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 2

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

COURSE CO-DIRECTORS:
Paul Auwaerter, MD
David N. Gilbert, MD
Roy M. Gulick, MD, MPH
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

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), 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, 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**

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

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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.

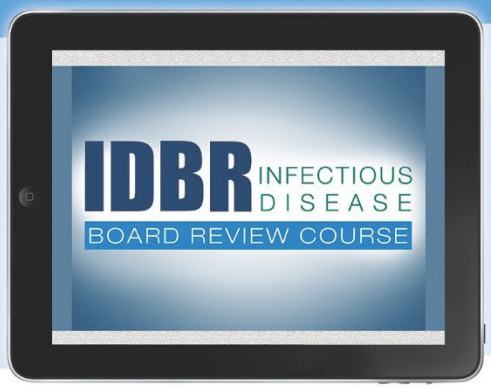
To Access the App via PC:

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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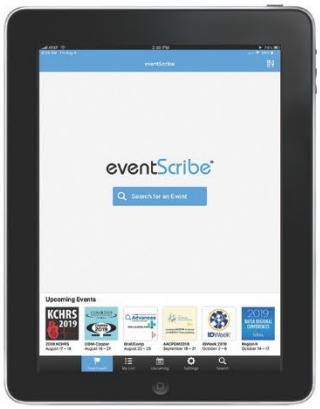

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Event Code **IDBR2023**

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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Both planners also resolved financial disclosures

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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
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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 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

QP4

Daily Question Preview 4

Dr. Roy Gulick (Moderator)

QP4 – Daily Question Preview: Day 4

Moderator: Roy Gulick, MD

Daily Question Preview: Day 4

Moderator: Roy Gulick, MD, MPH

8/2/2023

PREVIEW QUESTION INFECTIOUS DISEASE BOARD REVIEW 2023

4.1 **A 43-year-old man with HIV has CD4 900-1200 and HIV RNA consistently <200 copies over the last 11 years.**

Do you recommend starting ART?

A) Yes, all current guidelines recommend starting.

B) No, he's a long-term non-progressor and doesn't need ART.

C) No, he should wait until his viral load level is confirmed >200 copies/ml.

D) No, he should wait until CD4 is confirmed <500 cells/uL.

1 of 2

PREVIEW QUESTION INFECTIOUS DISEASE BOARD REVIEW 2023

4.2 **You have been monitoring a 36 year old man with HIV, CD4 ~350, VL 636,000 who is now ready to start ART, but wants the "simplest regimen possible."**

Which of these regimens do you recommend?

A) IM cabotegravir/rilpivirine

B) tenofovir alafenamide/emtricitabine/rilpivirine

C) abacavir/lamivudine + efavirenz

D) dolutegravir/lamivudine

E) tenofovir alafenamide/emtricitabine/bictegravir

1 of 2

PREVIEW QUESTION INFECTIOUS DISEASE BOARD REVIEW 2023

4.3 **28 year old man with HIV on TDF/emtricitabine + atazanavir/ritonavir for 2 years with HIV RNA <50 cps/ml and CD4 200s→300s presents for routine follow-up; labs reveal HIV RNA 98 cps/ml and CD4 352.**

What do you recommend?

A) Obtain genotype.

B) Obtain genotype and phenotype.

C) Repeat HIV RNA at next visit.

D) Change regimen to TAF/emtricitabine/bictegravir to improve adherence

1 of 2

PREVIEW QUESTION INFECTIOUS DISEASE BOARD REVIEW 2023

4.4 **A 55-year-old with HIV not previously on rx, CD4 320 and HIV RNA 67,000 cps/ml**

Lab testing reveals: toxoplasma Ab+; CMV Ab+; HAV total Ab+; HBV surface Ag+, core Ab+, surface Ab-; HCV Ab-; RPR NR

1 of 3

PREVIEW QUESTION INFECTIOUS DISEASE BOARD REVIEW 2023

4.4 **Of the following, which ART regimen would you recommend?**

A) abacavir/lamivudine/dolutegravir

B) abacavir/lamivudine + atazanavir (boosted)

C) dolutegravir/lamivudine

D) tenofovir (TAF or TDF)/emtricitabine + darunavir (boosted)

2 of 3

QP4 – Daily Question Preview: Day 4

Moderator: Roy Gulick, MD

PREVIEW QUESTION INFECTIOUS DISEASE BOARD REVIEW 2023

4.5 A 26-year-old woman with HIV on abacavir/lamivudine + efavirenz with CD4 630 and VL suppressed below detection becomes pregnant.

What do you recommend regarding ART?

A) Discontinue ART until 2nd trimester.
B) Change abacavir to zidovudine.
C) Change efavirenz to bictegravir.
D) Continue current regimen.

1 of 2

PREVIEW QUESTION INFECTIOUS DISEASE BOARD REVIEW 2023

4.6 38yo female with 1 day of sore throat and fever.

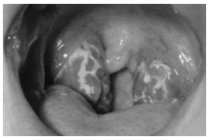
Childhood history of anaphylaxis to penicillin.

Physical exam

T=102.3

HEENT-tonsillar purulence

Neck-Tender bilateral anterior LAN



Labs:

Rapid strep antigen test negative

1 of 3

PREVIEW QUESTION INFECTIOUS DISEASE BOARD REVIEW 2023

4.6 What is the most appropriate antimicrobial treatment?

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

2 of 3

PREVIEW QUESTION INFECTIOUS DISEASE BOARD REVIEW 2023

4.7 A 32-year-old woman is seen for a sore throat and fever for 4 days .

Recently returned from her sister's wedding in Kazakhstan.

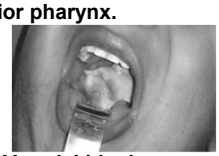
She c/o odynophagia, and a low-grade fever. Today, she noted a choking sensation, prompting medical evaluation.

1 of 4

PREVIEW QUESTION INFECTIOUS DISEASE BOARD REVIEW 2023

4.7 Exam:

- HEENT: Submandibular swelling with gray exudate coating posterior pharynx.
- An S3 gallop is heard.



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

2 of 4

PREVIEW QUESTION INFECTIOUS DISEASE BOARD REVIEW 2023

4.7 The most likely diagnosis is?

A) Streptococcal pharyngitis
B) Kawasaki disease
C) Vincent angina
D) Diphtheria
E) Candida

3 of 4

QP4 – Daily Question Preview: Day 4

Moderator: Roy Gulick, MD

PREVIEW QUESTION INFECTIOUS DISEASE BOARD REVIEW 2023

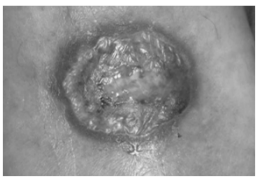
4.8 **Sweet Syndrome is most likely to occur in a patient with which of the following conditions?**

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

1 of 2

PREVIEW QUESTION INFECTIOUS DISEASE BOARD REVIEW 2023

4.9 **A patient has a slowly enlarging ulcerated skin lesion on his shin after being hit by a soccer ball.**



1 of 3

PREVIEW QUESTION INFECTIOUS DISEASE BOARD REVIEW 2023

4.9 **Which of the following is the most likely diagnosis?**

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

2 of 3

PREVIEW QUESTION INFECTIOUS DISEASE BOARD REVIEW 2023

4.10 **38 y/o healthy physician; periodic travel to South Africa for work.**

6 years ago: pos TST; poor adherence with isoniazid preventive therapy.

Now 5 weeks of fever, chills, night sweats, 10-lb wt loss, productive cough.

1 of 4

PREVIEW QUESTION INFECTIOUS DISEASE BOARD REVIEW 2023

4.10 **CXR RUL cavitary lesion.**

Sputum Xpert MTB/RIF: "MTB detected" & "Rifampin resistance not detected."

HIV negative, LFTs normal.

2 of 4

PREVIEW QUESTION INFECTIOUS DISEASE BOARD REVIEW 2023

4.10 **What is the best course of action?**

A) Prescribe 9 months of isoniazid for presumed latent TB infection
B) Do nothing pending culture results
C) Start TB treatment with rifampin, isoniazid, PZA, ethambutol
D) Start TB treatment with rifampin, isoniazid, PZA
E) Start TB treatment with a regimen for multidrug-resistant TB

3 of 4

QP4 – Daily Question Preview: Day 4

Moderator: Roy Gulick, MD

PREVIEW QUESTION INFECTIOUS DISEASE BOARD REVIEW 2023

4.11 **24 y/o M from Zambia, in U.S. for community college, recently tested HIV-positive, CD4 400, not yet on ART.**

Prominent anterior cervical lymph node but well-appearing, normal BMI, normal liver and renal chemistries, mild anemia.

Lymph node biopsy grows M. tuberculosis in culture.

1 of 3

PREVIEW QUESTION INFECTIOUS DISEASE BOARD REVIEW 2023

4.11 **Best course of action regarding timing of TB therapy and HIV therapy?**

A) Start ART immediately, defer TB tx

B) Start TB tx immediately, defer ART until completes 6 months TB tx

C) Start TB tx immediately, and start ART within about 8 weeks

D) Start both TB tx AND ART immediately

2 of 3

PREVIEW QUESTION INFECTIOUS DISEASE BOARD REVIEW 2023

4.12 **•25 year old black woman presents with fatigue**

•History of IV Heroin use; intermittently takes TDF/FTC PreP

•Exam no edema

•Work up in ER shows creatinine 8.4 BUN 79; mild anemia; mild acidemia

1 of 4

PREVIEW QUESTION INFECTIOUS DISEASE BOARD REVIEW 2023

4.12 **•In ER 10 weeks earlier; normal renal function**

•U/A high grade proteinuria

•US of kidneys: Normal to increase size; no obstruction

•Rapid HIV test positive

2 of 4

PREVIEW QUESTION INFECTIOUS DISEASE BOARD REVIEW 2023

4.12 **Which of the following is the most likely cause of her renal failure?**

A) Volume depletion / ATN

B) Heroin Associated Nephropathy

C) HIVAN

D) Membranous glomerulonephritis

E) Tenofovir Toxicity (PrEP)

3 of 4

PREVIEW QUESTION INFECTIOUS DISEASE BOARD REVIEW 2023

4.13 **•35 year old man presents with complaints of increasing fatigue, headache, SOB / DOE**

•HIV diagnosed 4 mos ago with PCP; intolerant to TMP/SMX

•Now on TAF / FTC / BIC + PCP Prophylaxis with Dapsone

1 of 4

QP4 – Daily Question Preview: Day 4

Moderator: Roy Gulick, MD

PREVIEW QUESTION INFECTIOUS DISEASE BOARD REVIEW 2023

4.13 •Claims adherence to all meds;

"Doesn't miss a dose!"

•Normal PE

•Pulse Ox 85%; CXR no abnormalities

•ABG: 7.40 / 38 / 94/ 96% (room air)

2 of 4

PREVIEW QUESTION INFECTIOUS DISEASE BOARD REVIEW 2023

4.13 Which of the following is the most likely underlying cause of his symptoms?

A) Recurrent PCP
B) IRIS Reaction
C) Drug toxicity
D) Pulmonary Embolus
E) Patent Foramen Ovale

3 of 4

PREVIEW QUESTION INFECTIOUS DISEASE BOARD REVIEW 2023

4.14 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.

1 of 3

PREVIEW QUESTION INFECTIOUS DISEASE BOARD REVIEW 2023

4.14 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)

2 of 3

PREVIEW QUESTION INFECTIOUS DISEASE BOARD REVIEW 2023

4.15 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.

1 of 3

PREVIEW QUESTION INFECTIOUS DISEASE BOARD REVIEW 2023

4.15 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+.

2 of 3

32

Clinical Manifestations of Human Retroviral Diseases and Slow Viruses

Dr. Frank Maldarelli

32 – Clinical Manifestations of Human Retroviral Diseases and Slow Viruses

Speaker: Frank Maldarelli, MD

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

Clinical Manifestations of Human Retroviral Diseases and Slow Viruses

Frank Maldarelli, MD
Bethesda, MD

2/28/2023

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

Disclosures of Financial Relationships with Relevant Commercial Interests

- None

Adults and Children Estimated to be Living with HIV 2022

Total Infections: 39 million [30.2 million – 45.1 million]
29.8 million accessing antiretroviral therapy
HIV prevalence is increasing: 1.3 million new infections; 630,000 deaths in 2022

UNAIDS

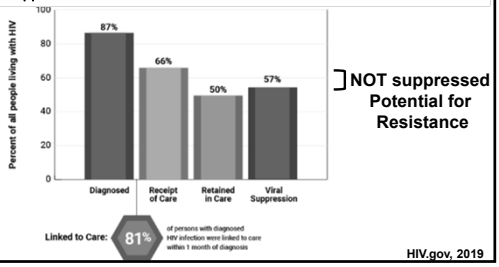
Current US Epidemic:
75% Male
70% Persons of Color

Men who have Sex with Men: 68%
Heterosexual Contact 22%
IVDU 10%

CDC, 2020

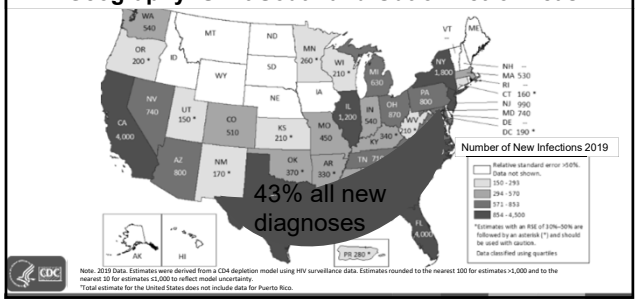
HIV Eradication Goals NOT Met

90 % Diagnosed: Close
90% Undergoing Antiretroviral Therapy: NOT Met
90% Viral RNA Suppressed: NOT Met

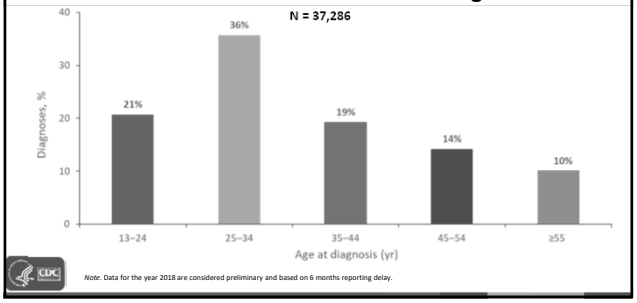


HIV.gov, 2019

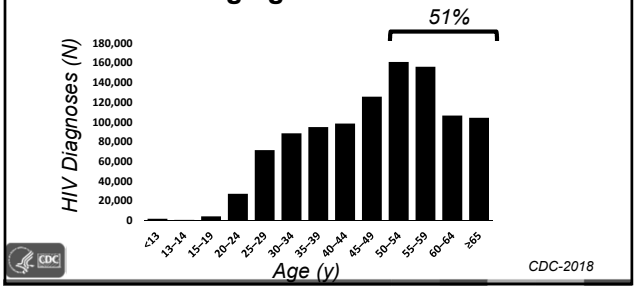
Trends in the US Epidemic:
Geography: Shift South and Out of Metro Areas



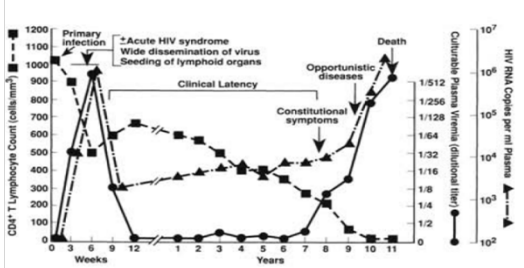
Trends in the US Epidemic: Incident Cases Remain Young



Trends in the US Epidemic: Aging Prevalence



HIV Infection Course

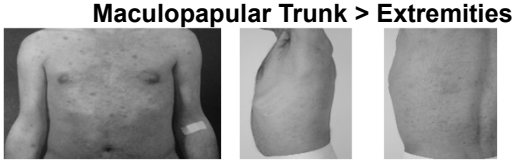


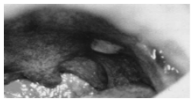
Acute HIV Syndrome

Sign/symptom	Percent Reporting NEJM Review	Kenyan sex workers	HIVNET
Fever	>80-90	53	55
Fatigue	>70-90	26	56
Rash	>40-80	9	16
Headache	32-70	44	33
Lymphadenopathy	40-70	7	35
Pharyngitis	50-70	15	43
Myalgia or arthralgia	50-70	24	39
Nausea, vomiting or diarrhea	30-60	18	12-27
Night sweats	50	nd	nd
Aseptic meningitis	24	nd	nd
Oral ulcers	10-20	nd	6
Genital ulcers	5-15	3	nd
Thrombocytopenia	45	nd	nd
Leukopenia	40	nd	nd
Elevated LFTs	21	nd	nd
Too ill to work	nd	44	58

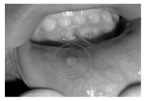
Primary HIV-1 Infection Syndrome

Maculopapular Trunk > Extremities





Enanthem



Aphthous ulcer

HIV Diagnosis: Question #1

A 23 year old man presents with a history of unprotected receptive anal sex with known HIV-infected man, and one week of fever, adenopathy. HIV-1/2 ELISA is reactive, viral RNA level 500,000 c/ml. He is started immediately on antiretrovirals. His supplemental assay is negative, and repeat assays sent 3 weeks, 3 months, and one year after starting antiretrovirals are also negative.

