. PCP gave cephalexin 2d ago.

Which of the following is true

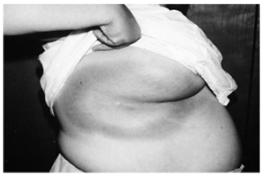
A. Lack of response to cephalexin is consistent with erythema migrans
B. Lack of systemic symptoms makes this unlikely to be Lyme disease
C. Ordering *B. burgdorferi* 2-tier serology will likely confirm Lyme disease
D. Whole blood *B. burgdorferi* PCR is superior to serology in early infection
E. Tick should be submitted for detection of *B. burgdorferi* by PCR

28 – Lyme Disease

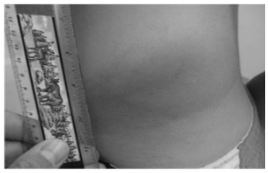
Speaker: Paul Auwaerter, MD

Early, localized LD: Erythema migrans

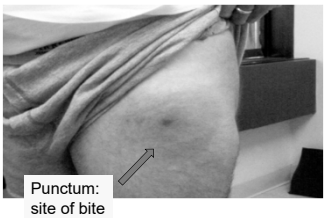
Classic: "bull's eye"
with central clearing upon expansion



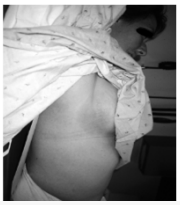
Most common: homogeneous, pink-red ovoid



Typical Erythema Migrans

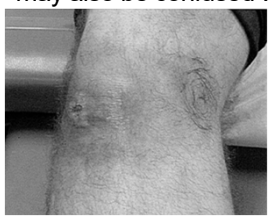


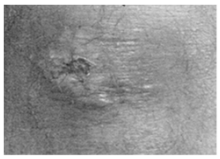
Punctum:
site of bite



Lesions: occur typically below neck and above knees & elbows

Spider bite?: differential diagnosis may also be confused with MRSA, cellulitis



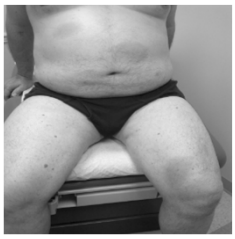


Less typical erythema migrans:
skin punch biopsy *B. burgdorferi* culture positive (research labs only)

Erythema migrans

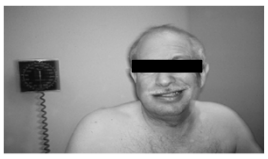
- Primary lesion: occurs 3-30d [7-14d average] @ site tick bite site
  - > 5cm = more secure diagnosis
    - Ddx: includes cellulitis, tinea, erythema marginatum, tick hypersensitivity reaction (smaller)
  - Diagnosis: characteristic rash + epidemiology
    - Serologic testing not recommended, rash sufficient
    - Acute serology negative 40-70% in early Lyme disease
- Most lesions with minimal local symptoms
  - ~70% experience flu-like problems (fever, HA, myalgia)

Early, Disseminated Lyme disease (1)



- Multiple Erythema Migrans
  - Often smaller and less red than primary lesion
  - Always ill:
    - Fever
    - Flu-like symptoms
    - Headache

Early, Disseminated Lyme disease (2)



- Neuroborreliosis
  - Aseptic meningitis
    - Lymphocytic predominance
  - Cranial nerve palsy
    - CN VII (facial)
      - Most common
      - Bilateral CN VII may occur
      - Other CN palsies: seen less
        - e.g., III, VI, VIII
  - Radiculoneuritis
  - Mononeuritis multiplex

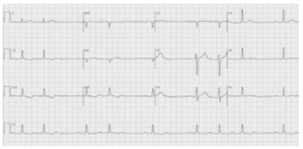
Diagnosis – Facial Palsy

- Facial Palsy: up to 25% due to *B. burgdorferi* (Long Island NY)[1]
- Serology may take 4-6 wks turn positive
  - (if untreated, recheck if negative and suspicious)
- Lumbar puncture
  - Not required
- Most would recover without antibiotic therapy[2]
  - Main role of abx: prevent later disease manifestations

[1]Neurology 1992; 41:1268.
[2]Laryngoscope 1985; 95:1341. Clin Infect Dis. 2006 Nov 1;43(9):1089

Early, Disseminated Lyme disease (3)

- 19M collapsed outside VT college cafeteria
  - Lacrosse athlete, not well for ~ 1 month



- Lyme carditis
  - 1°, 2° or 3° block
    - May be variable
    - 3° most identified since symptomatic
      - May need temporary pacer
      - Complete heart block usually resolves within several days of antibiotic, lesser block may take weeks

PA2

Question # 3

IDBR 2023 PREVIEW QUESTION

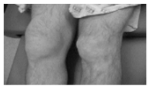
56M Long Island, NY with R knee pain and swelling x 3 weeks. Thought this was a wrenched knee from yardwork.

No fever, rash, tick bite or Lyme disease history

PMH: HTN, hyperlipidemia

PE: afebrile, mildly warm knee, moderate effusion, reduced ROM

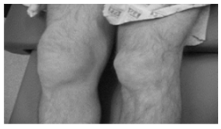
Labs: nl CBC



Which of the following is usually true for Lyme arthritis?

A. If untreated, the knee swelling will not remit
B. *B. burgdorferi* PCR synovial fluid ~ 100% sensitivity
C. Synovial fluid WBCs >50,000 cells/mL
D. Synovial fluid *B. burgdorferi* culture ~100% sensitivity
E. Serum *B. burgdorferi* 2-tier testing ~100% sensitivity

Late Lyme disease (1): Lyme arthritis



- Recurrent mono- or oligo-arthritis
  - Knee most common
    - Large, cool effusions
    - Baker's cysts may develop
  - Other large joints possible + TMJ
- Afflicts ~30% untreated patients (historically 50-60%)
- May remit, recur in different joints over period of wks to mos w/o abx Rx

Ann Int Med 1987; 107:725
Lantos, CID Nov 30, 2020

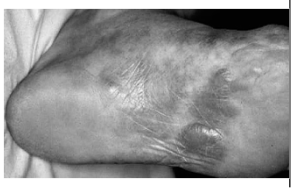
Late Lyme disease (2): Neurologic

- Encephalopathy:
  - Cognitive dysfunction, objective
  - Due to systemic illness, rather than true CNS infection
- Encephalitis: rare
  - Objective neurological or cognitive dysfunction
  - White matter changes on MRI or abnormal CSF
  - CSF: (+) lymphocytic pleocytosis, Bb antibody
- Peripheral neuropathy: rare (controversial)
  - Pain or paresthesia
  - Diffuse axonal changes on EMG/NCV

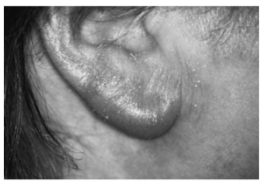
Late Lyme disease (3): Dermatologic

Europe only

Acrodermitis chronica atrophicans (Europe)



Borrelia Lymphocytoma (Europe)



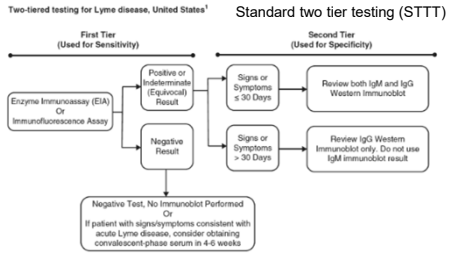
Question # 4

- 49F complains of four years of fatigue, headache, poor sleep and joint aches since trip to London UK
  - PMH: TAH/BSO
  - Medications: hormone replacement
  - SH: Married, accountant. Lives in central Pennsylvania. Two dogs, often sleep in bed.
  - PE: normal
  - Labs: normal CBC, ESR, TSH
    - *B. burgdorferi* serology: EIA (not done), IgM WB 3/3 bands, IgG 1/10

Question # 4

- What is the best recommendation at this time?

A. Doxycycline 100 mg twice daily x 14 days
B. Doxycycline 100 mg twice daily x 28 days
C. Repeat Lyme serology (two tier: EIA w/ reflex WB)
D. Borrelia burgdorferi PCR (whole blood)
E. Neither additional Lyme disease testing nor treatment



Standard two tier testing (STTT)

Laboratory testing

- Two tier serology: not needed for erythema migrans
  - First: total Ab screen – ELISA or EIA
  - If positive, second tier reflexes to immunoblots (IB)
    - IgM: ≥ 2/3 bands, use only if < 4 wks of symptoms
      - High rates false (+)
    - IgG: ≥ 5/10 bands, more reliable
      - Alternative criteria (different bands): less specific
  - Often negative in early infection (first 2-3 weeks)
  - May need acute/convalescent for confusing rashes or neuroborreliosis
  - Serology: may remain (+) for decades including IgM

MMWR 1995;44:590
Clin Infect Dis 2001;33(6):780-5

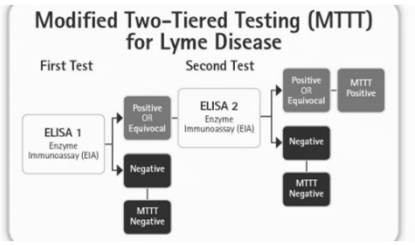
Modified Two-tier (2-EIA) vs. STTT

- 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

MTTT: Faster, Cheaper, Better (early LD)



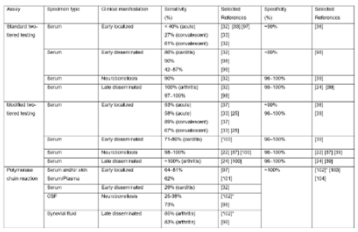
Diagnostics: Lyme arthritis

- 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



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 Cefuroxime 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 Cefuroxime axetil	14-21
	IV[c]	Ceftriaxone	14-21
Arthritis	Oral	Doxycycline or Amoxicillin or Cefuroxime axetil	28

[a]Further details regarding adult and pediatric dosing can be found in the 2021 Guideline.
[b]Ranges are given if available studies are insufficient to determine the optimal duration.
[c]Cefotaxime and penicillin G are alternative IV options.
[d]Parenteral therapy is used for hospitalized patients, who, with improvement, may transition to oral antibiotics to complete the treatment course.