ELISA remains reactive. HIV-2 assay is negative.

Viral RNA on therapy is <40 c/ml.

HIV Diagnosis: Question #1 continued

Which of the following is correct explanation for the absence of positive results with the supplementary HIV test:

A. The patient was infected with a strain of HIV-1 that was not detected by the confirmatory assay
B. The patient is HIV-infected but did not develop a positive results with the supplementary assay because of the early antiretroviral therapy intervention
C. The patient never had HIV infection.
D. The patient had HIV but is now cured of HIV and antiretrovirals can safely be stopped

Early Antiretroviral Therapy

- Prompt reduction in HIV-1 RNA
- Potential blunting of humoral immune response
- Confirmatory assay may remain negative
- HIV-1 DNA PCR has been useful in documenting infection

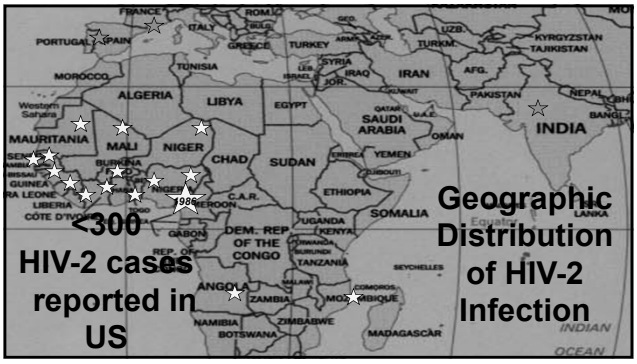
HIV Clinical Presentation: Question #2

A 49 year old woman from Guinea-Bissau has a reactive HIV-1/2 ELISA and a HIV Geenius positive for HIV-2 and negative for HIV-1.

CD4 cell count is 350 cells/µl.

Which of the following is correct?

A. HIV-2 is less pathogenic than HIV-1 so she only needs therapy with one antiretroviral drug
B. She should not be treated with protease inhibitors because HIV-2 is naturally resistant to PIs.
C. She should not be treated with NNRTI therapy because HIV-2 is naturally resistant to NNRTIs.
D. Use of routine HIV-1 viral load assays is useful in patient management



HIV-1 and HIV-2

Characteristic	HIV-2	HIV-1
Epidemiology		
Geography	West /Central Africa	Worldwide
Local Distribution	Urban=rural	Urban>rural
Prevalence	Stable or Decreasing	Increasing
Pathogenesis		
Average age at diagnosis	45-55	20-34
Maternal-fetal (without RX)	0-4%	20-35%
Kaposi Sarcoma	Less common (10X)	More common
Therapy	NRTI, PI, INSTI, Corec **NOT** NNRTI **NOT** Fusion	NRTI, PI, NNRTI INSTI, Corec, Fusio
Diagnosis		
Screening	HIV1/2 ELISA	HIV1/2 ELISA
Confirmatory	Supplemental (e.g., Geenius)	Supplemental Qual. HIV RNA)
Monitoring	HIV-2 RNA Assay	HIV-1 RNA assay

Question #3

A 42 year old man from the Haiti presents with fever, moderate respiratory distress, and nonproductive cough. HIV-1/2 ELISA is reactive and discriminatory test is positive for HIV-1. A PCR test of the induced sputum is positive for *Pneumocystis jiroveci*. On evaluation the lymphocyte count is 2,000 cells/µl; the CD4 count is 750 cells/µl and the hematology technician remarks that some of the lymphocytes are "flower cells". Which of the following is most correct in explaining these findings:

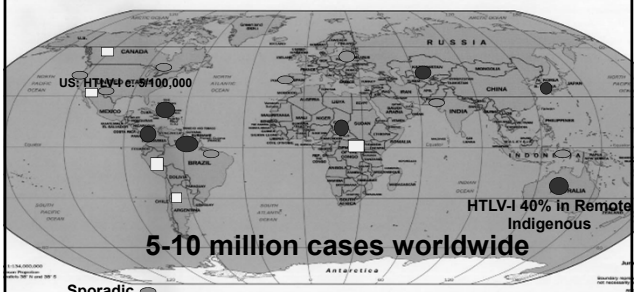
A. The patient has HIV and B cell lymphoma
B. The patient has HIV infection and the elevated CD4 count is due to steroids used in the treatment of the *Pneumocystis* pneumonia
C. The patient has HTLV-1 infection only the HIV test is a false positive
D. The patient has both HIV infection and HTLV-1 infection

Question #4

A 25 year old pregnant woman immigrant from southern Japan was referred to you for evaluation of a positive HTLV-I western blot. Which of the following statements is true:

A. The risk of HTLV-I transmission can be entirely eliminated by caesarean section.
B. The risk of HTLV-I transmission will be entirely eliminated by not breastfeeding.
C. Breastfeeding will provide sufficient immunity to prevent infection with HTLV-I.
D. The risk of HTLV-I transmission will be significantly decreased but not entirely eliminated by avoiding breastfeeding.
E. There is no risk of HTLV-I disease. In this ethnic group, the HTLV-I test was likely a false positive.

HTLV DISTRIBUTION



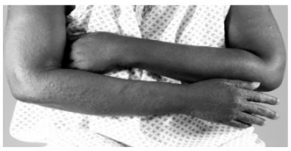
HTLV-I Transmission, Pathogenesis, Diagnostics

- Treansmission
  - Breastfeeding
    - Prolonged duration: 20-30% seroconvert if breastfed >12 mos
    - High maternal HTLV proviral load in breastmilk: 28.7 infections/1000 person months with 1.5% HTLV+ lymphs
  - Sexual
  - Transfusion
  - Risk of seroconversion: 40-60%
- Pathogenesis
  - Spread to CD4+ T cells
    - 1-4% of all CD4 cells become infected - multilobed nuclei "flower cells"
    - Spread is NOT continuous, but controlled shortly after infection takes place
    - Infection maintained in CD4 by persistence and clonal expansion
- Laboratory diagnosis by sequential testing ELISA/Western blot FDA approved
  - Can distinguish HTLV-I from HTLV-II

Question #5

37 year old Jamaican female with diffuse pruritic rash (right), bone pain with lytic bone lesions.

WBC: 50,000, 90% lymphocytes



Which is most likely cause of her presentation?

A. HTLV-I
B. HTLV-II
C. HIV-1
D. HTLV-IV

HTLV-I Acute T cell Leukemia (ATL)

- **Disease Onset**
  - Long Latency (>30 years)
  - Small pediatric series in South America
- **Epidemiology**
  - Approximately 1% of HTLV- I infected adults
  - M>F (Japan); M=F (Jamaica)
- **Associated syndromes**
  - Infectious
    - TB, MAC, Leprosy
    - PCP
    - **Recurrent Strongyloides**
    - Scabies esp. Norwegian scabies
  - Noninfectious-hypercalcemia+lytic bone lesions
- **Therapy**
  - Cytotoxic chemotherapy
  - AZT+Ifn
  - Transplant
  - Mogamulizumab (Poteligeo, anti-CCR4 monoclonal)
    - APPROVED in Japan for ATL
    - In US FDA approved for relapsed or refractory Sezary or mycosis fungoides
  - Lenalidamide in trials

Question #6

38 year old woman from Jamaica presents with weakness, unsteadiness of several months duration and has recently developed incontinence. Neurologic exam notes hyperreflexia ankle clonus, and positive Babinski reflex

WBC = 7500 cells/µl

CD4 T cell = 1000 cells/µl

CSF cell count: 10 cells/mm^3 (lymphocytes)

CSF protein: 75 mg/dl

Question #6 Continued

The etiologic agent associated with this illness is also associated with

A. Acute T cell leukemia
B. Multiple sclerosis
C. Variant Creutzfeldt-Jacob
D. Hemorrhagic cystitis

HTLV-I Tropical Spastic Paraparesis /HTLV-1 Associated Myelopathy

- Epidemiology
  - <1% of HTLV-I develop HAM/TSP
  - The second most common neurologic syndrome in Jamaica after stroke
  - Latency may be short--several years
  - Female predominance

HTLV-I TSP/HAM

- Presentation
  - Spastic paraparesis
    - Lower>upper
    - Proximal>distal
  - Bladder disturbance
  - Hyperreflexia
  - Positive Babinski reflex
- Differential Diagnosis
  - Cord compression
  - B12 deficiency
  - Syphilis
  - HIV-1 myelopathy
  - Multiple sclerosis

Therapy of HTLV-I TSP/HAM

- Corticosteroids
  - May slow progression and reduce disability
- Mogamulizumab (Poteligeo, anti-CCR4 monoclonal)
- Teriflunomide in trials (FDA- Approved for MS; pyrimidine synthesis inhib)
- Antiretroviral therapy is NOT effective

Question #7

62 year old man from Jamaica with rheumatoid arthritis has not responded to several antirheumatic drugs including the methotrexate that he is currently taking. He is now being considered for treatment with rituximab. He is hepatitis B positive (surface antibody positive, surface antigen negative) and HTLV-1 positive (antibody and PCR). He will continue to receive Tenofovir + FTC to prevent HBV reactivation, and you are consulted regarding the development of HTLV-I drug resistance. Which of the following is most correct:

A. He at risk for the development of HTLV-I drug resistance with this two drug combination. He should receive an additional reverse transcriptase inhibitor like doravirine.
B. He at risk for the development of HTLV-I drug resistance with this two drug combination. He should receive an integrase inhibitor like dolutegravir
C. He at risk for the development of HTLV-I drug resistance with this two drug combination. He should also receive a protease inhibitor like darunavir.
D. He is not at risk for the development of HTLV-I drug resistance.

Question #8

A 56 year-old HTLV-I infected woman is diagnosed with multiple myeloma. She has never had complications from HTLV-I infection and is otherwise eligible for autologous bone marrow transplant. You are consulted regarding her eligibility for chemotherapy vs. chemotherapy and autologous bone marrow transplant

Which of the following is most correct:

A. She should not undergo autologous BMT because of reduced overall survival from ATL or other secondary malignancy in the post transplant period
B. She should not undergo autologous BMT because of the high risk of graft failure
C. She can undergo autologous BMT, but she should be treated with antiretroviral therapy from induction, until she recovers her counts (WBC>500 cells/µl)
D. She can undergo autologous BMT; her 3 year survival is equivalent to individuals withough HTLV-I infection.

Pearls

HTLV-1 Infection
- Asymptomatic -95%
- Acute T cell Leukemia
- HAM/TSP
- But also
  - Bronchiectasis
  - Uveitis
  - Rheumatologic syndromes
  - Lymphocytic pneumonitis
  - Infective Dermatitis (pediatric)
- "Flower" cells
  - Lymphocytes with HTLV provirus present
  - Frequency in HIGHER in ATL and HAM/TSP
  - NOT an indication for specific therapy

Associated Infections
- Strongyloides hyperinfection
- Norwegian Scabies
- Pneumocystis
- MAC

HTLV-II
Not a cause of disease
A distractor

Thanks to Tamara Nawar, Ying Taur, Anna Kaltsas (SKMC, NYC)

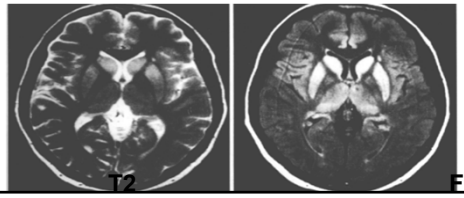
Slow Viruses

Prion Disease Question #1

68 y. o. butcher who is an avid hunter presents with dementia progressing over 4 months, myoclonus, MRI below, periodic sharp waves on EEG.

Acquisition of this illness was most likely due to:

A. Contact with elk brains
B. Contact with sheep brains
C. Contact with pork brains
D. A spontaneous event

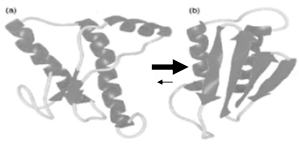


Prion Diseases: Transmissible Spongiform Encephalopathies

- **Spontaneous (N=~6000 worldwide per year)**
  - Sporadic Creutzfeldt-Jakob disease (sCJD)
- **Associated with specific exposure**
  - Ingestion of beef from cows with Bovine Spongiform Encephalopathy
    - Denoted "Variant CJD", "vCJD" (N ~ 220 total cases)
      - Blood transfusion from individual with vCJD (4 cases)
  - Human brains
    - Kuru (N= ~2700 total cases)
- **Associated with a medical procedure (N ~ 450 total cases)**
  - Iatrogenic
  - Denoted "iCJD"
- **Hereditary (N ~600-900 worldwide per year)**
  - Familial (fCJD)
  - Gerstmann-Straussler-Sheinker (GSS)
  - Fatal Familial Insomnia (FFI)
  - Fatal Sporadic Insomnia (FSI)

Prion Disease Pathogenesis A. Initiation

The prion protein is a host protein with a normal and abnormal conformation



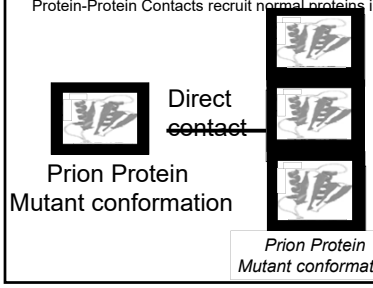
NORMAL ABNORMAL

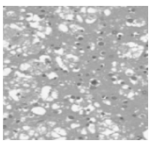
Transition to abnormal conformation is rare but essentially irreversible

Naturally occurring mutations favor interconversion

Prion Disease Pathogenesis B. Propagation

Protein-Protein Contacts recruit normal proteins into abnormal conformation





Spontaneous Creutzfeldt-Jacob Disease (sCJD) Epidemiology

- Most common human Transmissible Spongiform Encephalopathy (TSE)
  - 95% cases
- Incidence estimated 1 per million
  - US: 0.1/million in <55 yo, 5.3/million >55 yo
  - Mean age of onset is 60 years

Dementia Comparison

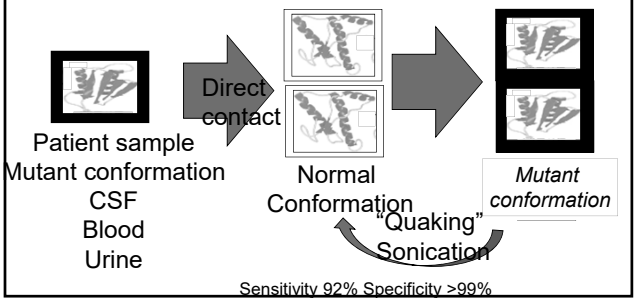
Type	Protein	Clinical	Course	Path	MRI
sCJD	Prion	Myoclonus	<2 y	Spongif. Degen.	Caudate Striatum Thalamus
Alzheimer	Apo E4, Tau	Memory Language	>4 y	Neurofib. tangles	Hippocampus White matter
Lewy Body	α- Synuclein	Parkinsonian Visual hallucin.	>4 y	Lewy Bodies	Less common
Multi-infarct	Atheroma	Focal	Incremental	Vascular	Caudate,Pons Thalamus Ovoid Nuc

Prion Disease Question #2

A 68 year old man with dementia progressing over the last 6 months undergoes evaluation. Which of the following CSF results is most consistent with Creutzfeldt Jakob Disease: .

A. 14-3-3 protein: Positive
B. RT-QuIC: Positive
C. T-tau protein: 3000 pg/ml (normal 0-1150 pg/mL)
D. Aβ42: 1250 pg/mL (normal >1026 pg/mL)

Abnormal Prion Detection RT-QuIC

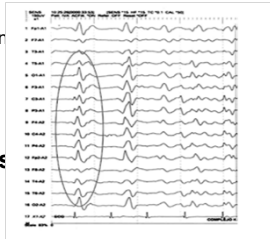


Sensitivity 92% Specificity >99%

Spontaneous Creutzfeldt-Jacob Disease (sCJD)

Typical Clinical Presentation

- Rapid progression
- RT-QuIC elevated abnormal prion protein
- 14-3-3 not specific for sCJD
- Classic Clinical Triad
  - **Dementia**
  - **Myoclonus**
  - **EEG: periodic sharp waves**



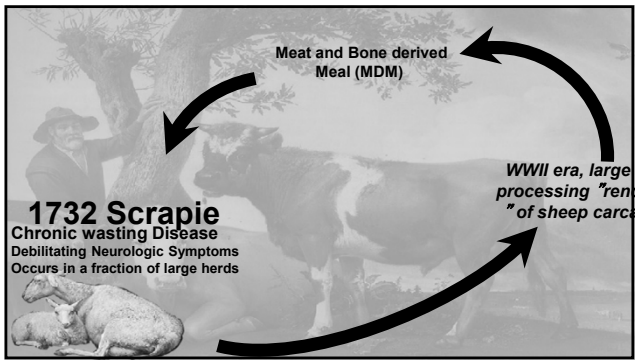
Herran, BMC Neurology 2018

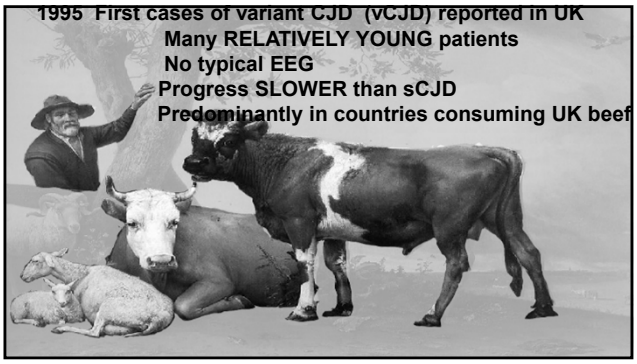
Prion Disease Question #2

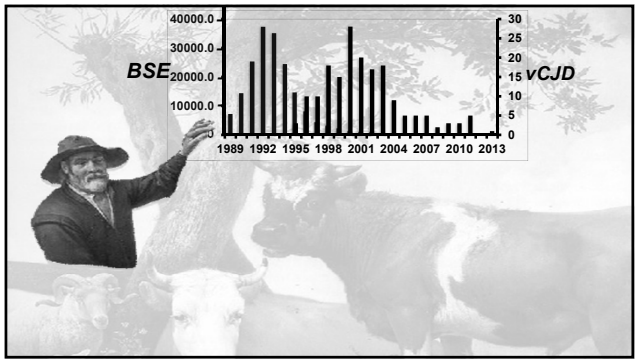
A 35 year old man presents with dementia progressing over the last year. He was born in rural Indonesia, lived in London from 1985 – 2010, then moved to Philadelphia.

Which of the following diseases is most likely the cause of his symptoms:

A. Kuru
B. Variant Creutzfeldt-Jacob Disease
C. Familial Creutzfeldt-Jacob Disease
D. Rabies





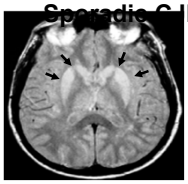


Numbers of vCJD Cases Worldwide

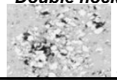
• United Kingdom:	178
• France:	28
• Spain:	5
• **US:**	**4**
• **(ALL infections acquired OUTSIDE of US)**	
• Ireland:	4
• Netherlands, Italy:	3
• Portugal, Canada:	2 each
• Saudi Arabia, Japan, Taiwan:	1 each

(Nat'l CJD Res. Surv. Unit, U. Edinburgh, www.cjd.ed.ac.uk 2019)

sCJD
Sporadic CJD

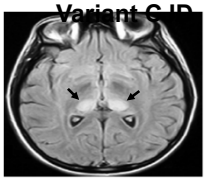


T2 axial proton weighted
Putamen and caudate head
"Double hockey stick sign"

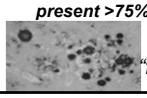


"Abnormal Prion accumulation"

vCJD
Variant CJD



T2 axial proton weighted
"Pulvinar Sign"
present >75% cases



"florid plaques"

Prion Diseases Question #4

A 49 year old man recently emigrated from Japan presents with rapidly progressing dementia. He underwent a meningioma resection with dura mater graft in Japan 35 years ago.He is an avid deer hunter and consumes venison.

What is the most likely cause of his dementia:

A. Iatrogenic CJD from the dura mater graft
B. CJD from eating deer.
C. HTLV-I
D. Spontaneous CJD

Iatrogenic CJD ~450 cases

Definite Causes

- Pituitary extracts
  - Human Growth Hormone
  - Delay may be >30 y
- Dura mater grafts
  - Mostly Lyodura brand
- Transplants (RARE)
  - Corneal
  - Pericardium
  - Liver
- Instrumentation/Laboratory accident
  - NeurosurgeonsImplantable Neurosurgical-implanted EEG, stereotactic procedures

No Link

- Vaccines
- Feces
- Saliva
- Sputum
- Bovine insulin
- Semen, vaginal secretions

CJD and Recommendations

•Patient

- Detailed history
- Blood/urine testing for presence of prions RT-QuIC
- Referrals
- Resources

•Family members

- Detailed history/Detailed discussion
- No role for RT-QuIC routine screening for presence of prions in blood or urine
- Genetic testing for prion variants may be useful
- Referrals
- Resources

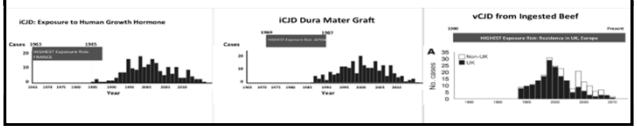
Summary

	sCJD	iCJD	vCJD
Source	Spontaneous event	Human growth hormone Dura mater graft	Ingested beef
Distribution	Worldwide	Human growth hormone: US, Europe Dura mater graft: Japan	Linked to Beef originating largely in UK. US cases all have travel history
Median Age (y)	68	51	28
Progression	SHORTER	shorter	LONGER
EEG	Typically abnormal	few data but abnormal	NOT Typically abnormal
MRI Basal ganglia	"Double Hockey Stick"	Few Data, Double Hckey Stick	"Pulvinar sign"
Pathology	Abnormal Prion Protein deposits	Abnormal Prion Protein deposits	"Florid Plaques"

Prions Reference Material

Transmissible Spongiform Encephalopathy:Time and Place

Mode of transmission	Geographic Region	Risk Window
Beef ingestion	UK, France, Europe	1980-present
Human growth hormone	France	1963-1985
Dura mater graft	Japan	1969-1987



Kuru "shivering,trembling"

- Fore tribe Papua New Guinea
- Ritual mourning w/cannibalism
- Older females, children (especially female)
- Progressive Ataxia w/dementia
  - Ambulant, leaning (pictured)
  - Sedentary
  - Terminal "laughing death"
  - "Florid plaques" (inset) on H+E
- No maternal/fetal transmission
- New cases would have been infected as children
- No cases <40 y.o. since 1991

CJD and Blood Supply

- Transfusion-associated vCJD rarely documented (N=4, UK)
- NO documented transfusion-associated sCJD
- No FDA approved tests to detect transmission
- Deferral
  - Dura mater graft or human growth hormone
  - Donors with CJD or family history of CJD
  - Residence in Europe after 1980
  - Transfusion in Europe after 1980
  - Bovine insulin after 1980 unless certain that insulin was not from UK

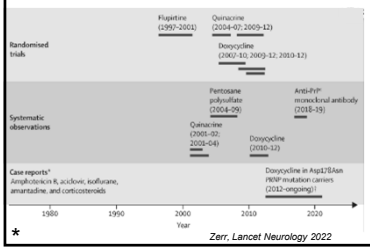
Transmissible Spongiform Encephalopathy

Infection Control Issues

- **Universal precautions**
- **No confirmed occupational transmissions**
  - CJD in health care workers occurs, occupational links have been suggested
- **Incinerate single use instruments**
- **Inactivate other instruments and materials**
  - 1N NaOH
  - autoclave 121° C, 15 psi 30 min
  - Formic acid for tissue sections
  - Alternatives include hypochlorite (20,000 ppm chlorine) + autoclave
  - REMEMBER: Infectivity is STABLIZED by alcohol, formalin, or glutaraldehyde
- **WHO infection control guidelines**
  - **http://www.who.int/csr/resources/publications/bse/whocdscsraph2003.pdf?ua=1**

Transmissible Spongiform Encephalopathy

Multiple trials BUT NO FDA Approved Therap



* *Zerr, Lancet Neurology 2022*

PRN100 Antibody Under Study

Anti-Prion antibody/G4 isotype
UK /J. Collinge/N=6
Achieved antibody levels in CSF
No disease reversal
?stabilization of rating scales

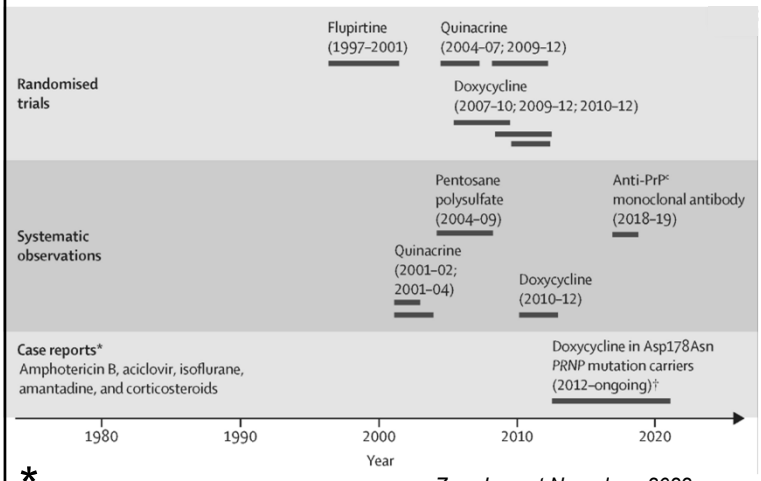
Future: Disaggregase

Resources

- **RT-QuIC: Case Western**
  - **https://case.edu/medicine/pathology/divisions/national-prion-disease-pathology-surveillance-center/resources-professionals/contact-and-shipping-information**
- **Epidemiology**
  - **https://www.cdc.gov/prions/cjd/resources.html**
- **Patient support**
  - **https://cjdfoundation.org/other-resources**
- fmaldarelli3@gmail.com

Transmissible Spongiform Encephalopathy

Multiple trials BUT NO FDA Approved Therapy



Zerr, Lancet Neurology 2022

PRN100 Antibody Under Study

- **Anti-Prion antibody/G4 isotype**
  - **UK /J. Collinge/N=6**
    - **Achieved antibody levels in CSF**
    - **No disease reversal**
    - **?stabilization of rating scales**

Future: Disaggregase

33

HIV-Associated Opportunistic Infections I

Dr. Henry Masur

33 – HIV-Associated Opportunistic Infections I

Speaker: Henry Masur, MD

HIV-Associated Opportunistic Infections I

Henry Masur, MD, FIDSA, MACP
Clinical Professor of Medicine
George Washington University

6/2/2023

Disclosures of Financial Relationships with Relevant Commercial Interests

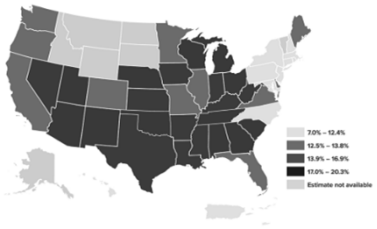
- **None**

Question 1

For which of the following infections would life long suppressive therapy be indicated for a patient with a CD4 count <50 cells and a high viral load, regardless of subsequent success of ART regimen in terms of CD4 count and viral load

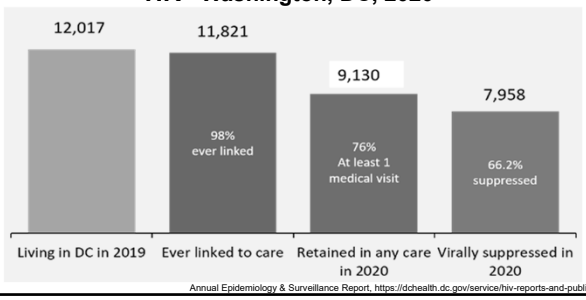
a. Disseminated histoplasmosis
b. Cryptococcal meningitis
c. Coccidiodes meningitis
d. Miliary tuberculosis
e. Disseminated Mycobacterium avium complex

Percent of People with Undiagnosed HIV by State, 2018



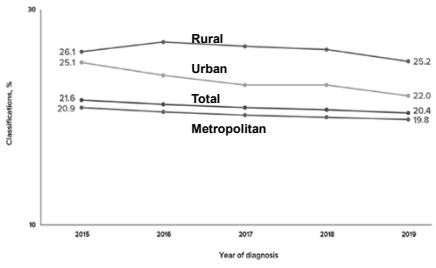
https://www.cdc.gov/hiv/policies/strategic-priorities/mobilizing/status-of-hiv.html