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

28 – Lyme Disease
Speaker: Paul Auwaerter, MD

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

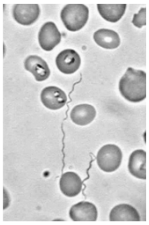
Lyme disease: co-infections

- 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

B. miyamotoi--Ixodes spp. vector

Neither Lyme disease nor Relapsing Fever

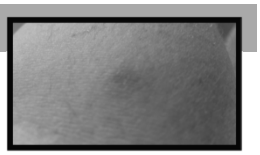


Telford, et al. Clin Lab Med 2015; 35(4):867

- Serosurvey New England: 0.8-4.0%
- Likely underdiagnosed
- Sx: HA, fever, chills, myalgia
- Not like relapsing fever:
  - No rigor, ↓ BP
  - May resemble HGA
    - Leukopenia, thrombocytopenia, LFT abnl
  - Opportunistic pathogen?
- Dx: not widely available
  - rGlpQ EIA
  - PCR
  - Spirochetes on fluid H&E
  - Doesn't appear to frequently cross-react with B burgdorferi Ab
- Treatment: likely identical as for LD

PA2

Question # 5



42M just returned from a hiking trip Colorado, a tick on his arm removed 2d earlier. Now heading out of town for a beach vacation.

Today, intense itching and redness at the site he thinks may be larger (~1cm) than yesterday. He is otherwise well.

The best course of action would be:

A. Doxycycline 200mg x single dose
B. Doxycycline x 14d
C. Doxycycline x 30d
D. Cefuroxime x 14d
E. Observation

I. scapularis tick bite prophylaxis

B. burgdorferi transmittal

- Tick attachment time
  - < 24 h: 0/58 (0%)
  - < 48 h: 4/50 (8%)
  - < 72 h: 36/52 (69%)

JID 2001; 183:773-8

Infection risk in highly endemic areas

Intervention	Risk	95% CI
No tick found	20%	
Removing tick	2.2%	[1.2-3.9%]
Single 200mg dose doxycycline*	0.4%	[0.02-2.1%]
10d doxy	0%	[0-0.97%]

*200 mg given with 72h of tick bite

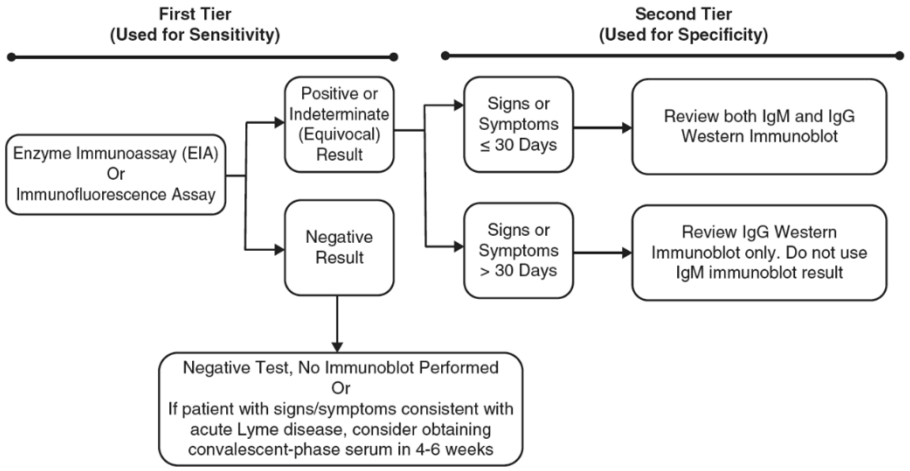
J Antimicrob Chemother 2010;65:1137-1144
N Engl J Med 2001; 345:79-84

Lyme disease: some pearls

- No need for serology if diagnosing erythema migrans
- *B. burgdorferi* IgM immunoblot most common cause of misdiagnosis
- Late Lyme arthritis: always seropositive
  - No evidence that seronegative Lyme exists in patients with long-term symptoms
- Lab evidence of LD essential unless hx of EM exists
- Prolonged antibiotic treatment doesn't improve resolution of subjective symptoms

Two-tiered testing for Lyme disease, United States[1]

Standard two tier testing (STTT)



[1]Adapted from MMWR 1995

*

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) 89% (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	98–100%	[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

Lyme disease: Initial Regimens

Treatment

Disease Manifestation	Route	Medication[a]	Duration (days)[b]
Lyme disease			
Erythema migrans	Oral	Doxycycline or Amoxicillin or Cefuroxime axetil	10 14 14
Meningitis/radiculopathy	Oral IV[c]	Doxycycline Ceftriaxone	14-21 14-21
Cranial nerve palsy	Oral	Doxycycline	14-21
Encephalomyelitis	IV[c]	Ceftriaxone	14-28
Carditis	Oral IV[d]	Doxycycline or Amoxicillin or Cefuroxime axetil Ceftriaxone	14-21 14-21
Arthritis	Oral	Doxycycline or Amoxicillin or Cefuroxime axetil	28

[a]Further details regarding adult and pediatric dosing can be found in the 2021 Guideline.
[b]Ranges are given if available studies are insufficient to determine the optimal duration.
[c]Cefotaxime and penicillin G are alternative IV options.
[d]Parenteral therapy is used for hospitalized patients, who, with improvement, may transition to oral antibiotics to complete the treatment course.

Lantos et al, IDSA/AAN/ACR Lyme Guideline, CID 2021; 72(1)e1-e48

*

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

29

Hospital Epidemiology

Dr. Michael Klompas

29 – 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

6/28/2023

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**

Topics

- **Fomites:** beware of hands, fingernails, and equipment
- **Air:** droplets? aerosols? masks?
- **Water:** the source of all evil
- ***Clostridioides difficile* & *Staph aureus*:** you are your own enemy
- **Devices:** the other source of all evil
- **Cluster investigation:** find the missing link

Question #1

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

Question #2

What is the most common healthcare-associated pathogen?

A. *Pseudomonas aeruginosa*
B. *Staphylococcus aureus*
C. *Klebsiella pneumoniae*
D. *Candida albicans*
E. *Clostridioides difficile*

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 #3

A surgical colleague calls you because 2 of his patients developed *Candida albicans* surgical site infections following spine surgeries. You review the hospital's microbiology records and confirm that this is very unusual. What are potential sources for this cluster?

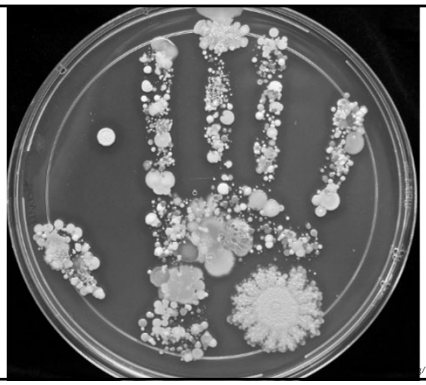
A. Scrub nurse wearing artificial nails
B. Disruption of laminar airflow in the operating room
C. Contamination of intravenous fluids used during surgery
D. Failure of peri-operative blood glucose control
E. Use of broad-spectrum antibiotics for peri-operative prophylaxis

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

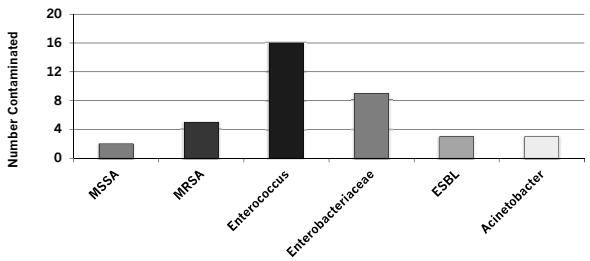
Gupta, *ICHE* 2004;25:210-215
Gordon, *ICHE* 2007;28:743-744
Foca, *N Engl J Med* 2000;343:695-700
Parry, *Clin Infect Dis* 2001;32:352-7
McNeil, *Clin Infect Dis* 2001;33:317-323
Marmral, *ICHE* 2003;24:749-52



y/Tasha Sturm/Cabrillo College

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

Promote healthy hand skin & fingernails

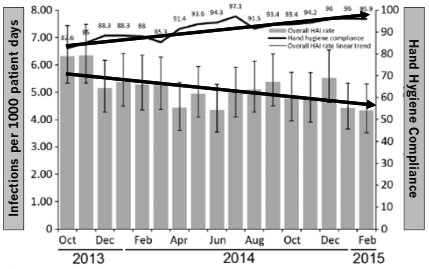
- Fingernails should be short, healthy, and natural
- Perform hand hygiene per the WHO's Five Moments
- Alcohol-based hand rub typically preferred over soap & water
- Take steps for primary and secondary prevention of dermatitis

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



* Sickbert-Bennett, Emerg *Infect Dis* 2016;9:1628-1630

Question #4

IDBR 2023 PREVIEW QUESTION

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	Case 2	Case 3
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	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	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 treatment
- **Prophylactic regimens**
  - 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 #5

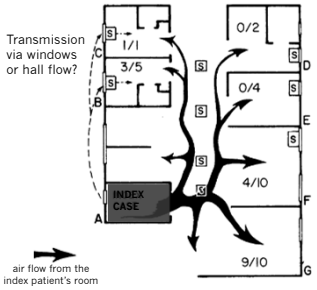
IDBR 2023 PREVIEW QUESTION

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 the same room as someone who has 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**

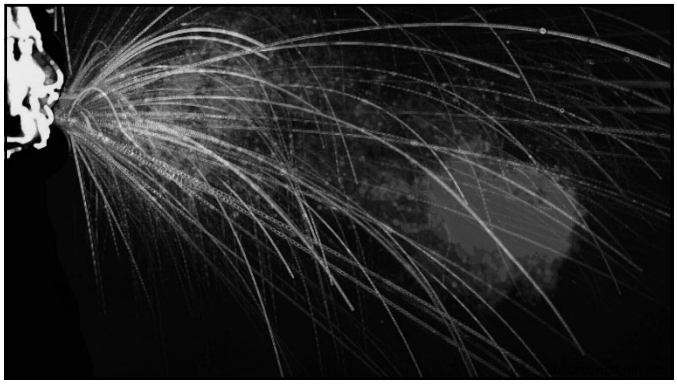
Immune Status	Vaccinate?	VariZIG?	Furlough d8-21?	Monitor d8-21?
Fully vaccinated, seropositive, prior Dx	**No**	**No**	**No**	**Yes**
Partially vaccinated	**Yes**	**No**	**Depends[2]**	**Yes**
Unvaccinated & seronegative	**Yes**	**No**	**Yes**	**Yes**
Unvaccinated & unable to vaccinate[1]	**No**	**Yes[3]**	**Yes[4]**	**Yes**

[1] Vaccine contraindicated in pregnant or immunocompromised
[2] Furlough if vaccine only given >5d after first exposure
[3] Or valacyclovir d7-13 if VariZIG not available
[4] Furlough d8-28 if given VariZIG

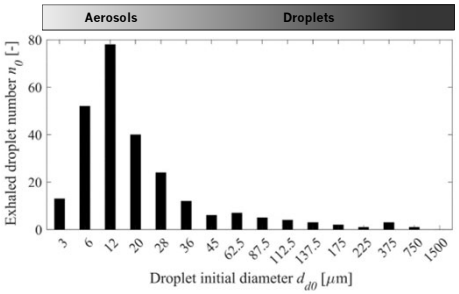
Question #6

Your vaccinated co-worker is convinced she caught SARS-CoV-2 at work despite wearing a surgical mask for all patient encounters. She did care for a patient who was diagnosed with SARS-CoV-2 infection on hospital day 4 following an elective admission for breast surgery. Your boss asks if it is possible your co-worker was infected by this patient despite wearing a surgical mask?