HIV Care Continuum among People Living with HIV Washington, DC, 2020



Annual Epidemiology & Surveillance Report, https://dchealth.dc.gov/service/hiv-reports-and-publications

AIDS at Time of Diagnosis 2015-2019, United States
20-25% PWH Continue to Present Late in Disease



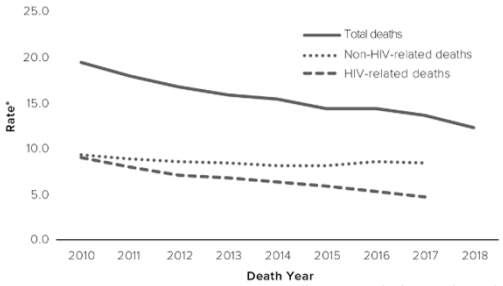
https://www.cdc.gov/hiv/library/reports/hiv-surveillance/vol-26-no-2/index.html

Primary Cause of Death among People Diagnosed with HIV by Year of Death, District of Columbia, 2015-2019

	2015	2016	2017	2018	2019
Cause of Death	%	N %	%	%	%
HIV-related causes	18.3	28.9	28.2	31.3	25.0
Non-AIDS Defining Malignancies	9.8	15.1	16.4	13.3	9.5
Cardiovascular	14.4	14.5	19	24.5	18.0
Substance Use	1.3	1	0.7	1.1	0.5
Accidental Death	7.2	12.2	12.5	10.1	11.5
Other**	10.8	47	15.4	15.8	11.0
Unknown	38.2	9.3	7.9	4	24.5
Total	100	100	100	100	100

Annual Epidemiology & Surveillance Report, https://dchealth.dc.gov/service/hiv-reports-and-publications

Among people with HIV, deaths from all causes decreased mainly because of declines in HIV-related deaths



https://www.cdc.gov/hiv/statistics/deaths/index.html

Question #2

PREVIEW QUESTION

- **An asymptomatic patient with a new diagnosis of HIV (CD4 = 10 cells/uL and HIV Viral Load 300,000 copies/uL is started on antiretroviral therapy (dolutegravir plus tenofovir alafenamide/emtricitabine)**
- **His labs are unremarkable as is his chest xray**
- **His serum toxoplasma IgG is positive**
- **He asks whether you want to add prophylaxis for pneumocystis pneumonia but warns you that twice when he has taken sulfonamides he has developed hives and laryngeal edema**

What would you recommend regarding PCP and Toxo prophylaxis?

A. No chemoprophylaxis: his viral load should fall quickly, and his CD4 will rise quickly in response to this first exposure to antiretroviral therapy
B. Trimethoprim sulfamethoxazole plus solu-medrol dose pak
C. Dapsone
D. Aerosol pentamidine plus pyrimethamine
E. Atovaquone

Question #3

PREVIEW QUESTION

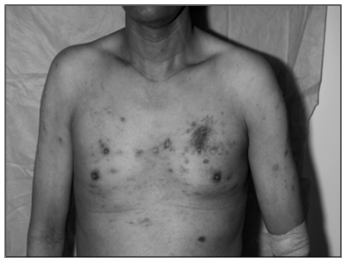
The patient whose photo is shown is HIV positive (CD4=10 cells/uL, VL=2 mil copies) and has noted these lesions developing on his trunk, face and extremities over the past 8 months.

He has had low grade fevers for several months.

For your differential diagnosis, what besides Kaposi sarcoma would be the most likely cause of these lesions and their associated fever?

Question #3

PREVIEW QUESTION



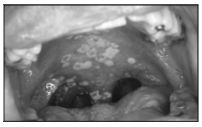
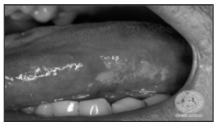
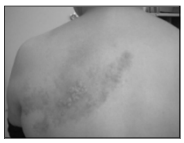
Question #3

PREVIEW QUESTION

The most likely cause of these skin lesions, if they are not Kaposi sarcoma, is:

A. HHV-6
B. CMV
C. Cryptococcus neoformans
D. Bartonella
E. Rhodococcus

Clinical Indicators of Immunosuppression

Cardinal AIDS-Defining Illnesses

- **Pneumocystis pneumonia**
- **Toxoplasma encephalitis**
- **CMV Retinitis**
- **Disseminated Mycobacterium avium complex/Tuberculosis**
- **Chronic cryptosporidiosis/microsporidiosis**
- **Kaposi Sarcoma**

Is COVID-19 an HIV Related Opportunistic Infection?

- **Not testable**
  - Controversial whether excess morbidity/mortality is related to HIV or to co-morbidities such as obesity, hypertension, diabetes etc
  - Not relevant to diagnosis, therapy
  - Prudent to emphasize vaccine and other preventive measures

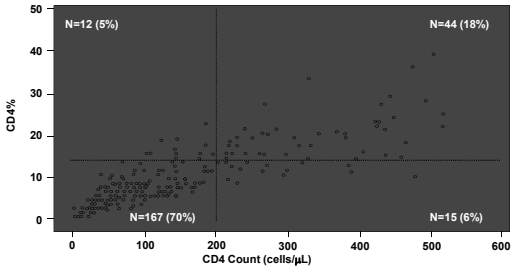
PS: Monkeypox could be presented in terms of prior US cases linked to travel or to the 2003 pet shop related outbreaks but…. the current outbreak in MSM will NOT show up on exam—too new and too many unresolved issues!!

Susceptibility to Opportunistic Infections Patients with HIV

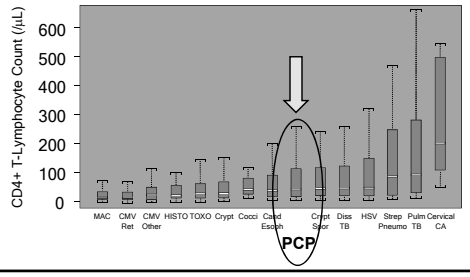
- **CD4 Count**
  - Current count is most important
  - Prior nadir count is much less important
- **Viral Load**
  - Independent risk factor for OIs

At What CD4 Counts Do Opportunistic Infections Occur?

Scatterplot of CD4 Number vs CD4 Percent Within 6 Months of HIV-Associated PCP



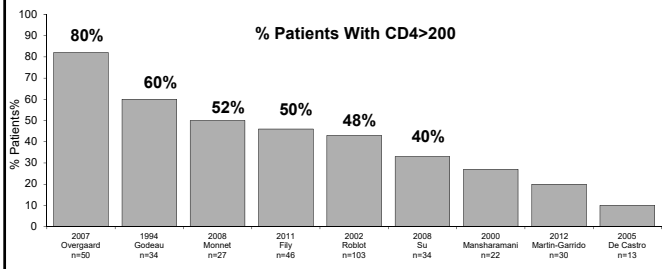
CD4+ Lymphocyte Counts Are Excellent Predictor of the Occurrence of Opportunistic Infections for HIV/AIDS



CD4 Counts in Non-HIV Patients

- **Low CD4 Count**
  - Susceptible to PCP
- **High CD4 Count**
  - Not necessarily protected from PCP

WARNING For Non-HIV Patients
CD4 Count Are Not A Sensitive Indicator of PCP



Messiaen. *Transpl Infect Dis.* 2017;19:e12651.

What is the Most Effective Intervention to Prevent Opportunistic Infections and Neoplasms Regardless of CD4 Count and Viral Load?

What is the Most Effective Intervention to Prevent Opportunistic Infections and Neoplasms Regardless of CD4 Count and Viral Load?

Antiretroviral Therapy

When to Start ART Following Opportunistic Infection

You Have Seen This Question!!

A 52-year-old woman without known HIV is diagnosed with PCP
- **HIV Ab test positive**
- **CD4 103, HIV RNA 135,000 copies/ml**
- **She is still intubated on day 4 of IV trimethoprim-sulfa and corticosteroids**

When should she start ART?

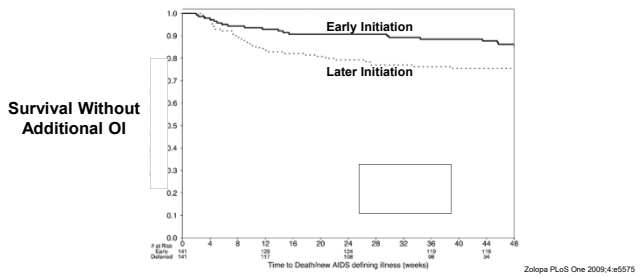
A. Immediately
B. In the next 2 weeks
C. After completing 21 days of trimethoprim-sulfa
D. At her first outpatient clinic visit

When to Start ART Following Opportunistic Infection

- **Most OIs**
  - **Within 2 weeks of diagnosis**

ART Initiation Following HIV Related Opportunistic Infections

Early Favors Survival



Zolopa PLoS One 2009;4:e5575

When to Start ART Following Opportunistic Infection

- **Tuberculosis: 2-8 weeks after initiation RX**
  - CD4<50 or Pregnant-within 2 weeks of diagnosis
  - CD4>50-within 8 weeks of diagnosis
- **Cryptococcal Meningitis: 4-6 weeks after initiation of RX**
  - Sooner if mild and if CD4<50
  - Later if severe
- **"Untreatable" OIs, i.e., PML, Cryptosporidiosis**
  - Start immediately

Primary and Secondary OI Prophylaxis

These Are Guidelines But They Are Based on 1980-1990 ART

- **Primary Prophylaxis**
  - **PCP (CD4 <200, ~~oral candida, prior AIDS Defining~~)**
  - **Toxo (CD4 <100, old or new positive anti Toxo IgG)**
  - **Cocci (CD4<250, IgG or new positive cocci IgM**
  - **~~MAC (CD4 < 50)~~ ---NIH/CDC/IDSA guideline has eliminated this for all practical purposes**
  - *****
- **Secondary Prophylaxis /Chronic Suppression**
  - **PCP**
  - **Toxo**
  - **MAC**
  - **CMV**
  - **Cryptococcus**
  - **Histoplasma**
  - **Coccidio**

***Some experts would give Histo primary prophylaxis with itraconazole in high risk situations if CD4<150 and would not use histo serology in decision (not reliable)**

Prophylaxis NOT Routinely Recommended in US

Primary	Secondary
• Candida	Candida*
• Cryptococcus	
• HSV	HSV*
• VZV	VZV*
• CMV	
• MAC	

***Secondary Prophylaxis would be reasonable if recurrences were frequent or severe**

Discontinue Prophylaxis/Chronic Maintenance

Board might consider this a "look up"

Primary Prophylaxis	CD4 Count Due to ART
– PCP or Toxo	>200 x 3 months
– PCP	(>100 and VL<50)

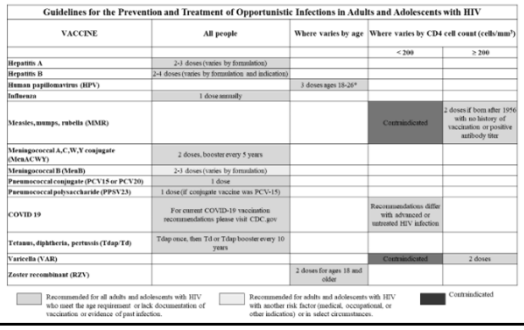
Secondary Prophylaxis/Chronic Maintenance	
– PCP	>200 x 3 months
– Toxo	>200 x 6 months
– Crypt	>200 x 6 months
– MAC	>100 x 6 months + 12 m Rx
– CMV	>100 x 3-6 months*

Primary Coccidiomycosis Prophylaxis 2023 OI Guideline

Testing
- **Once or twice yearly testing for seronegative patients**

Primary Prophylaxis
- **Do not administer in endemic area if serology negative**
- **Within the endemic area**
  - New positive IgM or IgG serology and
  - CD4 count is <250 cells (BIII) and
  - No Active Disease
- **Regimen**
  - Fluconazole 400mg qd until CD4>250 and fully suppressed viral load

OI Guidelines Vaccination Recommendations



*

OI Gu…endations

This Is All Oversimplified, But for the Exam

- **Avoid Live Vaccines at CD4 counts < 200**
  - **MMR, Varicella, Oral Typhoid, Yellow Fever**
- **Avoid attenuated intranasal influenza at all CD4**
- **All COVID-19 vaccines are recommended at all CD4**
- **Emphasize HAV, HBV, Meningococcus ACWY, Pneumococcus**
  - **All higher incidence in HIV than non HIV**
- **Administer RZV (Shingrix) to HIV age >18 years**
  - **(ACIP differs from OI Guideline)**
- **For pneumococcus, when in doubt use PCV 20**
- **Administer Mpox if possibly exposed or likely to be exposed**
- **Post vaccine titers recommended**
  - **HBV, HAV**

Pneumococcal Vaccine for Persons With HIV

Bottom Line: Give Polyvalent Pneumococcal Conjugate 20 and Then See Details

- Administer either 15-valent pneumococcal conjugate vaccine (PCV15) or 20-valent (PCV20)
- If PCV15 is used, a dose of 23-valent pneumococcal polysaccharide vaccine (PPSV23) should be administered at least 8 weeks later.

Who Should be Vaccinated for HBV

- **People without chronic HBV infection and without immunity to HBV infection (anti-HBs <10 mIU/mL)**
  - The specific regimens are too granular and changing to likely be on exam
  - NIH/IDSA perspective re rechecking
    - 1-2 months post vaccine and then annually and boost responders if annual level <10mIU/ml

Who Should be Vaccinated for HBV

Anyone PWH Who Is Not Actively Infected or Is Seronegative

- **The specific regimens are too granular and changing to likely be on exam**
- **Annual testing of HBV serology is now recommended by NIH Guideline with booster if <10IU**
- **Patients without chronic HBV and without immunity to HBV**
  - Vaccinate with double-dose of three-dose series of single antigen hepatitis B vaccine (Recombivax□ or Engerix□) or combined HepA-HepB at 0, 1, and 6 months—NIH OI Guidelines 2023—this means two injections rather than one
  - Heplisav is also recommended esp IF a two dose regimen is desired
  - Check anti-HBs titers 1 to 2 months afterward
    - If the anti-HBs titer is ≥10 m IU/mL, no further vaccination is needed
    - If the titer is <10 m IU/mL, then administer a four-dose revaccination series using double doses (BI) or consider Heplisav-B®
    - Because of waning immunity, some experts would check anti-HBs annually and would give a booster dose if levels fall below 10mIU/mL, particularly if patients have on going risk factors
- **Note**
  - Patients with isolated anti-HBc and negative HBV DNA should be vaccinated
    - If after one dose, HB AB is >100 IU, no more vaccine is needed
    - If after one dose, HBV AB is < 100 IU/ml complete the series
  - Whether to defer vaccination in patients with CD4<350 is too controversial and complicated for exam

HBV Non-Responders

- **Definition**
  - Anti-HBs <10 international units/mL 1 month after vaccination series
- **Options: Not testable**
  - Switch to other recombinant vaccine, i.e., GSK to Merck or vice versa
  - Double dose of recombinant vaccine (if that was not the initial regimen)
  - Four dose regimen
  - Heplisav adjuvant vaccine

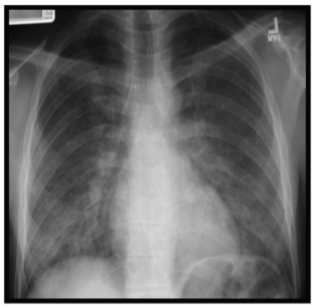
HBV Immunization for Persons with Isolated Anti HBc

- **Recommend one standard dose of HepB vaccine followed by checking anti-HBs level at 1–2 months.**
  - If the titer is >100 mIU/mL, no further vaccination is needed,
  - If the titer is <100 mIU/mL, a complete series of HepB vaccine should be completed, followed by anti-HBs testing
- **If the anti-HBs quantitative titer is not available**
  - Recommend complete HepB vaccine series
  - Follow-up quantitative anti-HBs testing

Post Exposure to HBV for PWH

- **Prior vaccine with documented response**
  - Nothing needed
- **Prior vaccine with NO response measured**
  - Administer single dose
- **No prior vaccine**
  - HBIG if within 7 days of percutaneous and 14 days of sexual exposure
    - Might not be necessary for patients on tenofovir or lamivudine
  - Full vaccine series simultaneously with HBIG
  - https://www.cdc.gov/mmwr/volumes/67/rr/rr6701a1.htm

HIV Associated Pulmonary Disease



Etiology of HIV Associated Pulmonary Disorders

Common	Uncommon	Rare
• Pneumococcus	• Aspergillus	• CMV
• Hemophilus	• Histo/Cocci	• MAC
• Pneumocystis	• Staphylococci	• HSV
• Tuberculosis	• Toxoplasma	
• "Atypicals/viral"	• Lymphoma	
	• Kaposi sarcoma	

Respiratory Disease in Patients with HIV
Do Not Focus Only on OIs!