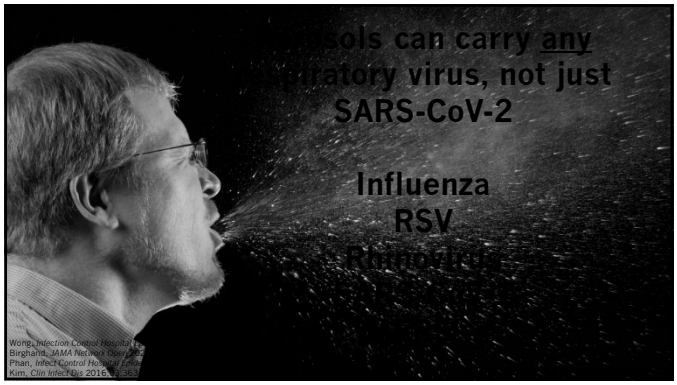
A. No, surgical masks provide excellent protection against respiratory viruses
B. No, breakthrough infections are very unusual in vaccinated people
C. No, SARS-CoV-2 in HCWs is almost always acquired outside the hospital
D. Yes, surgical masks provide partial protection against respiratory viruses
E. Yes, surgical masks do not provide any protection against respiratory viruses



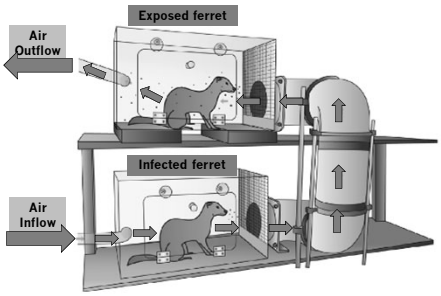
People Produce Respiratory Particles in a Range of Sizes



Chen, *Building and Environment* 2020;176:106859



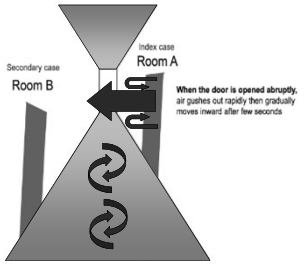
Transmission via Aerosols



- Ferret model used to assess aerosol transmission
- 4 uninfected ferrets exposed to ferrets infected with SARS-CoV-2 & influenza
- Airflow between cages via closed pipe, 1.1m long, 4 right-angle turns
- 2/4 ferrets exposed to SARS-CoV-2 infected
- 4/4 ferrets exposed to influenza infected

Kutter, *Nature Communications* 2021;12:1653

Aerosol Transmission in Humans: Quarantine Hotels

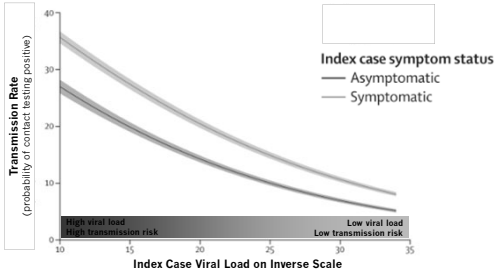


- Multiple case reports of transmission between unrelated travelers staying in quarantine hotels in Hong Kong, Singapore, New Zealand...
- Quarantine hotels have very strict rules requiring guests to stay in their own room at all times (video monitoring)
- Transmission presumed due to
  - Prolonged dwell time in poorly ventilated room leading to high concentration of virus in the air
  - Escape of virus laden air into stagnant corridors when room door is opened
  - Entry of virus laden air into nearby rooms when their residents subsequently open their doors

Wong, *Lancet Regional Health – Western Pacific* 2022;18:100360

Viral Load Predicts Transmission Risk

Secondary attack rates amongst 1,173,643 contacts of 6,263,786 index cases, UK, Jan 2021-Jan 2022

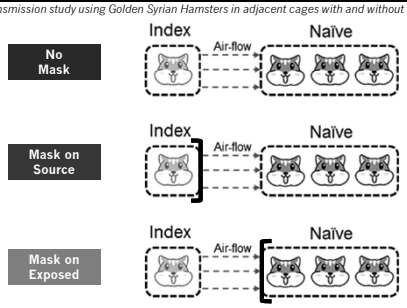


Eyre, *Lancet ID* 2023;ePub PMID 37001541

How good is your surgical mask?

Medical Masks are Good! … But Not Perfect

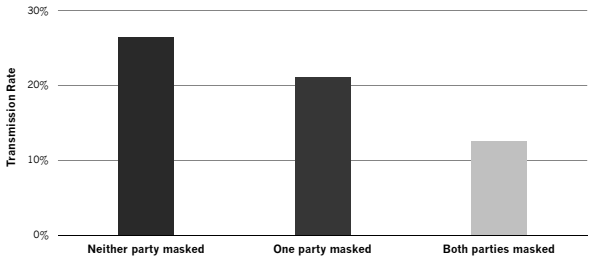
Transmission study using Golden Syrian Hamsters in adjacent cages with and without tightly fixed surgical masks between cages



Chan, Clin Infect Dis 2020;71:2139-2149

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 Can 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

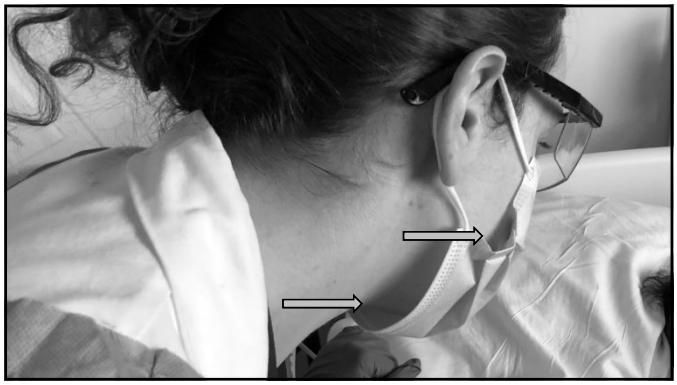
Even days
Patients unmasked
Ward air ported to guinea pig group 2

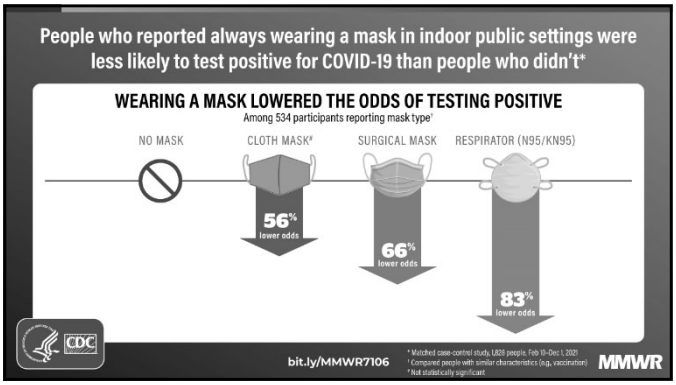
36/90 (40%) Infected

69/90 (77%) Infected

Masking patients associated with 56% decrease in TB transmission to guinea pigs

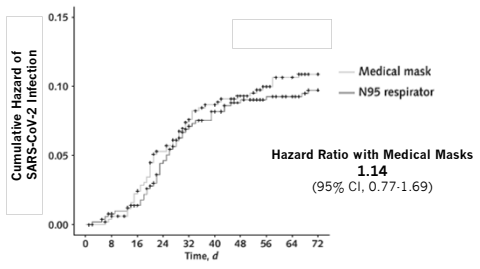
Dharmadhikari, *AJRCCM* 2012;185:1104-1109





What about the RCTs of Medical Masks vs N95s?

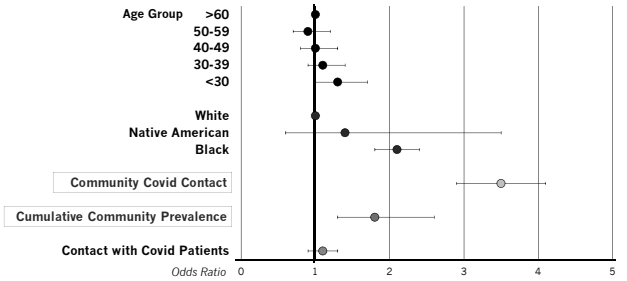
1009 healthcare workers randomized to N95s vs medical masks for routine care of patients with suspected or confirmed Covid-19



Loeb, *Ann Intern Med* 2022;175:1629-1638

Risk Factors for Healthcare Worker Infections

Seropositivity analysis amongst 24,749 healthcare workers, 4 U.S. healthcare systems in MD, GA, and IL



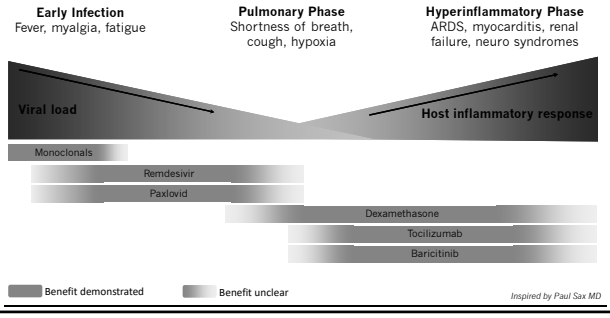
Jacob, *JAMA Network Open* 2021;4(3):e211283

Question #7

Which of the following healthcare workers is at greatest risk of getting infected with SARS-CoV-2 by a patient?

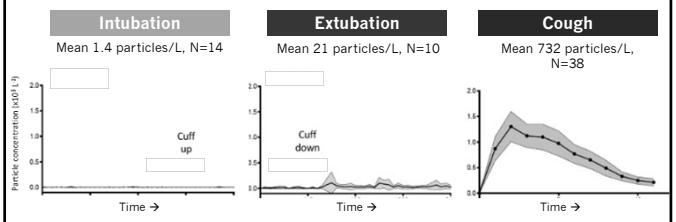
A. Anesthesiologist performing intubations for elective surgeries (PPE = surgical mask)
B. Nurse working in ICU looking after COVID patients on high flow O2 (PPE = N95, eye protection, gown, gloves)
C. Psychiatrist counselling healthy outpatients in person in her office (PPE = surgical mask)
D. Food services worker dropping off food trays for patients in COVID and non-COVID rooms. (PPE = none)

The Sickest are Sometimes the Least Contagious



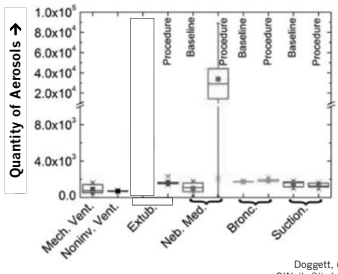
How many aerosols does intubation generate?

Continuous aerosol monitoring using an optical particle sizer in an operating room



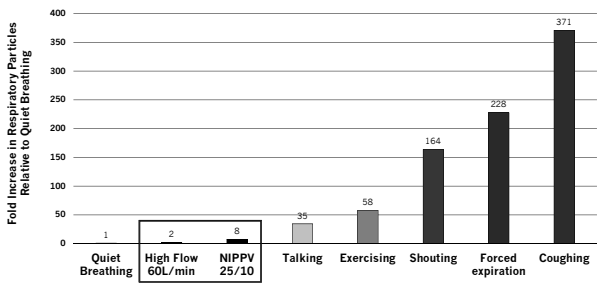
Brown, *Anesthesia* 2021;76:174-181

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

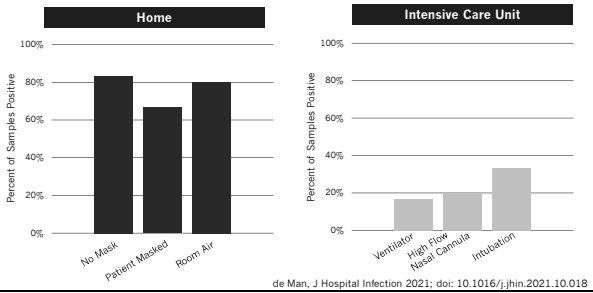
Impact of High Flow O2 on Respiratory Emissions



Wilson 2021, medRxiv, doi: 10.1101/2021.02.07.21251309

SARS-CoV-2 Air Sampling: ICU vs Home

Air sampling for SARS-CoV-2 RNA in rooms of Covid positive patients in ICU vs home



de Man, J Hospital Infection 2021; doi: 10.1016/j.jhin.2021.10.018

Risk & Protection Exists on a Continuum

Factors That Increase Risk	Factors That Decrease Risk
High community incidence	Low community incidence
Higher viral load	Lower viral load
Symptoms	Lack of symptoms
Proximity	Distance
Longer exposure	Brevity
Poor ventilation	Good ventilation
Lack of masking	Mask on patient
Lack of vaccination	Mask on provider
	N95 > KN95 > facemask
	Vaccination

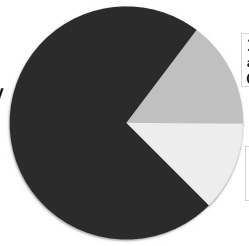
Question #8

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 toilet seat of the shared bathroom in his room
C. From the food provided by the hospital
D. 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

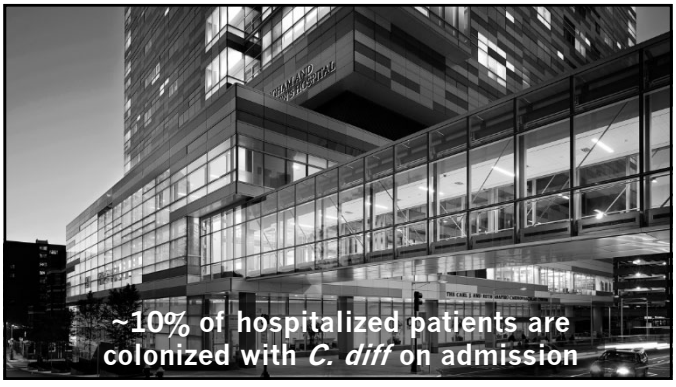


73% unrelated to any other isolate

15% related to another isolate
and hospital contact possible
(overlapping admission, same or different ward)

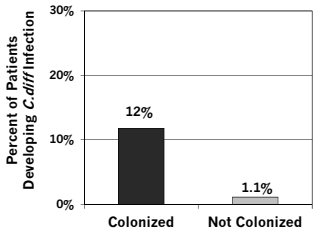
12% related to another isolate
but no record of community or hospital contact with another symptomatic patient

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

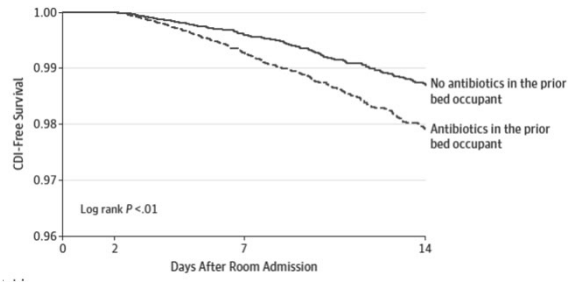
Prior Room Occupant Flagged for *C.diff* **11.0%**

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

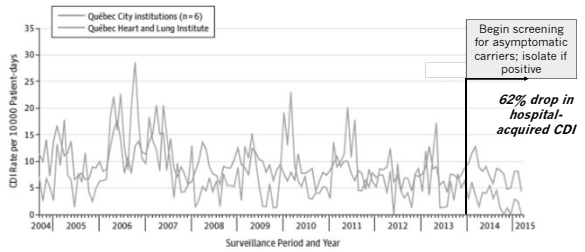
Impact of Prior Bed Occupant's Antibiotic History and Current Bed Occupant's *C.diff* Risk



JAMA IM 2016;176:1801-1808

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



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Longtin, *JAMA Internal Med* 2016;176:796-804

Essential Practices to Prevent *C.difficile* in Hospitals

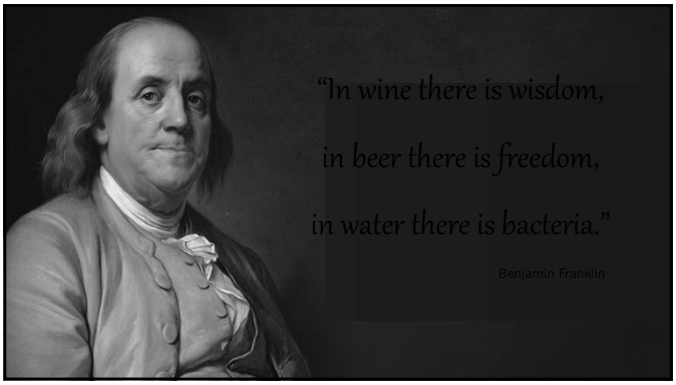
- Encourage appropriate use of antimicrobials through implementation of an antibiotic stewardship program
- Implement diagnostic stewardship to assure appropriate use and interpretation of *C.difficile* testing
  - Guide or limit use of PCR, aid in interpretation
  - Avoid testing patients if no significant 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 #9

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 and all 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?



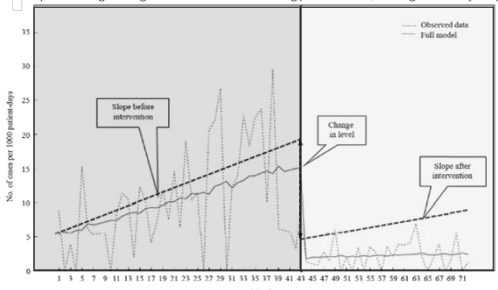
Water Avid Pathogens

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

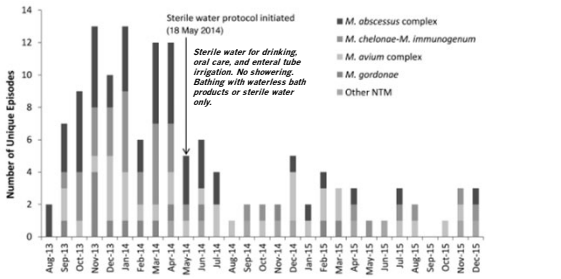
Incidence of ICU-acquired MDR gram negatives before vs after removing patients' sinks, Bellvitge University Hospital, Barcelona



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 #10

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?

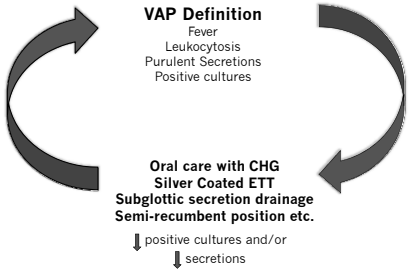
A. Silver coated endotracheal tubes
B. Oral care with chlorhexidine
C. Daily toothbrushing
D. Placing patients in the lateral Trendelenburg position
E. Probiotics

The VAP Prevention Paradox

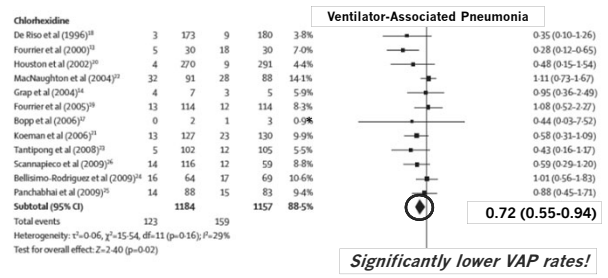
	VAP Rates	Vent Days	ICU Days	Hospital Days	Death
Oral care with chlorhexidine	↓	—	—	—	—
Silver-coated endotracheal tubes	↓	—	—	—	—
Subglottic secretion drainage	↓	—	—	—	—
Head-of-bed elevation	↓	—	—	—	—