- **Non-Infectious**
  - **Congestive Heart Failure** **(Age, cocaine, pulm hypertension)**
  - **Pulmonary emboli** **(Increased risk)**
  - **Drug toxicity** **(Abacavir, Lactic acidosis, dapsone)**
  - **Neoplastic** **(KS, Lymphoma, Lung CA)**

Respiratory Disease in Patients with HIV
Do Not Focus Only on OIs!

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  - **Pulmonary emboli** **(Increased risk)**
  - **Drug toxicity** **(Abacavir, Lactic acidosis, dapsone)**
  - **Neoplastic** **(Kaposi sarcoma, Lymphoma, Lung CA)**
- **Non-Opportunistic Infections**
  - **Community acquired** **(Influenza and MRSA)**
  - **Aspiration** **(Opioid related, nosocomial)**
  - **Septic Emboli** **(IV catheters, endocarditis)**

Approach to Diagnosis and Therapy of Pneumonia in PWH

Parameter	Example
• Rapidity of Onset	> 3 days: PCP, TB, <3 days: Bacteria, viral
• Temperature	Afebrile: Neoplasm, PE, CHF
• Sputum	Scant: PCP, Virus, TB Purulent: Bacteria
• Physical Exam	Normal: PCP Consolidation: Bacteria
• Xray	Suggestive But Never Diagnostic

Pneumococcal Disease in Persons with HIV Infection

- **CD4<200**
  - Frequency enhanced
  - Severity/Extrapulmonary Complications Enhanced
- **CD4>350**
  - Frequency: Enhanced
  - **Severity: No difference**
- **Comorbidities Predisposing to Pneumococci Over-Represented in HIV**
  - Opioid Use Disorder, Etoh, Tobacco, Lack of Immunization
  - COPD, CHF, Obesity, MRSA colonization, Liver Disease

Are There Strategies for Reducing Bacterial Pneumonias in Patients with HIV Infection?

Strategies to Reduce Incidence of Pneumonia for Patients with HIV

- **Patient Focused Strategies**
  - Antiretroviral Therapy
  - Pneumococcal vaccine
  - Influenza vaccine
  - Tobacco cessation
- **Environmental Strategies**
  - Immunize contacts and community (esp children)
    - Pneumococcal and Hemophilus vaccines
    - Influenza vaccine

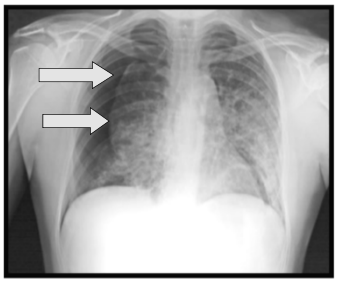
Question #3

- **A 28-year-old male with HIV (CD4 count = 10 cells) presents to the ER 4 weeks of malaise and mild cough, and now has bilateral interstitial infiltrates and a right sided pneumothorax.**
- **The patient lives in Chicago, works in an office and has never left the Midwest and no unusual exposures.**
- **The most likely INFECTIOUS cause of this pneumothorax is:**

HIV and Covid

- **No increased susceptibility**
- **Probably increased severity**
  - Likely related to CD4 count, viral load, other co-morbidities
- **Drug interactions**
  - Integrase inhibitors and Paxlovid have no interactions
  - Cobicistat and Ritonavir contain regimens likely OK with Paxolovid
  - ART and Remdesivir no interactions

HIV Patient with Shortness of Breath



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The patient lives in Chicago, works in an office and has never left the Midwest and no unusual exposures.

The most likely INFECTIOUS cause of this pneumothorax is:

A. Cryptococcosis
B. Blastomycosis
C. PCP
D. CMV
E. Aspergillosis

Pneumocystis Jirovecii (Formerly *P. carinii*)

- **Taxonomy**
  - Fungus (no longer Protozoan)
- **Epidemiology**
  - Environmental source unknown
- **Life Cycle**
  - Unknown
- **Transmission**
  - Respiratory

Host Susceptibility to PCP

- **CD4 < 200 cells/µL --(90% of cases)**
- **CD4% <14**

Clinical Features of PJP in Pre-AIDS Era, (n=168)

No Feature is Present 100% of Initial Presentations

Symptom	% Patients
• Dyspnea	91%
• Fever	66%
• Cough	47%
Productive	7%
Non-productive	40%
• Signs	
– Cyanosis	39%
– Rales	33%

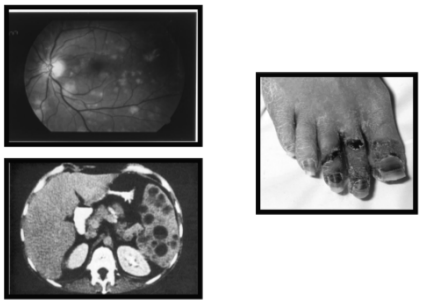
Walzer, Ann Intern Med 1974

PCP is More Subacute in Persons With HIV Than Other Immunosuppressed Persons

Sign or Symptom	HIV (n=48)	Non-HIV (n=38)
Symptom		
Fever	81%	87%
Cough	81%	71%
Shortness of breath	68%	66%
Duration of symptoms,	28 days	5 days
Temp> 38°C	76%	92%
PaO_2	69 mm Hg	52 mm Hg
A-a gradient	41 mm Hg	59 mm Hg
% with normal ABG	5-20%	

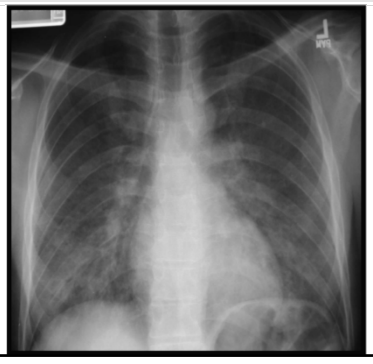
Kovacs et al. Ann Intern Med 1984

Uncommon Manifestations of PCP

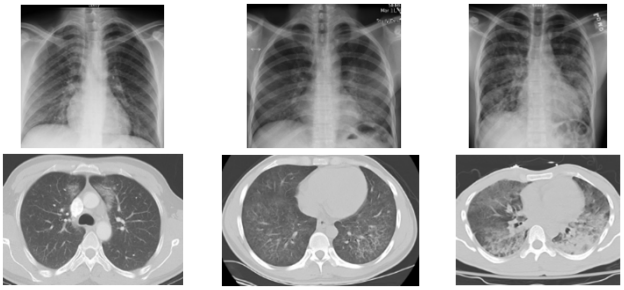


Imaging of PCP

- **Early-CT is never normal!**
  - Reticular (interstitial)
  - Nodular (interstitial)
  - Ground Glass (sparing periphery)
- **Later-Progression from Interstitial**
  - Consolidation (late finding)
  - Upper Lobe Cysts (thin walled)
  - Pneumothorax
    - (cyst and bronchopleural fistula)



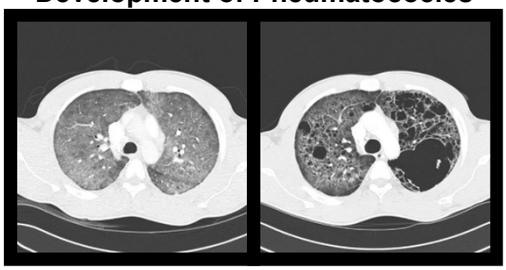
HIV Related PCP



Asymptomatic Incidental Finding

⇩

Development of Pneumatocoeles



May 23 June 13

Radiologic Patterns Associated with Documented Pneumocystis Pneumonia

- **Most Frequent**
  - **Diffuse symmetric interstitial infiltrates progressing to diffuse alveolar process**
    - **Butterfly pattern radiating from hilum**

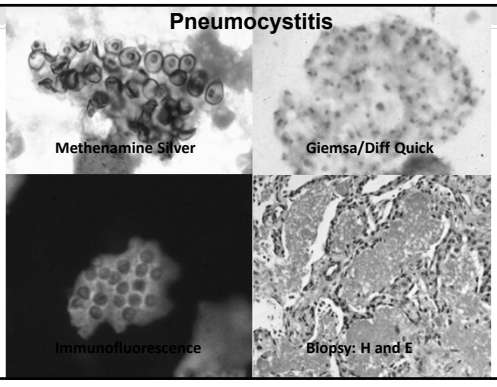
Radiologic Patterns Associated with Documented Pneumocystis Pneumonia

- **Other Patterns Recognized**
  - **(Other concomitant infectious or neoplastic disease processes?)**
  - **Lobar infiltrates**
  - **Upper lobe infiltrates**
  - **Pneumothorax**
  - **Solitary nodules**
  - **Cavitating lesions**
  - **Infiltrates with effusions**
  - **Asymmetric or unilateral processes**
  - **Normal chest x-ray**

Diagnosis of Pneumocystis Pneumonia

Specimen Acquisition	1957 ↓ 2023	Organism Detection
Open lung biopsy		Methenamine silver
Transbronchial biopsy		Immunofluorescence
Bronchoalveolar lavage		Giemsa / Diff Quik
Induced sputum		PCR

Pneumocystitis



PCR
For Diagnosis of Pneumocystis in Bronchoalveolar Lavage

- **Highly sensitive in BAL**
  - Not useful in blood/serum/plasma
- **High biologic specificity**
  - Positive result might be infection or disease
  - Cycle number (copy number)helpful but not definitive

PCR
For Diagnosis of Pneumocystis in Bronchoalveolar Lavage

- High
  - No
- High
  - Po
  - Cy

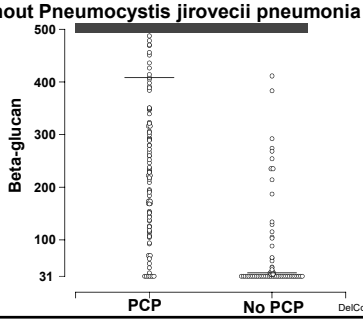
Negative BAL PCR rules out PCP

Positive BAL PCR *might* be PCP
- **Colonization vs Disease**

Is There A Serologic Test for PCP? No!

- **Serum Antibody or PCR Test**
  - Not useful…yet
- **LDH**
  - Sensitivity depends on severity
  - Non-specific-elevated in many lung diseases
- **Beta Glucan**
  - Sensitive but not specific
  - Maybe useful for
    - Heightened suspicion of PCP if BAL or sputum not feasible
    - Following response to Rx

Distribution of β-glucan Results at Baseline in Those With and Without Pneumocystis jirovecii pneumonia (PCP)



Sax PE. *Clin Infect Dis* 2011

DelCorpo. Clini Microb and Infection 2020

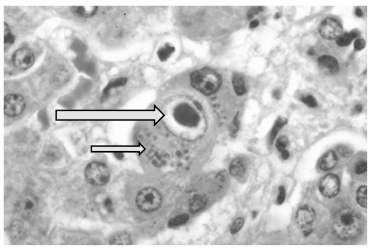
Question #5

- **A 45-year-old woman with HIV (CD4 = 50 cells/uL, HIV viral load = 500,000 copies/uL) presents with fever, shortness of breath, room air P02 =80mm Hg) and diffuse bilateral infiltrates and is started on TMP-SMX. The bronchoalveolar lavage is positive for pneumocystis by direct fluorescent antibody test.**
- **The cytology lab reports several CMV inclusion bodies in the BAL.**

The best course of action in addition to considering antiretroviral therapy would be:

A. To add ganciclovir to the TMP-SMX regimen
B. To add prednisone to the TMP-SMX regimen
C. To add ganciclovir plus prednisone to the TMP-SMX regimen
D. To add ganciclovir plus IVIG to the regimen
E. To add nothing, ie continue TMP-SMX alone

CMV Cytology



Eosinophilic Intranuclear Inclusion and Coarse Basophilic Cytoplasmic Inclusions

CMV Almost Never Causes Pneumonia In HIV Infected Pts

CMV is a marker of more severe immunosuppression but not usually the cause of pneumonia…<u>in this population</u>

Question #6

A patient with HIV infection newly diagnosed (CD4=10, VL= 200,000 copies/uL) was started on the following medications: efavirenz, emtricitabine, tenofovir, dapsone, fluconazole clarithromycin.

Ten days later the patient returns with headache, shortness of breath, a normal chest CT

Pulse oximetry shows an O2 saturation of 85%

A stat ABG is ordered which shows pH 7.40, pO2=96mmHg, pCO2 =39mm Hg, O2 Sat 96%.

The ABG lab reports methemoglobinemia = 25%

The most likely cause of this patient's syndrome is:

A. Pneumocystis pneumonia
B. Pulmonary Kaposi sarcoma
C. Fluconazole interaction with another drug
D. Dapsone
E. Clarithromycin

Methemoglobinemia = Methemoglobin>3%

Causes: Many: Dapsone and topical anesthetics notorious
Also chloroquine, primaquine, sulfa, nitrofurantoin

Therapy: Stop drug +/- methylene blue, ascorbic acid, transfusions

D. Dapsone
E. Clarithromycin

Answer #5

Methemoglobinemia = Methemoglobin>3%

Unlike normal hemoglobin, methemoglobin does not bind oxygen and as a result cannot deliver oxygen to the tissues

Symptoms: Headache to dyspnea to delirium and organ ischemia to death start occurring at methg >10%; >30% is life threatening

Detection
Too complicated for IDBR due to improving technology
Many systems measure methemoglobinemia directly
look for high P02, low O2 Sat and…report of methemoglobin

Causes: Many: Dapsone and topical anesthetics notorious
Also chloroquine, primaquine, sulfa, nitrofurantoin

Therapy: Stop drug +/- methylene blue, ascorbic acid, transfusions

Question #7

A 50-year-old male with HIV and PCP is receiving pentamidine 4 mg/kg IV over 1 hr qd.

On the ninth day of therapy, while awaiting transportation home, he has a syncopal episode.

An EKG done by the code team is normal.

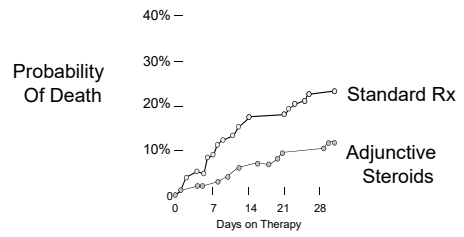
What Non cardiac toxicity of pentamidine would be most likely

A. Hyponatremia
B. Seizure
C. Hypoglycemia
D. Hypertensive crisis and stroke
E. Pulmonary embolus

Therapy for Pneumocystis Pneumonia

- **Specific Therapy**
  - **First Choice**
    - Trimethoprim-Sulfamethoxazole
  - **Alternatives**
    - Parenteral Pentamidine
    - Atovaquone
    - Clindamycin-Primaquine
- **Adjunctive Corticosteroid Therapy**
  - **Moderate to Severe PCP**
    - Room air p02 less than 70mmHg or A-a gradient >35mm Hg

Likelihood of Death in Patients with Moderate-Severe PCP Receiving Corticosteroids (n=251)



(Bozette, NEJM 5/90)

Would the ID Board Exam Ask You About Pulse Oximetry?

- **Target SpO2 92% to 96% seems logical**
- **SpO2 <92% or >96% may be harmful**

Decisions Based on Pulse Oximetry

- **Many different types of hospital, home, and personal oximeters**
  - Some are more accurate than others
  - Some measure carboxy or methemoglobinemia
- **SpO2 is not the Same as SaO2**
  - Sp02 is often 1-2% higher or lower than SaO2 but in a few patients there is greater discrepancy
    - "Occult Hypoxemia"
  - Dark pigment makes a difference (skin color, nail polish etc) as does hypotension, shivering and motion, unusual Hgs
  - Changes in Sp02 may lag SaO2 by a few minutes

Decisions Based on Pulse Oximetry

- **Do discrepencies between SaO2 and SpO2 matter clinically**
  - Look for trends
  - Use your brain
  - Keep SpO2 above 90% but for dark pigment….above 96%?

A Question That Could Be on Boards

- **What drugs <u>should only be given after</u> <u>screening</u> for Glucose-6-Phosphate Dehydrogenase**
  - **G6PD is common and nationality is increasingly difficult to define as a predictor**
- **Presentation (Dx Dilemma-Due to G6PD Deficiency or Acute Malaria)**
  - **Hemolysis, jaundice, back and abdominal pain 2-4 days post drug exposure**
  - **Smear shows hemolytic pattern and "Heinz bodies"**
  - **Hemoglobinuria, high retic count**
- **Drugs**
  - Dapsone, Primaquine, Tafenoquine
  - Many others less important-quinolones, nitrofurantoin
- **Diagnosis (too complicated for exam)**
  - **Qualitative assay -urgent situations; Quantitative for less urgent**
  - **What level of deficiency requires drug avoidance---complicated**
  - **Testing after hemolysis can be misleading**

How to Manage Patients Who Are Failing TMP-SMX

- **Average Time to Clinical Improvement**
  - **4-8 Days**
- **Radiologic Improvement**
  - **Lags clinical improvement**

Reasons to Deteriorate During Treatment for PCP

- **Fluid overload**
  - Iatrogenic, cardiogenic, renal failure (Sulfa or Pentamidine related)
- **Anemia**
- **Methemoglobinemia**
  - Dapsone, primaquine
- **Pneumothorax**
- **Unrecognized concurrent infection**
- **Immune Reconstitution Syndrome (IRIS)**

Reasons to Deteriorate During Treatment for PCP

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  - Iatrogenic, ca… …entamidine related)
- **Anemia**
- **Methemoglob**
  - Dapsone, prim
- **Pneumothora**
- **Unrecognized**
- **Immune Reco**

<u>Patients Failing TMP-SMX Not Testable!</u>

- **Whether to Switch**
- **When to Switch**
- **What to Switch To**
- **How to Manage Steroid Dosing**

Can *Pneumocystis Jiroveci* Become Resistant to TMP-SMX?

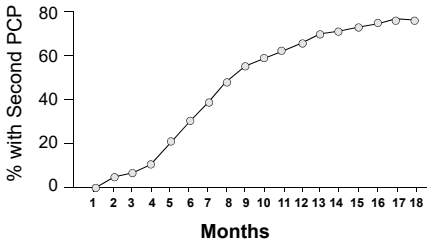
Toxicities of TMP-SMX and Pyrimethamine-Sulfadiazine

Drug	Toxicities
TMP-SMX	↓WBC, ↓Plat, ↑LFT, ↑Creat, ↑Amylase, rash, fever, pruritus, "Sepsis" syndrome-distributive shock Hyperkalemia and increased serum creatinine (TMP competes with K and creat for excretion) Cross reactivity: dapsone (± 50%)
Pyrimethamine-Sulfadiazine	Similar to TMP-SMX Folinic acid necessary (not folate) to prevent cytopenias

Toxicity and Other Considerations Regarding Antipneumocystis Therapy

Drug	Issues
Pentamidine - IV	Hypotension-rate related ↑Creatinine, ↑Amylase, ↓WBC ↑ Early and then ↓Glucose Associated with↑Creatinine May occur days-wks post therapy Torsade de Pointes
Atovaquone	Poor absorption if low fat diet Rash, N + V, diarrhea, LFT

Without ART or Chemoprophylaxis Second Episodes of HIV Associated PCP Are Amazingly Common



Fischl/ACTG 002, 10/88

Indications for Primary and Secondary PCP Prophylaxis

Start	CD4 < 200 cells/uL (14%) ~~Oral candidiasis~~ ~~AIDS Defining Illness~~ ~~Prior PCP~~
Stop	CD4 >200 cells/µL x 3 M (Consider Stoppin: CD4 100-200 and VL<50 x 3M)
Restart	CD4<200 cells/µL

Non HIV---When Is PCP Prophylaxis Indicated

Poor Data----------NOT TESTABLE

- **Corticosteroids**
  - ≥20mg prednisone x 1 month if also additional immunosuppressive condition
- **Renal transplant**
  - 6-12 months and longer if high doses of immunosuppressive
- **Human stem cell transplant**
  - Start after engraftment and for duration of immunosuppression, esp if Graft vs Host
- **Lung transplant**
  - Lifelong
- **Certain primary immunodeficiencies**
  - Lifelong
- **Certain drugs**
  - Fludarabine, Idelalisib, probably ibrutinib, Temsirolimus
- **Some Biologics**
  - Rituximab-for 6 months after induction and during maintenance
  - TNF inhibitors (Remicade (infliximab), Enbrel (etanercept), Humira (adalimumab),Alemtuzumab (Campath)
    - Continue until At least 2 months post therapy or CD4 > 200, whichever is later

Primary or Secondary Prophylaxis Agents for Pneumocystis Pneumonia

- **First Choice**
  - TMP-SMX
- **Other Options**
  - Aerosol pentamidine **OR**
  - Atovaquone **OR**
  - (Monthly IV pentamidine-poor data in adults) **OR**
  - (Dapsone)

Thank You!

OI Guidelines Vaccination Recommendations

Guidelines for the Prevention and Treatment of Opportunistic Infections in Adults and Adolescents with HIV

VACCINE	All people	Where varies by age	Where varies by CD4 cell count (cells/mm^3)	
			< 200	≥ 200
Hepatitis A	2-3 doses (varies by formulation)			
Hepatitis B	2-4 doses (varies by formulation and indication)			
Human papillomavirus (HPV)		3 doses ages 18-26*		
Influenza	1 dose annually			
Measles, mumps, rubella (MMR)			Contraindicated	2 doses if born after 1956 with no history of vaccination or positive antibody titer
Meningococcal A,C,W,Y conjugate (MenACWY)	2 doses, booster every 5 years			
Meningococcal B (MenB)	2-3 doses (varies by formulation)			
Pneumococcal conjugate (PCV15 or PCV20)	1 dose			
Pneumococcal polysaccharide (PPSV23)	1 dose (if conjugate vaccine was PCV-15)			
COVID 19	For current COVID-19 vaccination recommendations please visit CDC.gov		Recommendations differ with advanced or untreated HIV infection	
Tetanus, diphtheria, pertussis (Tdap/Td)	Tdap once, then Td or Tdap booster every 10 years			
Varicella (VAR)			Contraindicated	2 doses
Zoster recombinant (RZV)		2 doses for ages 18 and older		

Recommended for all adults and adolescents with HIV who meet the age requirement or lack documentation of vaccination or evidence of past infection.

Recommended for adults and adolescents with HIV with another risk factor (medical, occupational, or other indication) or in select circumstances.

Contraindicated

*

34

HIV Diagnosis

Dr. Frank Maldarelli

34 – HIV Diagnosis

Speaker: Frank Maldarelli, MD

HIV Diagnosis

Frank Maldarelli, MD
Bethesda, MD

2/28/2023

Disclosures of Financial Relationships with Relevant Commercial Interests

- None

Question #1

A 26 year old otherwise healthy gay white man has his first HIV test as part of a new health plan. The fourth generation test is antibody reactive and antigen non-reactive. A supplemental third generation HIV-1/2 ELISA is non-reactive, and an HIV RNA test does not detect HIV RNA. The most likely explanation for these results is

A. This person HIV-infected and is an elite controller
B. This person is HIV-infected but is in the window period for HIV infection
C. This person is infected with an HIV variant that is not detected by the supplemental test
D. This person is not HIV-infected

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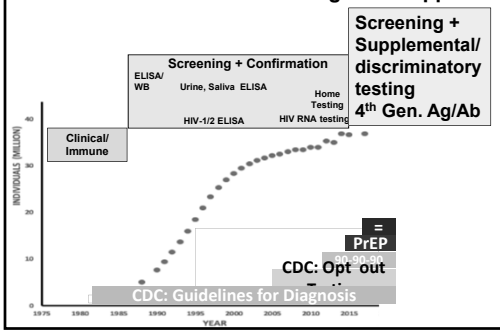
HIV Diagnosis: New Modalities and New Terminology Old Limitations Persist

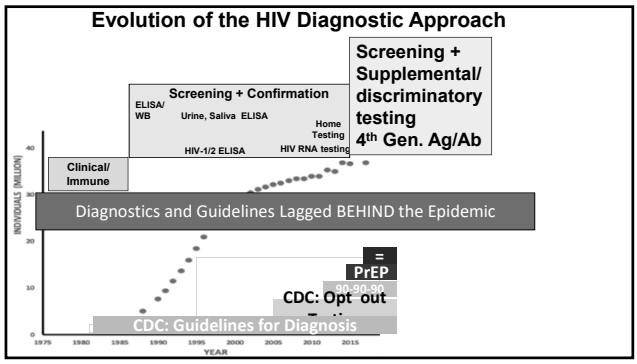
- HIV Diagnosis
  - History
  - Physical
  - Laboratory testing
- Two Step Diagnostic Approach
- No Laboratory Test is Perfect
- False positive results require resolution

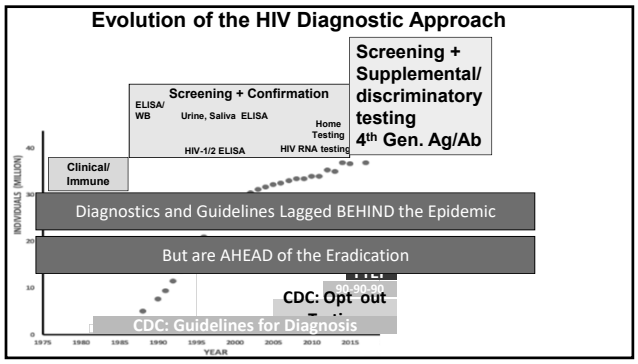
Evolution of the HIV Diagnostic Approach



34 – HIV Diagnosis

Speaker: Frank Maldarelli, MD



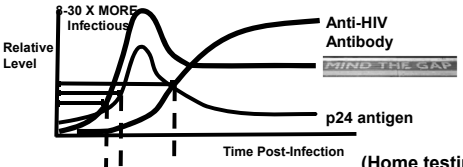


Question#2

27 year old female commercial sex worker working in Washington DC visits your clinic and requests PrEP. She shows you her home HIV test, which she took yesterday, and which is non-reactive. She has normal laboratory results and a negative pregnancy test. Which of the following is most appropriate next step

A. **She can immediately initiate PrEP with tenofovir-FTC with no additional testing**
B. **She requires additional testing with fourth generation Ag/Ab HIV test to determine whether she is infected with a non-B subtype of HIV-1 that is not detected by the home HIV test.**
C. **She requires additional testing with fourth generation HIV test to determine whether she has early HIV infection not detected by the home HIV test.**
D. **She should not initiate PrEP because PrEP does not work well in women**

HIV Detection: There is always a Window Period



(Home testing ≥ 3 months)

21 days 3rd Gen. Antibody only detection
16 days HIV p24 4th Gen. Antibody and p24 detection
11 days HIV Nucleic acid testing (NAT) detection

CDC 2014

Detecting HIV Infection TWO STEPS

- **Screening - Highest Sensitivity**
  - **4th gen ELISA for HIV antibody + p24 antigen detection**
  - **Qualitative HIV RNA**
- **Supplemental/Discriminatory - Highest Specificity**
  - **GEENIUS**
    - **Confirms HIV-1 or HIV-2**

Diagnosis of Early HIV Infection

- **HISTORY, PHYSICAL, LABORATORY TESTING**
- **Most sensitive Modalities**
  - **4th Generation**
  - **HIV RNA: APTIMA**
- **Less Sensitive Modalities**
  - **Oral or urine testing**
  - **Home testing (3 month window)**
  - **GEENIUS is LESS sensitive for EARLY infection compared with 4th gen testing**
- **FOLLOW UP and REPEAT testing**
- **Antiretroviral therapy may blunt serologic immune response from maturing**

Evaluation for HIV Infection during PrEP

- Every three months
- Includes detailed history and physical examination
- Ag/Ab (4th generation) testing preferred
- Viral RNA
  - Qualitative assay – FDA approved
  - Quantitative assay
    - >3000 copies/ml plasma cutoff
- DELAYED antibody emergence POSSIBLE in individuals infected during PreP with extended release cabotegravir

Question #3

You are following a couple who have had a planned pregnancy. The man is HIV positive and 100% adherent with first line therapy with Tenofovir+3TC+Dolutegravir; The woman has had monthly fourth generation HIV testing, which has been non-reactive throughout the first two trimesters; on the most recent visit the man has an HIV RNA was <20 c/ml, but the woman has shows HIV antigen negative and HIV antibody positive. The most appropriate next step is

A. Obtain the HIV viral RNA test to find out how high the viral load is, and begin antiretroviral therapy immediately

B. Consider laboratory error, repeat the same 4th generation test

C. Perform supplemental testing with third generation discriminatory testing

D. Reassure the couple that the woman is not infected and the test is just a false positive

HIV Testing During Pregnancy

- False positive results with antibody testing are possible
- May be specific for individuals tests and persist during pregnancy
- Testing with viral RNA testing can resolve most issues
  - Qualitative tests (e.g., APTIMA) ARE FDA-APPROVED for testing
    - Expensive and generally longer turn around
  - Quantitative testing are NOT FDA-APPROVED for diagnosis
    - Rapid turnaround but low level results are possible
- Rapid screening reactive during labor in previously untested
  - Initiate therapy
  - Do not wait for supplemental results

Question#4

A 65 yo American male has had unprotected sex with men for many years. The HIV-1/2 ELISA is reactive and supplemental testing is positive for HIV-1. Viral RNA level is <50 copies/ml and CD4 count is 700 cells/µl. He has never been on antiretroviral therapy and has no history of travel outside the US. Which of the following is most likely:

A. The patient is in the window period of HIV-1 infection.

B. The patient is chronically infected with HIV-1 and has a viral load too low to be detected because he is a long term non progressor.