Klompas, *Critical Care* 2009;13:315

Circularity Between VAP Prevention Practices and the VAP Definition



Oral Care with Chlorhexidine: Significantly *Lower* VAP Rates



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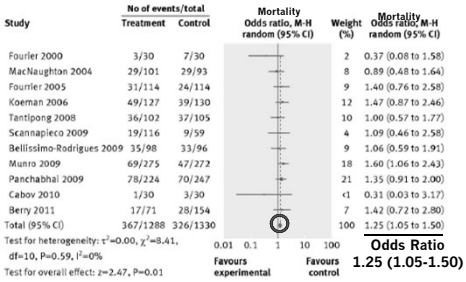
Lancet Infectious Disease 2011;11:845

Oral Care with Chlorhexidine: Significantly *Higher* Mortality Rates



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BMJ 2014;348:g2197

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 #11

You are part of a multidisciplinary team that has been working diligently to implement processes and practices to lower 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 cathether
- 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 #12

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 + 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

Nasal isolates compared to blood isolates in 219 patients with *Staph aureus* bacteremia. 82% matched

von Eiff, NEJM 2001;344:11-16

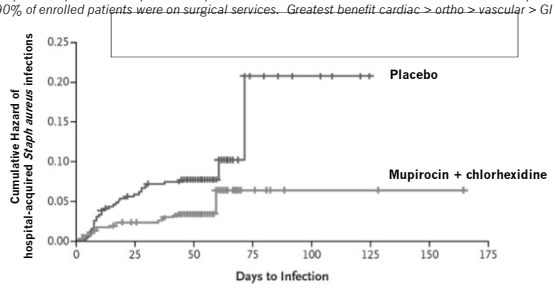
Surgical Site Infections

Nasal isolates compared to wound isolates in 39 patients with *Staph aureus* SSIs. 85% matched

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

Nasal MRSA screen

If positive, isolate

Screen and Decolonize

Nasal MRSA screen

If positive, isolate & decolonize with CHG baths x 5 days *+ mupirocin x 5 days*

Universal Decolonization

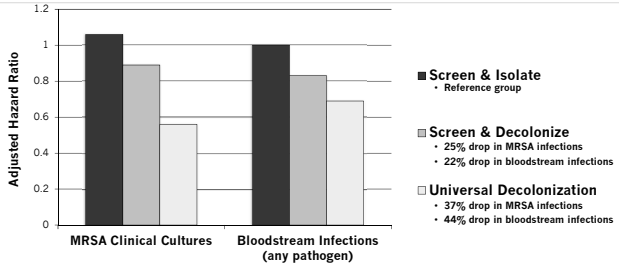
No screening

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

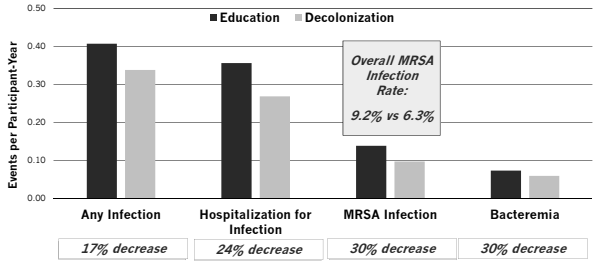
REDUCE MRSA cluster-randomized trial, 74 ICUs, 43 hospitals, 74,256 patients



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

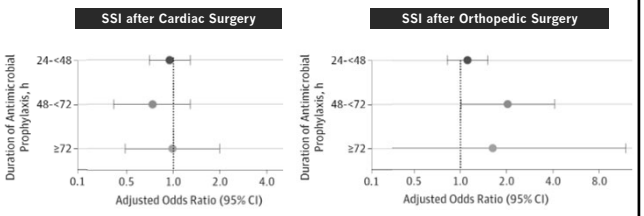
Question #13

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. 0-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…

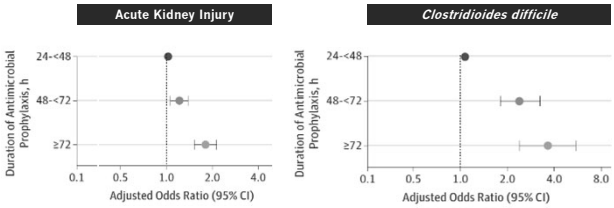
Retrospective analysis of association between duration of peri-operative antibiotic prophylaxis and adverse events in 79,058 patients who underwent orthopedic, colorectal, and vascular procedures, VA hospitals, 2008-2013



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

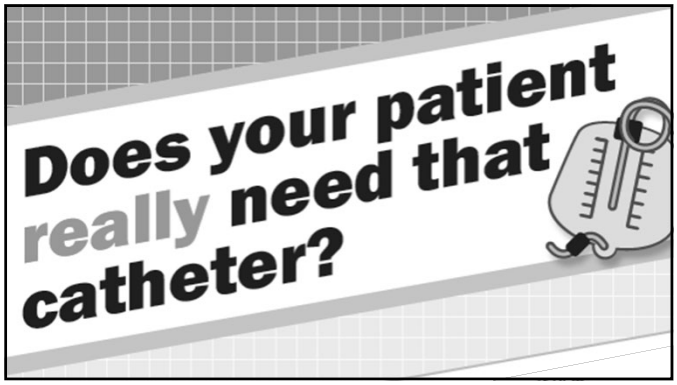
Question #14

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. You are driven to do all you can to protect her from hospital complications. 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. Start prophylactic cranberry extract
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

Recommendations to Prevent CAUTI

- Conduct daily assessment of the presence and need for indwelling urinary catheters
- Avoid using indwelling urinary catheters by using alternative urine-collection / measurements strategies
  - external suction catheters
  - condom catheters
  - daily weights for volume changes
  - bladder scanners
  - intermittent straight catheterization
- Aseptic technique for insertions
- Careful catheter maintenance
  - Use a closed system.
  - Replace if breaks in the closed system
  - Keep drainage bag below bladder
  - Empty bags q.shift and before transport
  - Do not pre-emptively change catheters to prevent infection
- Regular surveillance and feedback of infection rates



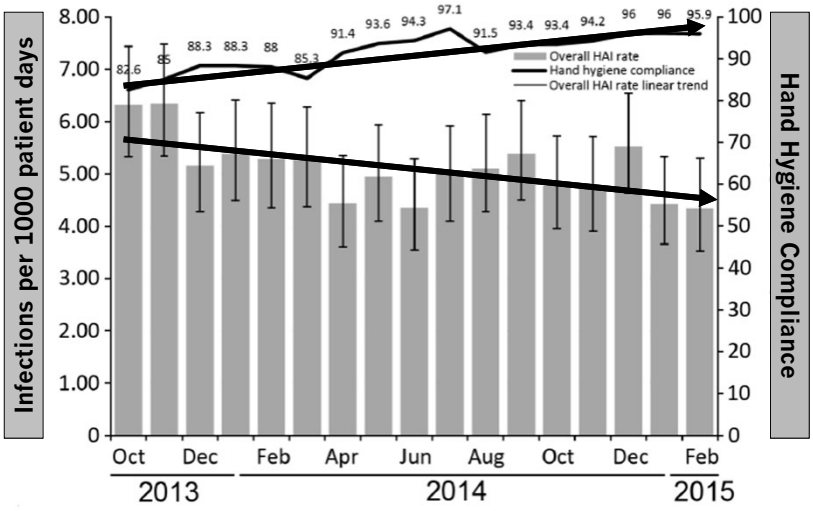
Accepted Indications:

- 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

Summary

- Pneumonia is the most common hospital-acquired infection
- *C. difficile* is the most common hospital-acquired 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 procedures, 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.

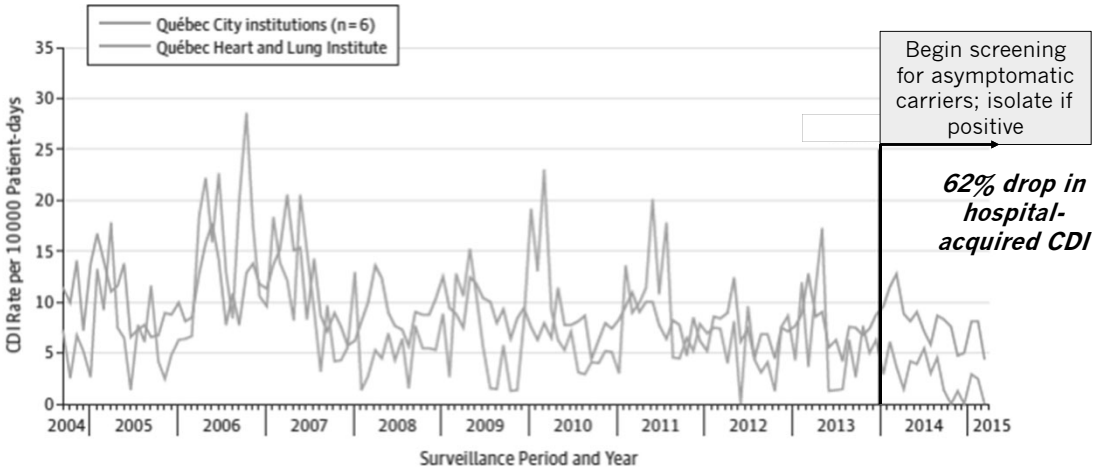
Better Hand Hygiene, Fewer Healthcare Associated Infections



* Sickbert-Bennett, Emerg *Infect Dis* 2016;9:1628-1630

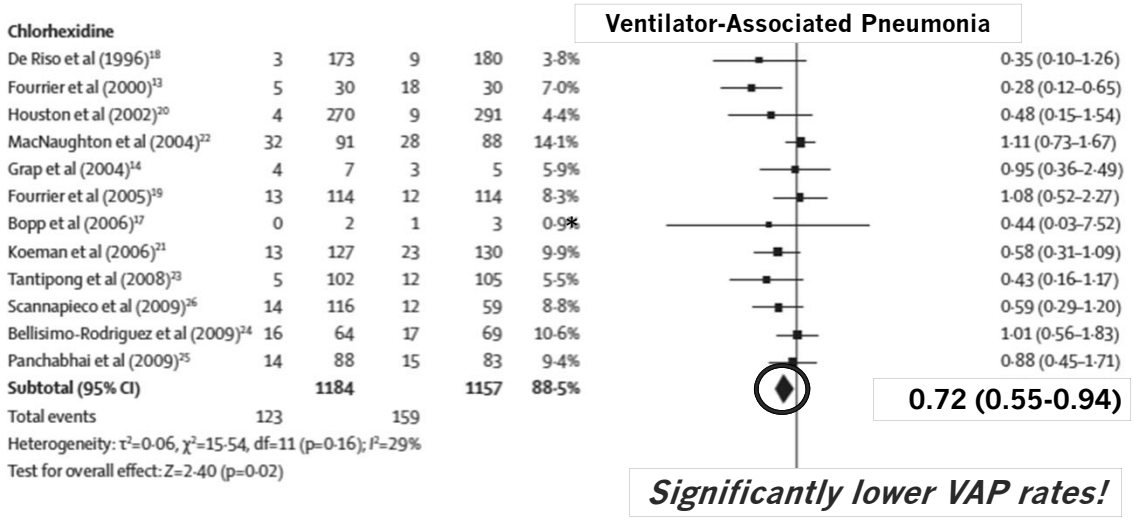
Impact of *C.diff* Screening & Isolation on *C.diff* Infections