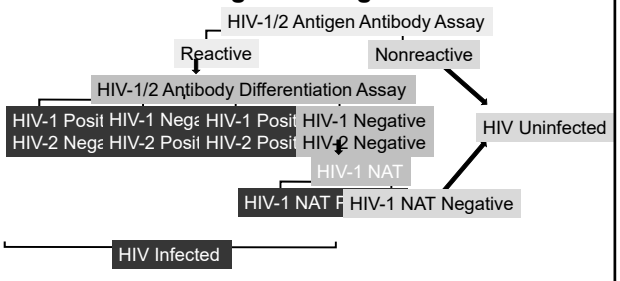
D. The patient is not infected with HIV-1 or -2, all tests are false positive.

E. The patient is infected with non-B subtype of HIV-1

HIV-1 Long Term Non-Progressors

- Represents authentic HIV infection
- ELISA REACTIVE
- SUPPLEMENTAL POSITIVE
- HIV RNA may not be detectable
- Slow disease progression
- Associated with specific HLA subtypes

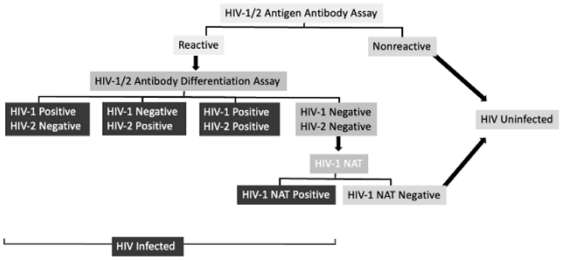
HIV Diagnostic Algorithm



34 – HIV Diagnosis

Speaker: Frank Maldarelli, MD

HIV Diagnostic Algorithm



Question #5

A 68 year old man undergoing PrEP (cabotegravir) comes for routine PrEP visit. He reports multiple partners (male and female) and engages in receptive anal sex with partners who do not use condoms. His prior 4th generation test was 6 months ago and was nonreactive. He admits that he has been going out to clubs more frequently after COVID restrictions eased. He does not use condoms. Ten days ago, he developed fever 101° F, cough . A covid test was positive. He feels better but not back to his usual state of health. The 4th generation test is now reactive. His other laboratory results include

CD4: 250 cells/µl (14%; prior CD4 was 1000 cells/µl; 55%)

Which of the following is most correct

A. Tell him the Covid test was a false positive, he has HIV, and should start TDF+FTC+ Rilpivirine

B. Tell him the HIV test is a false positive and continue PrEP

C. Tell him he may have HIV infection, send supplemental testing and continue PrEP

D. Tell him he may have HIV infection, send supplemental testing and switch to TDF+FTC+ Rilpivirine

HIV Testing and False Positives

- Numerous recent examples for false positive results
  - Acute infection
    - African trypanosomiasis
  - Heterophile antibodies
    - Workers in pork processing plant
  - Rheumatologic diseases
  - Metastatic cancer
  - Pregnancy
  - …

HIV Testing

- **Opt-out testing is Recommended by IDSA and CDC**
  - **Patients are informed that an HIV test will be conducted unless they explicitly decline to be tested.**
  - **Written consent in this setting is incorporated into intake**
  - **Counseling is available**
- **Opt-in: NOT Recommended by IDSA and CDC**
  - **Patients need to initiate the request for HIV infection**
- **Requirements for testing:FIVE C's:**
  - **Counseling**
  - **Consent**
  - **Confidentiality**
  - **Correct test results**
  - **Connection to prevention care and treatment**

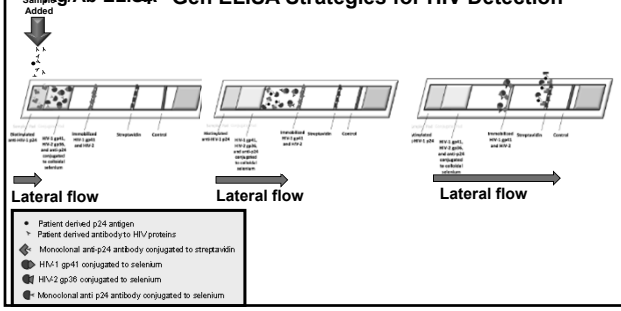
Pearls for Board Exam

- **HIV Testing is Comprehensive**
  - **Non-B Subtypes are all detectable**
  - **HIV-2 has an approved diagnosis**
  - **Long term Non-Progressor**
    - **ELISA reactive / Supplemental Positive**
- **Resources:**
  - **https://www.cdc.gov/hiv/guidelines/testing.html**
  - **Fmaldarelli3@gmail.com**
  - **Reference slides follow**
- **No test is perfect**
  - **4th Gen less sensitive**
    - **Acute**
    - **PEP/PrEP**
    - **Early Antiretroviral therapy**
  - **False Positives**
    - **Pregnancy**
  - **Mind the gap**
    - **Long gap for Home testing**
- **Board exam isn't perfect either - Don't overthink it!**

A. 4th generation Ag/Ab ELISA

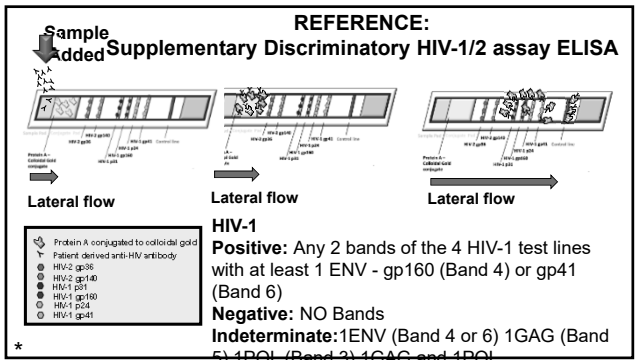
REFERENCE:

4th Gen ELISA Strategies for HIV Detection

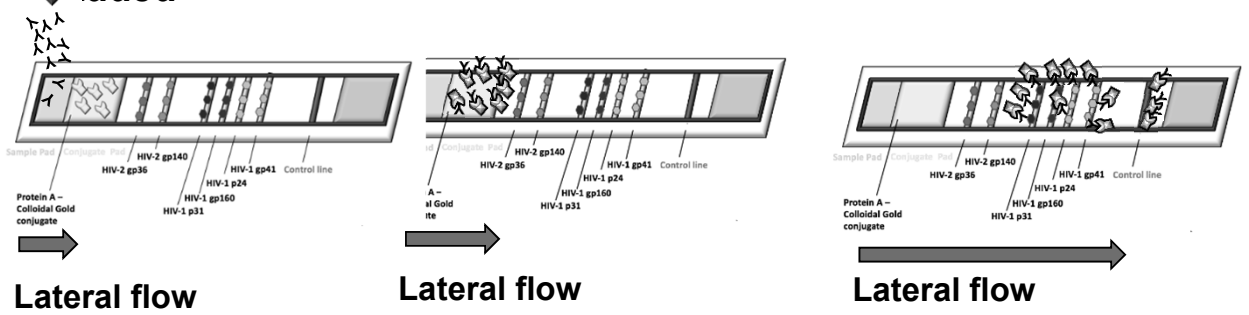


34 – HIV Diagnosis

Speaker: Frank Maldarelli, MD



REFERENCE:
Supplementary Discriminatory HIV-1/2 assay ELISA



- Protein A conjugated to colloidal gold
- Patient derived anti-HIV antibody
- HIV-2 gp36
- HIV-2 gp140
- HIV-1 p31
- HIV-1 gp160
- HIV-1 p24
- HIV-1 gp41

HIV-1

Positive: Any 2 bands of the 4 HIV-1 test lines with at least 1 ENV - gp160 (Band 4) or gp41 (Band 6)

Negative: NO Bands

Indeterminate:1ENV (Band 4 or 6) 1GAG (Band 5) 1POL (Band 3) 1GAG and 1POL

*

35

Antiretroviral Therapy

Dr. Roy Gulick

35 – Antiretroviral Therapy

Speaker: Roy Gulick, MD

Antiretroviral Therapy (ART)

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6/23/2023

Disclosures of Financial Relationships with Relevant Commercial Interests

- **None**

ID Boards – Medical Content: 15% HIV

- Epidemiology (<2%)
  - Transmission
  - Testing and counseling
  - Initial laboratory evaluation
  - Prevention
- Pathogenesis (<2%)
  - Virology
  - Immunopathogenesis
  - Acute HIV infection
- Lab testing (<2%)
  - Diagnostic evaluation
  - Baseline evaluation
- HIV Treatment Regimens (4.5%)
  - ART drug classes
  - Adverse effects of treatment
  - Drug-drug interactions
  - When to start therapy
  - Selection of optimal initial regimen
  - Laboratory monitoring
  - Treatment-experienced patients

ID Boards – Medical Content: 15% HIV

- Opportunistic Infections (5%)
  - Prevention
  - When to start ART with an OI
  - IRIS
  - Bacteria; Mycobacteria; Fungi; Parasites; Viruses
- Malignancies (<2%)
  - Kaposi sarcoma (KS)
  - Lymphoma
  - Cervical cancer
  - Anal cancer
- Other complications of HIV (2%)
  - Heme, endocrine, GI, renal (including HIVAN), cardiac, pulmonary, HEENT, musculoskeletal, neuro, psych, derm
- Related issues (<2%)
  - Substance use
  - Organ transplantation
  - Primary care
  - Misc non-HIV complications
  - Pregnancy

Antiretroviral Therapy (ART)

- Questions
  - When to start?
  - What to start?
  - When to change?
  - What to change to?
- Treatment as Prevention
- HIV Drug Resistance / Case Scenarios
- ART for Special Populations

WHEN TO START?

Question #1

PREVIEW QUESTION

A 43-year-old man with HIV has CD4 900-1200 and HIV RNA consistently <200 copies over the last 11 years. Do you recommend starting ART?

A. Yes, all current guidelines recommend starting.
B. No, he's a long-term non-progressor and doesn't need ART.
C. No, he should wait until his viral load level is confirmed >200 copies/ml.
D. No, he should wait until CD4 is confirmed <500 cells/uL.

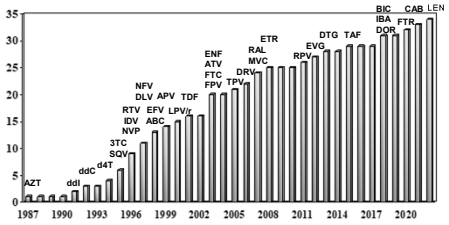
When to Start?: Chronic Infection

	AIDS/ symptoms	Asymptomatic			
		CD4 <200	CD4 200-350	CD4 350-500	CD4 >500
US DHHS 2023 www.clinicalinfo.hiv.gov	recommended				
IAS-USA 2023 Gandhi JAMA 2023;329:63-84	recommended				

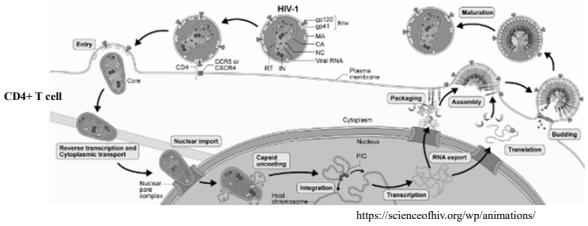
Goal of Antiretroviral Therapy

- To suppress HIV RNA (viral load level) as low as possible, for as long as possible
- To preserve or enhance immune function
- To delay clinical progression of HIV disease (and prolong healthy life)

Antiretroviral Drug Approval: 1987 - 2023



Life Cycle of HIV



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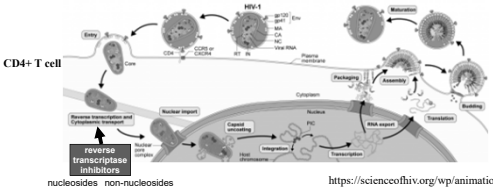
Life Cycle of HIV



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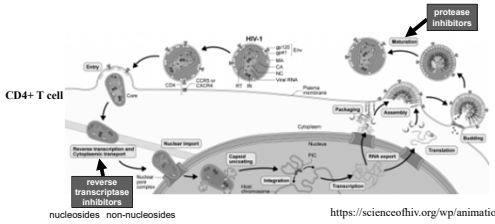
Life Cycle of HIV



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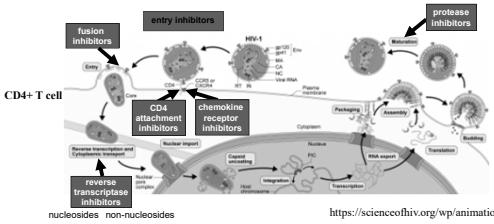

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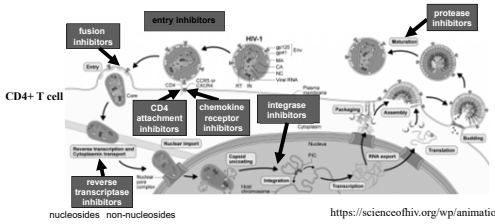
Life Cycle of HIV



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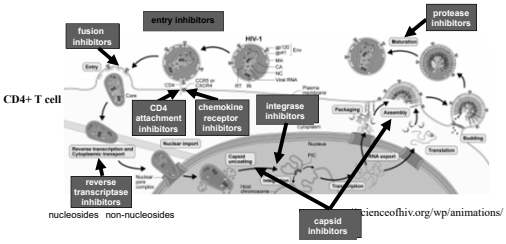

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Approved ART: 2023*

nucleoside/tide RTIs (NRTIs)
- zidovudine (ZDV, AZT)
- lamivudine (3TC)
- abacavir (ABC)
- emtricitabine (FTC)
- tenofovir (TAF, TDF)

NNRTIs
- nevirapine (NVP)
- efavirenz (EFV)
- etravirine (ETR)
- rilpivirine (RPV)
- doravirine (DOR)

protease inhibitors (PIs)
- saquinavir (SQV)
- ritonavir (RTV)
- indinavir (IDV)
- nelfinavir (NFV)
- lopinavir/r (LPV/r)
- atazanavir (ATV)
- tipranavir (TPV)
- darunavir (DRV)

integrase inhibitors (IIs)
- raltegravir (RAL)
- elvitegravir (EVG)
- dolutegravir (DTG)
- bictegravir (BIC)
- cabotegravir (CAB)

entry inhibitors (EIs)
- enfuvirtide (T-20, fusion inhibitor)
- maraviroc (MVC, CCR5 antagonist)
- ibalizumab (IBA, CD4 post-attachment inhibitor)
- fostemsavir (FTR, CD4 attachment inhibitor)

capsid inhibitors (CIs)
- lenacapavir (LEN)

*ddI, ddC, d4T, DLV, and APV (and FPV 1/24) discontinued from market

WHAT TO START?