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



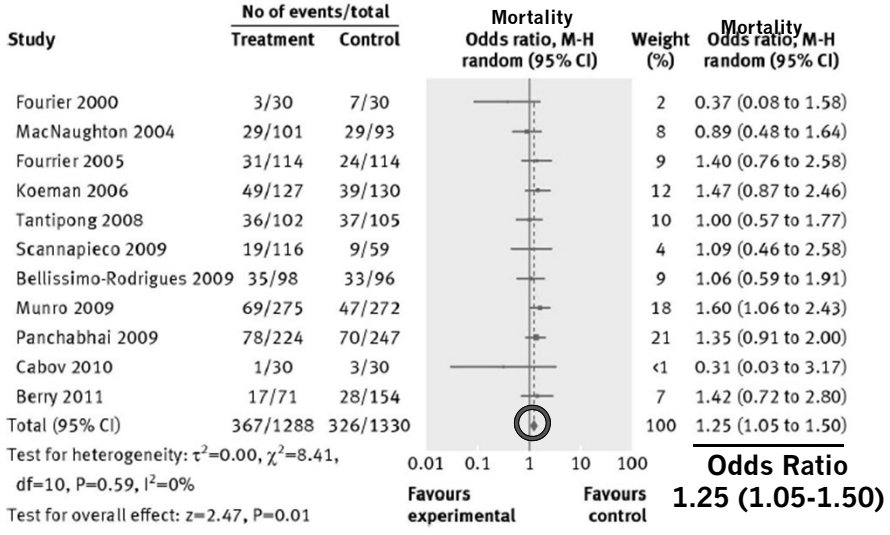
* Longtin, *JAMA Internal Med* 2016;176:796-804

Oral Care with Chlorhexidine: Significantly *Lower* VAP Rates



* *Lancet Infectious Disease* 2011;11:845

Oral Care with Chlorhexidine: Significantly *Higher* Mortality Rates



* *BMJ* 2014;348:g2197

30

Syndromes in the ICU that ID Physicians Should Know

Dr. Taison Bell

30 –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 Disease and International Health

7/25/2023

Disclosures of Financial Relationships with Relevant Commercial Interests

- **None**

Question 1: What proportion of patients in the ICU develop fever during their stay?

A. Less then 5%

B. Between 15-25%

C. Over 50%

D. Everyone. Absolutely everyone

Exam Blueprint: Critical Care Topics ~8-10%

Critical care medicine	General internal medicine
Systemic inflammatory response syndrome (SIRS) and sepsis	Malignancies
Ventilator-associated pneumonias	Hemophagocytic lymphohistiocytosis (Hemophagocytic syndrome)
Noninfectious pneumonias (eosinophilic and acute respiratory distress syndrome [ARDS])	Noninfectious inflammatory disorders (e.g., vasculitis, lupus, inflammatory bowel disease)
Bacterial pneumonias	Dermatologic disorders
Viral pneumonias	Hematologic disorders
Hyperthermia and hypothermia	Noninfectious central nervous system disease
Near-drowning and *Scedosporium* and *Pseudallescheria* infection	Bites, stings, and toxins
	Drug fever
	Ethical and legal decision making

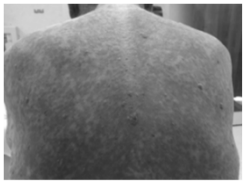
Question 2

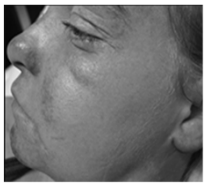
- You are asked to see a 35 year-old woman with a history of seizure disorder admitted to the ICU with a fever to 40°C, hypotension, and a maculopapular rash
- She is being empirically treated with vancomycin and piperacillin-tazobactam. Blood, urine, and sputum cultures (taken prior to antibiotic initiation) 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





30 –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
DDx	SLE, mycoplasma, viral hepatitis, mononucleosis
Treatment	Withhold offending agent, supportive care Steroids, CsA, IVIg are controversial. Mortality is high

Higher Risk Drugs Associated with DRESS

Anticonvulsants	Sulfonamides	Antibiotics
• Lamotrigine • Carbamazepine • Phenytoin • Oxcarbazepine • Phenobarbital	• Sulfasalazine • Dapsone • Trimethoprim-sulfamethoxazole • Sulfadiazine	• Vancomycin • Minocycline • Nevirapine • RIPE

Lower Risk Drugs Associated with DRESS

Beta-Lactams	Miscellaneous Meds
• Amoxicillin • Ampicillin • Piperacillin	• NSAIDs (celecoxib, ibuprofen, diclofenac) • Olanzapine • Fluoxetine • Imatinib • Sorafenib • Vemurafenib • Omeprazole • Raltegravir

Exanthematous drug eruptions

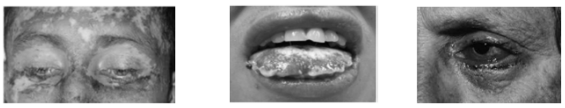
- T-cell-mediated, delayed type IV hypersensitivity reaction
- Diffuse maculopapular rash (morbilliform)
- Highest incidence with aromatic antiseizure medications: carbamazepine, phenytoin, and lamotrigine (1:100)

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 • Mucosal involvement uncommon • Facial edema • 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 too controversial for the exam

SJS/TENS and Toxic Epidermonecrolysis



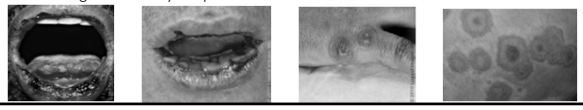
- Nikolsky sign
  - Slight rubbing of the skin results in exfoliation of the outermost layer
  - NOT specific for Stevens Johnson and TEN
    - Staph scalded skin syndrome (mostly children, no mucosal involvement)
    - Pemphigus
    - Others

30 –Syndromes in the ICU that ID Physicians Should Know

Speaker: Taison Bell, MD

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/TEN
- Causes: Infection > Drugs
  - Infections: HSV, Mycoplasma, many others
  - Cancer, autoimmune, drugs, etc
- Self Limiting in 10-14 days. Topical steroids or antihistamines



Extreme Hyperpyrexia (T>41.5C)

- Heat Stroke
  - Exertional (football player in July-August)
  - Non-exertional (Elderly)
  - Lack of hydration and/or inability to sweat
- Drugs
  - Cocaine, ecstasy etc.
- The Pyrexic Syndromes

Phoenix, AZ

Question 3

- You are called to the PACU to see a 29-year-old previously healthy man with a fever of 41.6°C and is 4 hours post-op from an ex-lap for perforated appendicitis.
- 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

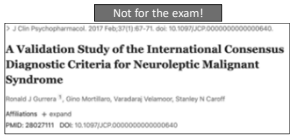
Malignant Hyperthermia

- Syndrome - Rare (~700 cases/year) but 5-10% mortality
  - Muscle contraction (masseter spasm) and rigidity → Rhabdomyolysis
  - Cardiovascular instability (sinus tachycardia, VT/VF)
  - Steep rise in CO2
  - Steep rate in rise of temperature
- Genetic defect
  - Ca++ transport in skeletal muscle
  - Autosomal dominant
    - (excessive calcium accumulation)
- Triggers
  - Any inhalational anesthetic aside from nitrous oxide
  - Classic: Halothane, succinylcholine (rarely)
  - Usually < 1 hour after trigger (but can be up to 10 hours)

Neuroleptic Malignant Syndrome (NMS)

- Frequent trigger = haloperidol
  - Any "neuroleptic" (antipsychotic)
  - Antiemetics such as metoclopramide
  - Withdrawal of antiparkinson drugs (L dopa)
  - Withdrawal from chronic cocaine use
- Features
  - Fever + Lead pipe rigidity
  - Mental status changes and autonomic dysfunction
  - Onset variable, but usually within the first 2 weeks of the trigger
- Management
  - Dantrolene (direct muscle relaxant)
  - Dopamine agonists (bromocriptine and others)

Not for the exam!


J Clin Psychopharmacol. 2017 Feb;37(1):67-71. doi: 10.1097/JCP.0000000000000640.

A Validation Study of the International Consensus Diagnostic Criteria for Neuroleptic Malignant Syndrome

Ronald J Gurrera [1], Gino Mortillaro, Varadaraj Velamoor, Stanley N Caroff

Affiliations + expand

PMID: 28027111 DOI: 10.1097/JCP.0000000000000640

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

Serotonin Syndrome

Clinical Characteristics of Serotonin Syndrome	
Pathogenesis	Excess Serotoninergic Activity • Therapeutic drugs, drug interactions, self poisoning
Triggers	• Linezolid = MAO Inhibitor • SSRI inhibitors (Bupropion) • Antiemetics (Granisetron) • Tricyclic antidepressants (amitriptyline)
Clinical Manifestations	• Acute onset (within 24 hrs of new drug/drug change) • Hyper-reflexive>bradyreflexia • Nausea, vomiting, diarrhea, tremors followed by shivering
Treatment	• Withdraw offending medication • Consider benzodiazepines and cyproheptadine

30 –Syndromes in the ICU that ID Physicians Should Know

Speaker: Taison Bell, MD

What to Look for on the Exam

	Malignant Hyperthermia	NMS	Serotonin Syndrome
Trigger	Inhaled anesthesia >>> succinylcholine	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 to within 2 weeks	Within 24 hours of starting a drug or increasing dose
Exam	Masseter spasm and/or other muscle rigidity	Mental status change with lead-pipe ridigity, dysautonomia, catatonia, mutism, stupor, coma	Shivering, myoclonus, n/v/d, hyper-reflexia, flush skin
Labs	Severe hypercarbia, rhabdomyolysis	CK rise, myoglobinemia	Nothing classic

Hypothermia: <35°C

- Causative Drugs
  - Beta blockers (metoprolol)
  - Alpha blockers (clonidine)
  - Opioids
  - Ethanol
  - Antidepressants
  - Antipsychotics
  - Aspirin
  - Oral hypoglycemics
- Syndrome
  - Hypotension due to fluid shifts
  - *Give broad spectrum antibiotics empirically if they fail to raise temperature 0.67C/hour
  - Consider adrenal or thyroid insufficiency
- Treatment
  - Rewarming
  - "ABC"s
    - Airway, Breathing, Circulation

Question 4

- You are called to the medical ICU to see a 47 y/o woman with a history of alcoholic cirrhosis with ARDS and shock
- Initially admitted to general medicine for encephalopathy in the setting of skipping lactulose doses
- On HD#3 developed ARDS, thought to be from aspiration
- Subsequently goes into distributive shock. Started on vancomycin and piperacillin-tazobactam
- Patient has daily fevers to 39°C and a persistent low-dose levophed requirement
- Labs: mild hyponatremia and hyperkalemia. Metabolic acidosis
- Micro: blood, urine, sputum, and ascitic fluid are benign
- Radiology: CXR with unchanged b/l multifocal opacities, RUQ USG benign, Abd CT benign

Which of the following would you give?:

A. Broader spectrum antibacterial treatment
B. Stress dose corticosteroids
C. Dantrolene
D. IVIG
E. Antifungal therapy

Differential Diagnosis of Shock

Ohm's Law $\longrightarrow$

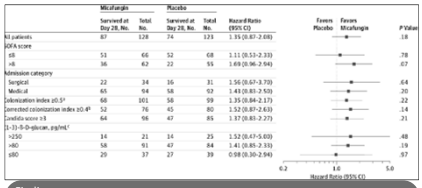
MAP = CO x SVR

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
- Immunocompetent
- Multiorgan failure
- ICU-acquired sepsis
- On MV at least 5d
- At least 4d broad spectrum Abx in prior week
- Candida colonization



Findings
- No difference in pts alive and free from invasive fungal infection at day 28
- Micafungin group had lower incidence of new proven invasive fungal infections (3% vs 12%, P = 0.008, fragility index = 3)
- No difference in survival at day 28 or day 90
- Minimal adverse events

*

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

30 –Syndromes in the ICU that ID Physicians Should Know

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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

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

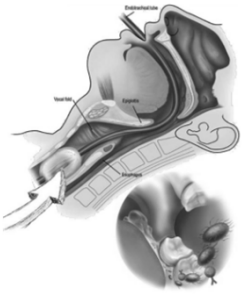
Antithrombosis (Activated Protein C)

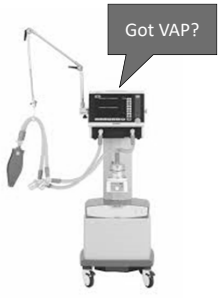
- Taken off the market

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





Institute for Healthcare Improvement Ventilator Care Bundle Components

- Head of bed elevation to 45°
- Daily awakening trials and assessment of extubation readiness
- Chlorhexidine oral care
- Stress ulcer and DVT prophylaxis

www.IHI.org/topics/VAP
O'Grady. JAMA 2012
Weavind. Curr. Anesth 2013

Ventilator Associated Pneumonia National Healthcare Safety Network

Pathogen	% of Isolates
Staph aureus	28%
Pseudomonas aeruginosa	25%
Klebsiella	10%
Enterobacter	8%
E. Coli	5%

StatPearls, Pneumonia Pathology, Aug 1, 2022

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

A 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.

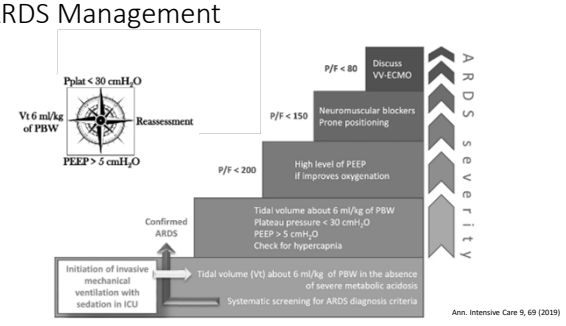
Which of the following is the most likely cause of her respiratory illness?

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

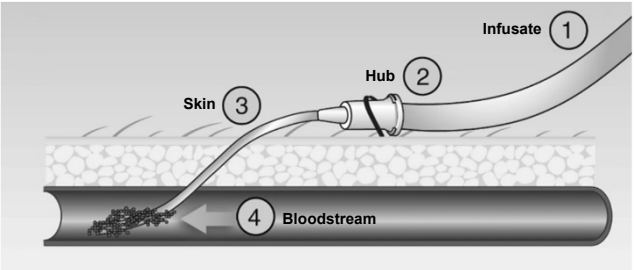


Ann. Intensive Care 9, 69 (2019)

30 –Syndromes in the ICU that ID Physicians Should Know

Speaker: Taison Bell, MD

CLABSI



Antiseptic Techniques: Catheter Insertion

Hand Hygiene	• Soap & water or alcohol-based rub before/after insertion (IB) • Sterile gloves while inserting (IA)
Skin Prep	• Chlorhexidine solution before insertion and during dressing changes (IA) • Allow to fully dry before insertion (IB)
Barrier	• Maximum barrier protection: cap, mask, sterile gown, sterile gloves and full sterile drape (IB)

CID 2011:52 (1 May)

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

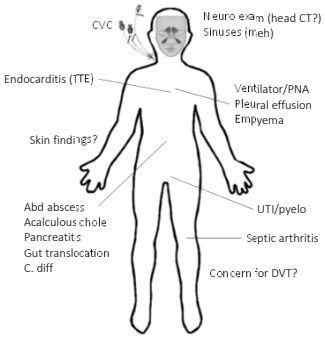
- Not likely testable on the boards
- They have a role, but not well defined

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

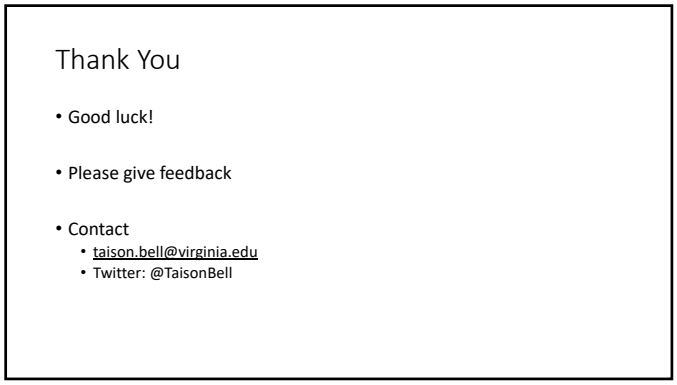
Approach

- Run med list
- Consider AI
- Pyrexic syndromes
- Unusual exposures?



30 –Syndromes in the ICU that ID Physicians Should Know

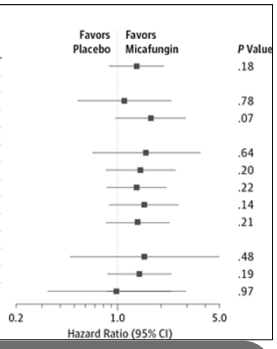
Speaker: Taison Bell, MD



Why not empiric antifungal? EMPIRICUS

Muti-center RCT of 260 Adults in ICU
- Immunocompetent
- Multiorgan failure
- ICU-acquired sepsis
- On MV at least 5d
- At least 4d broad spectrum Abx in prior week
- 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



Findings
- No difference in pts alive and free from invasive fungal infection at day 28
- Micafungin group had lower incidence of new proven invasive fungal infections (3% vs 12%, P = 0.008, fragility index = 3)
- No difference in survival at day 28 or day 90
- Minimal adverse events

*

JAMA. 2016;316(15):1555-1564

31

Pneumonia

Dr. Paul Auwaerter

31 – Pneumonia

Speaker: Paul Auwaerter, MD

Pneumonia

Paul G. Auwaerter, MD
Sherrilyn and Ken Fisher Professor of Medicine
Clinical Director, Division of Infectious Diseases
Johns Hopkins University School of Medicine

7/11/2023

Disclosures of Financial Relationships with Relevant Commercial Interests

- **Consultant: Gilead, Shionogi**
- **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

- 55 M 6d fever, malaise, severe headache, dry cough, myalgia
- PMH: HTN
- Meds: Lisinopril/HCT
- SH: Married, suburban Maryland,
  - Works in long-term care facility
  - Visited pet shop 10d earlier
    - Parakeets, cockatiels
  - Confided infidelity in last month

Exam: ill-toxic, 40ºC P88
BP100/70 RR18 O2 97% RA
Lungs: clear
Neck: supple
Cor: no murmurs
Skin: no rashes
LP: pending
Labs:
WBC 5200, 26% B
Sputum: 1+ PMNs, no organisms

Question 1

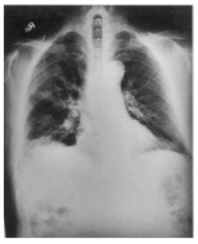
Which antibiotic will lead to the most rapid improvement?

A. Ceftriaxone

B. Gentamicin

C. Doxycycline

D. Trimethoprim/sulfamethoxazole

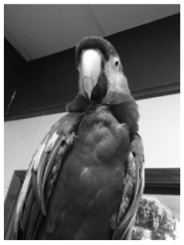


31 – Pneumonia

Speaker: Paul Auwaerter, MD

Chlamydia psittaci

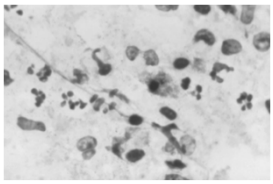
- AKA parrot fever, psittacosis, ornithosis
- Underdiagnosed
  - 1.03 % in studies of CAP
  - < 50 cases/yr in US
  - Most “atypical pneumonia”
- Risks: exposure to birds
  - May be healthy or ill
  - Pets, poultry, pigeons
  - Native birds
    - Lawn mowing



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	More than sx	Multifocal
Low Na^+	-	-	-	++
Doxycycline response	Rapid, < 48h	Prompt	Prompt	Slower

Adapted from Stewardson, Grayson. Inf Dis Clin N Amer 2010; 24(1):7

Case 2

69M c/o fever and dyspnea x 3 days
-Dry cough, pleuritic chest pain
-In nursing facility for L foot, C1-2, L4-5 osteomyelitis + MRSA bacteremia
Vancomycin (5d, rash) → Ceftaroline (4d, hives) → Daptomycin (11d)

PMH: Diabetes, HTN, COPD, R BKA, bedbound
SH: 40 PPD smoker, now vaping, Baltimore MD resident, hx substance use
Meds: methadone, insulin, nifedipine, Lisinopril/HCT, inhalers

PE: T101.4°F, P 106, RR 24, 02 sat 90% on 6L O_2
No lymphadenopathy, no JVD
Lungs: poor air movement, basilar crackles bilaterally
Cor: no murmur
Ext: no edema

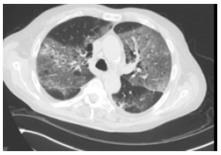
6.0 / 9.5 / 300K 54%^{N}, 12%^{L}, 24%^{E}

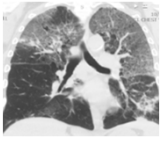
ESR 150 mm/hr Nl LFTs
CRP 15 mg/dL (0.0-0.5)

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.

31 – 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

PREVIEW QUESTION

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

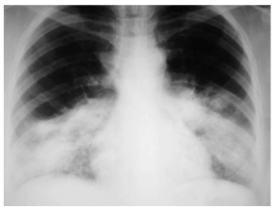
No improvement, febrile, respiratory culture negative
ID consultation called

Question 3

PREVIEW QUESTION

You are aware of a recent *Legionella mcdadei* outbreak in the hospital. Which test below, would most help you securing a diagnosis of *L. mcdadei* pneumonia?

A. Legionella urinary antigen
B. Legionella culture of respiratory secretions
C. Legionella PCR, respiratory
D. Legionella direct fluorescent antigen (DFA) stain of respiratory sample
E. Paired Legionella acute/convalescent serology



Pre-intubation CXR

Legionella pneumonia

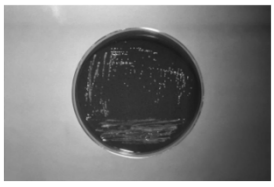
- Risks factors (and who to test)
  - Travel beyond home (e.g., hotel, hospital) last two weeks
    - May cause HAP
  - Severe pneumonia/ICU
  - Proximity to known outbreaks
  - Age > 50 yrs
  - Smoking
  - Comorbidities: diabetes, liver/renal dz, COPD, immunosuppressed
- Acquisition:
  - Aerosolization
  - Drinking water (aspiration)

1976 Bellvue Stratford Hotel, Philadelphia

Legionella

- Environmental/water pathogen
  - Ponds, lakes
  - Water systems (hot > cold), chillers, misters, A/C
  - May be nosocomial pathogen
- Legionellosis
  - Legionnaires' disease (99%)
    - Pneumonia
    - Most typical of the atypicals
  - Pontiac Fever (1%)
    - Febrile, flu-like illness
- Microbiology: 60 species
  - *L. pneumophila* serotype 1 (most common)

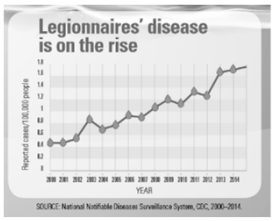
Legionella culture



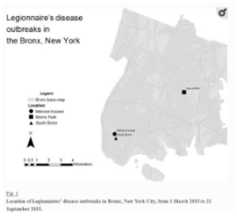
Culture media: BCYE agar
Small, pearly white colonies

Outbreaks: Known and Unknown Sources

- 5,000 cases/year U.S.
  - 20 Outbreaks
- 4X > cases since 2000
- 90% of CDC investigations caused by insufficient water system management
- WHERE?
  - Hotels
  - Long-term Care Facilities
  - Hospitals



Outbreaks: Known and Unknown Sources



MacIntyre CR, et al Emerg Microbes Infect 2018;7:36

Legionella diagnostics

Test	Sensitivity (%)	Specificity (%)	Notes
Culture	20-80	100	Slow, technically difficult, BCYE agar Detects all species
Urinary Ag	70-100	95-100	Only *L. pneumophila* serogroup 1, rapid, may cross-react occasionally w/ other serogroups
PCR	95-99	99	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, https://www.cdc.gov/legionella/clinicians/diagnostic-testing.html (accessed 2/8/23)
Avni, J Clin Micro. 2016;54(2):401–11; Muldyermans, Eur J Clin Microbiol Infect Dis 2019

	Legionnaires' disease	Pontiac fever
Clinical	Pneumonia	Flu-like symptoms
CXR	Consolidation, multifocal	No infiltrates
Epidemiology	Sporadic & epidemic	Epidemic
Onset after exposure	2-10 days	24-48 hrs
Attack rate	< 5%	> 90% (including healthy)
Diagnosis	Sputa: Culture Molecular tests DFA Urine antigen	No recovery of organism by culture Acute/convalescent serology Urine antigen, up to 50% in some reports
Mortality	10-30%	0 %

Case 4

23M cough, malaise, dyspnea, fever x 1 wk, just returning from overseas

PMH: negative, no asthma

Meds: atovoquone/proguanil

ROS: no diarrhea, had rash on feet/legs post marathon now resolved

SH: Laguna Phuket (Thailand) triathlon 3 wks earlier

Non-smoker

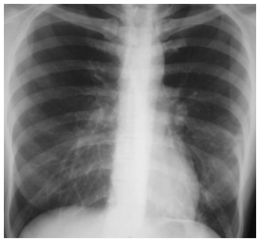
PE: Appears ill, BP 98/70, P 100
T 38.5ºC
No lymphadenopathy
Bronchial breath sounds lower fields, occasional wheezing
No murmur
No hepatosplenomegaly, abdominal tenderness
No rash

Studies

WBC 18,000
63N, 13L, 24E

CXR: mild bilateral patchy infiltrates

Blood smear: no parasites

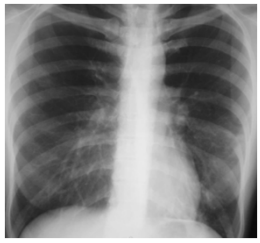


31 – Pneumonia

Speaker: Paul Auwaerter, MD

Which of the following is the most likely explanation?

A. Allergic bronchopulmonary aspergillosis
B. Hookworm infection
C. Malaria
D. Tropical pulmonary eosinophilia
E. Drug reaction



Löffler's syndrome

- Fever, malaise
- Respiratory symptoms: none—mild—moderate
- Migratory pulmonary infiltrates
- Peripheral eosinophilia
- Migration of parasites
- Dx:
  - Larvae in respiratory specimen
  - Stool O & P
- Treatment
  - Anti-helminthics
  - Corticosteroids
  - May spontaneously resolve

Acute eosinophilic pneumonia

- Features
  - Fever, cough
  - Hypoxemia
  - Diffuse, bilateral infiltrates
  - Eosinophils
    - Peripheral
    - BAL (> 10%)
    - Lung biopsy
- Drug causes:
  - Antibiotics:
    - Daptomycin
      - 38 reported cases (2018)
        - Male, elderly
        - Renal failure
      - Black box warning
    - Nitrofurantoin
    - Minocycline
    - Ampicillin
    - Sulfonamides
- Others:
  - NSAIDs
  - Phenytoin
  - L-tryptophan

Uppal, Antimicrob Resist Infect Control 2016;5:55;
Higashi, Intern Med 2018;57(2):253-258

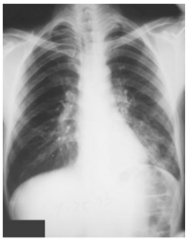
Acute or chronic eosinophilic pneumonia

- Helminthic
  - Migration (Loffler's)
    - Ascaris
    - Hooksworms
    - Strongyloides
  - Lung invasion
    - Paragonimiasis
- Tropical Pulmonary Eosinophilia (bronchospasm, chest findings minimal)
  - Wuchereria bancrofti
  - Brugia malayi
- Idiopathic hypereosinophilia
- Acute eosinophilic pneumonia
- Chronic eosinophilic pneumonia
- Allergic bronchopulmonary aspergillosis (ABPA)

Case 5:

INFECTIOUS DISEASE BOARD REVIEW 2023 PREVIEW QUESTION

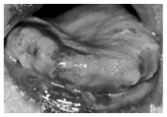
- 18F c/o fever, dry hacking cough, malaise x 3d
- Allergy: erythromycin (N/V)
- Appears well, T38ºC, RR 16, P 80, BP 110/70
  - Oropharynx: normal
  - TMs: normal
  - Chest: some crackles left lower lobe

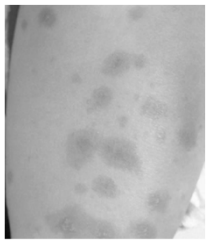


Case 5

INFECTIOUS DISEASE BOARD REVIEW 2023 PREVIEW QUESTION

- Azithromycin prescribed
- Next day, full body rash and mucosal lesions develop





Case 5

PREVIEW QUESTION

What is the most likely etiology?

A. Mycoplasma pneumoniae
B. Enterovirus D68
C. Measles
D. Lyme disease
E. Drug reaction (azithromycin)

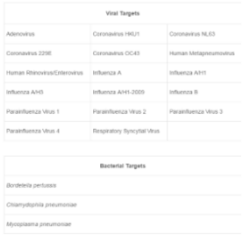
Mycoplasma pneumoniae

- "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



Film Array
Multiplex, 20 pathogens
Results in 1 hr

Viruses and some bacteria
Sensitivity: 87, 98-100%
Specificity: 89, 99-100%

Leons, Front Microbiol. 2016; 7: 448

Case 6

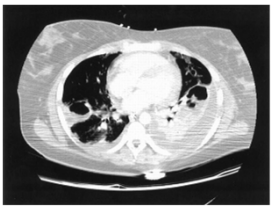
31F fever, cough, myalgia, headache, dyspnea over 1 week ago; February
- No help w/ azithromycin x 3d
- 18 mos daughter, recent bronchitis

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

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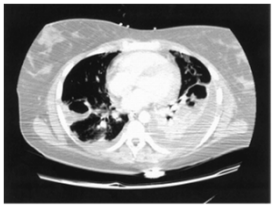

Era of molecular diagnostics

- 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)

GOOD LUCK ON THE EXAM

"In the Mortality Bills, pneumonia is an easy second, to tuberculosis; indeed in many cities the death-rate is now higher and it has become, to use the phrase of Bunyan 'the captain of the men of death.'"
— William Osler