Question #2

2023 PREVIEW QUESTION

You have been monitoring a 36 year old man with HIV, CD4 ~350, VL 636,000 who is now ready to start ART, but wants the "simplest regimen possible." Which of these regimens do you recommend?

A. IM cabotegravir/rilpivirine
B. tenofovir alafenamide/emtricitabine/rilpivirine
C. abacavir/lamivudine + efavirenz
D. dolutegravir/lamivudine
E. tenofovir alafenamide/emtricitabine/bictegravir

First ART Regimen: Individual Factors

- antiretroviral activity (VL, CD4, clinical responses)
- durability of responses
- baseline drug resistance
- tolerability
  - acute side effects
  - chronic side effects
- convenience (number of pills, dosing interval, food/fasting requirements)
- preserving future treatment options
- stage of HIV disease, concomitant illnesses and medications (drug-drug interactions)
- access and cost

Recommended Regimens (for most people) (1-2 NRTI + integrase inhibitor)

- Integrase inhibitor-based
  - **bictegravir**/tenofovir alafenamide (TAF)/emtricitabine
  - **dolutegravir**/abacavir/lamivudine (if HLA-B*5701 negative)
  - **dolutegravir** + tenofovir (TAF or TDF) + (emtricitabine or lamivudine)
  - **dolutegravir**/lamivudine (except HIV RNA >500,000 cps/ml, HBV surface antigen +, or no resistance results)

U.S. DHHS Guidelines 5/23/23 clinicalinfo.hiv.gov

Alternative Regimens (Certain Situations) (1)

- Integrase inhibitor-based (INSTI + 2 NRTI)
  - **elvitegravir**/cobicistat/tenofovir (TAF or TDF)/emtricitabine
  - **raltegravir** + tenofovir (TAF or TDF) + (lamivudine or emtricitabine)
- Protease inhibitor-based (Boosted PI + 2 NRTI)
  - In general, boosted darunavir preferred over boosted atazanavir
  - **darunavir**/(ritonavir or cobicistat) + tenofovir (TDF or TAF) + (lamivudine or emtricitabine)
  - **darunavir**/(ritonavir or cobicistat) + abacavir*/lamivudine
  - **atazanavir**/(ritonavir or cobicistat) + tenofovir (TDF or TAF) + (lamivudine or emtricitabine)

U.S. DHHS Guidelines 5/23/23 www.clinicalinfo.hiv.gov

Alternative Regimens (Certain Situations) (2)

- NNRTI-based (NNRTI + 2 NRTI)
  - **doravirine**/TDF/lamivudine or **doravirine** + TAF/emtricitabine
  - **efavirenz** + tenofovir (TAF or TDF) + (emtricitabine or lamivudine)
    - efavirenz 600 + TDF + (emtricitabine or lamivudine)
    - efavirenz 600 + TAF/emtricitabine
    - efavirenz 400/TDF/lamivudine
  - **rilpivirine** + tenofovir (TAF or TDF)/emtricitabine (if VL <100,000 cps/ml and CD4 >200)

U.S. DHHS Guidelines 5/23/23 www.clinicalinfo.hiv.gov

Alternative Regimens (Certain Situations) (3)

- Options when ABC, TAF, and TDF cannot be used
  - **dolutegravir** + lamivudine (except HIV RNA >500,000 cps/ml, HBV surface antigen +, or no resistance results)
  - **darunavir**/ritonavir + lamivudine
  - **darunavir**/ritonavir + raltegravir BID (if HIV RNA <100,000 cps/ml and CD4 >200)

U.S. DHHS Guidelines 5/23/23 www.clinicalinfo.hiv.gov

Choice of NRTIs

Combination	DHHS GL	Dosing	Toxicities	Considerations
tenofovir (TAF or TDF)/ **emtricitabine** (FTC)	recommended	1 tab qd	renal, bone (with TDF); ↓ toxicity with TAF	1-pill, once-daily formulations available
abacavir/ lamivudine (ABC/3TC)	recommended (with dolutegravir only) / alternative	1 tab qd	HSR (5-8%) (do HLA-B*5701 test)	ABC/3TC/DTG available; less effective with VL >100K; ??↑MI
zidovudine/ lamivudine (ZDV/3TC)	not recommended	1 tab bid	GI, anemia, lipoatrophy	toxicity

Based on DHHS Guidelines 5/23/23

Choice of NNRTIs

Drug	DHHS GL	Dose	Toxicities	Considerations
doravirine (DOR)	alternative	qd	↓ CNS toxicity than EFV; ↓ lipids	TDF/FTC/DOR (1 pill, once-daily)
efavirenz (EFV)	alternative	qd (600 or 400 mg)	CNS toxicity (50%), rash (10%), suicidality (rare)	TDF/FTC/EFV (1 pill, once-daily)
rilpivirine (RPV)	alternative	qd	not well absorbed with PPI	(TAF or TDF)/FTC/RPV (1 pill, once-daily with a meal); NOT for HIV RNA >100K or CD4 <200
nevirapine (NVP)	not recommended	qd or bid	hepatotoxicity, hypersensitivity	toxicity

Based on DHHS Guidelines 5/23/23

Choice of PIs

Drug	DHHS GL	Dose	Toxicities	Considerations
darunavir /(ritonavir or cobicistat) (DRV/r or c)	alternative; in general, preferred over ATV	qd (if no prior PI resistance) or bid	skin rash (rare);	active against PI-resistant viral strains
atazanavir /(ritonavir or cobicistat) (ATV/r or c)	alternative	qd	↑ indirect bilirubin, GI	avoid PPI; kidney stones (uncommon)
lopinavir/ ritonavir (LPV/r)	not recommended	bid or qd	diarrhea, ↑lipids	co-formulated

Based on DHHS Guidelines 5/23/23

Choice of Integrase Inhibitors

Drug	DHHS GL	Dosing	Toxicities	Considerations
bictegravir (BIC)	recommended with TAF/FTC	1 coform-ulated pill	few, ↑creat, wt gain	TAF/FTC/BIC (1 pill, qd); ↑ barrier to resistance
dolutegravir (DTG)	recommended with (TAF or TDF)/(FTC or 3TC) or ABC/3TC	50 mg qd (bid with II resistance)	few, ↑creat, CNS, neural tube defects (rare), wt gain	ABC/3TC/DTG (1 pill, qd); ↑ barrier to resistance
elvitegravir (EVG)	alternative with (TAF or TDF) /FTC/cobicistat	1 coform-ulated pill	mild GI	(TAF or TDF)/FTC/ EVG/cobicistat (1 pill, qd); drug interactions
raltegravir (RAL)	alternative with (TAF or TDF)/FTC	400 mg bid; 600 mg X 2 qd	few	twice-daily dosing; no co-formulations

Based on DHHS Guidelines 5/23/23

Selected Drug Interactions (1)

- Cytochrome P450 3A4 effects
- Most NNRTI (EFV, ETR, NVP, RPV – NOT DOR) are inducers
  - In general, ↓ levels of other metabolized drugs
- Concern with: rifampin/(rifabutin), ketoconazole/itraconazole, anticonvulsants, simvastatin/lovastatin, midazolam/triazolam, ergotamines
- HIV protease inhibitors
- maraviroc
- Some HCV drugs

Selected Drug Interactions (2)

- Cytochrome P450 3A4 effects
- PIs are inhibitors; ritonavir is the most potent inhibitor ever described; cobicistat is a potent inhibitor
  - In general, ↑ levels of other metabolized drugs
- Concern with: rifampin – cannot be used/(rifabutin), ketoconazole/itraconazole, anticonvulsants, simvastatin/lovastatin, midazolam/triazolam, ergotamines, St. John's Wort
- HIV NNRTI
- maraviroc
- HCV drugs

ART: What NOT to use as Initial therapy

- Monotherapy
- Nucleosides (NRTI)
  - 3 or 4 all-NRTI combination regimens
  - older drugs (e.g. zidovudine, didanosine)
- Non-nucleosides (NNRTI)
  - older drugs (e.g. nevirapine)
  - etravirine
- Protease Inhibitors (PI)
  - unboosted PIs
  - older drugs (fosamprenavir, indinavir, lopinavir, nelfinavir, ritonavir [except as a booster], saquinavir tipranavir)
- Entry inhibitors (EI)
- Some 2-drug regimens
  - IM CAB/RPV or DTG/RPV

Based on DHHS Guidelines 5/23/23

ART: Side Effects (1)

- **Life threatening**
  - hepatitis (NNRTIs, PIs)
    - nevirapine – women with CD4 >250; men with CD4 >400;
  - hypersensitivity reaction (HSR) (abacavir, nevirapine, etravirine)
    - abacavir HSR greatly reduced with HLA-B*5701 screening
    - stop nevirapine or etravirine for rash + constitutional symptoms
  - Stevens-Johnson syndrome (nevirapine, etravirine)
  - teratogenicity*
    - efavirenz = pregnancy category D
    - dolutegravir during conception/very early pregnancy → neural tube defects – RARE, not significantly ↑ vs. other ART

ART Side Effects (2)

- **Acute/early**
  - gastrointestinal (zidovudine, TDF, PIs, ?all ART)
  - anemia, neutropenia (zidovudine)
  - bone mineral density ↓ (TDF)
  - central nervous system (efavirenz, integrase inhibitors[?])
  - fatigue (zidovudine)
  - indirect hyperbilirubinemia (atazanavir, indinavir)
  - injection site reactions (enfuvirtide)
  - rash (NNRTIs)

ART Side Effects (3)

- **Chronic/longer term**
  - cardiovascular (abacavir??, PIs except atazanavir)
  - kidney stones (indinavir > atazanavir)
  - metabolic – glucose, lactate, lipids (older PIs)
  - morphologic –
    - fat loss – lipoatrophy (stavudine, zidovudine)
    - fat gain – lipohypertrophy (older PIs)
  - peripheral neuropathy (stavudine, zalcitabine, didanosine)
  - proximal renal tubular dysfunction (TDF)
  - weight gain (bictegravir, dolutegravir, TAF)

WHEN TO CHANGE?

ART Change

- Reasons: adverse events, drug-drug or drug-food interactions, pill burden, pregnancy, cost, simplification
- Fundamental principle: maintain virologic suppression
- Review ART history, prior ART-associated toxicities, cumulative drug resistance testing results
- Within-class or between-class Δ usually works if no resistance
- Specific regimens:
  - DTG/RPV; DTG/3TC; Boosted PI (ATV, DRV, LPV) + [3TC or FTC]; Boosted PI + II (e.g. DRV/r + DTG); IM CAB + RPV
  - Not recommended: monotherapy, boosted ATV + RAL, MVC-based
- Consideration: concomitant HBV infection

DHHS Guidelines 5/23/23

Why Does Treatment Fail Patients?

- ADHERENCE
- Baseline resistance or cross-resistance
- Prior use of antiretroviral therapy
- Less potent antiretroviral regimens
- Drug levels and drug interactions
- Tissue reservoir penetration
- Provider inexperience
- Other, unknown reasons

Question #3

IDWeek 2023 PREVIEW QUESTION

28 year old man with HIV on TDF/emtricitabine + atazanavir/ritonavir for 2 years with HIV RNA <50 cps/ml and CD4 200s→300s presents for routine follow-up; labs reveal HIV RNA 98 cps/ml and CD4 352.

What do you recommend?

A. Obtain genotype.
B. Obtain genotype and phenotype.
C. Repeat HIV RNA at next visit.
D. Change regimen to TAF/emtricitabine/bictegravir to improve adherence

When to change therapy?

Virologic failure

- VL undetectable – drug resistance unlikely
- VL <200 cps/ml (low-level viremia) – risk of resistance believed to be relatively low
- VL persistently >200 cps/ml – drug resistance often associated (particularly >500 cps/ml)
- Caution with change to newer VL assays and blips

Immunologic failure

- Associated factors:
  - CD4 <200 at ART initiation
  - older age
  - co-infections
  - meds
  - persistent immune activation
  - loss of regenerative potential
  - other reasons
- No consensus on definition or treatment

DHHS Guidelines 5/23/23

WHAT TO CHANGE TO?

What to change to?: U.S. DHHS Guidelines

- Review goal of therapy:
  - Maximal virologic suppression (HIV RNA below detection)
- Review ART history
- Assess adherence, tolerability, and PK
- Perform resistance testing while on drugs (or within 4 weeks of d/c of ART)
- Identify susceptible drugs/drug classes (e.g. fostemsavir, lenacapavir)
- Consider newer agents (expanded access or clinical trials)
- Goal:

  Design a regimen with 2 fully active agents (one with a high barrier to resistance: boosted darunavir, dolutegravir, [bictegravir]), or if no high-barrier drug available, 3 fully active agents

DHHS Guidelines 5/23/23

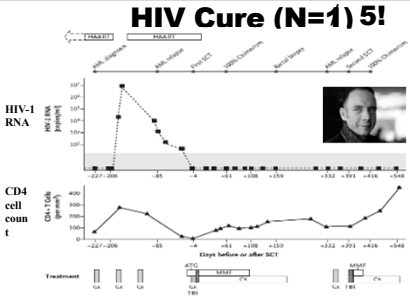
TREATMENT = PREVENTION

Treatment = Prevention

- HIV+ pregnant women *Fowler NEJM 2016;375:1726*
  - 3-drug ART ↓ transmission risk to child to 0.5%
- HIV+ men and women *Cohen NEJM 2016;375:830*
  - Suppressive ART ↓ transmission to sexual partners by 93%
- HIV- post-exposure prophylaxis (PEP) *CDC Guidelines*
  - 3-drug integrase inhibitor-based ART recommended for 4 weeks
- At-risk HIV- men and women
  Molina NEJM 2015, McCormack Lancet 2016; Choopanya Lancet 2013
  - PrEP ↓ HIV acquisition by sex >75-85% (TDF ♂ + ♀; TAF ♂ only; IM CAB ♂ + ♀)
  - PrEP ↓ HIV acquisition by injection drug use ~50%

CURE

HIV Cure (N=15!)



Hutter NEJM 2009;360:692

Cure #2
London
Gupta, et al
Nature 2019;568: 244-248.

Cure #3
NYC
Hsu, et al
Cell 2023;186:1115-1126

Cure #4
City of Hope
Dickter, et al
IAS 2022

Cure #5
Dusseldorf
Jensen, et al
Nat Med 2023;29:583-587

ART Controversies: Conclusions

- **When to start?** Any viral load or CD4 count and "when the patient is ready."
- **What to start?** Excellent options; integrase inhibitor-based regimens for most people.
- **When to change?** Evaluate virologic response; try to prevent emergence of resistance.
- **What to change to?** Use treatment history and drug resistance testing to design new regimen with 2 active drugs (1 with ↑ barrier to resistance) or 3 active drugs.
- **Treatment = Prevention** Treat HIV, offer PEP and PrEP

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- **Cornell HIV Clinical Trials Unit (CCTU)**
- Division of Infectious Diseases
- Weill Cornell Medicine
- AIDS Clinical Trials Group
- HIV Prevention Trials Network
- Division of AIDS/NIAID/NIH
- The patient volunteers!

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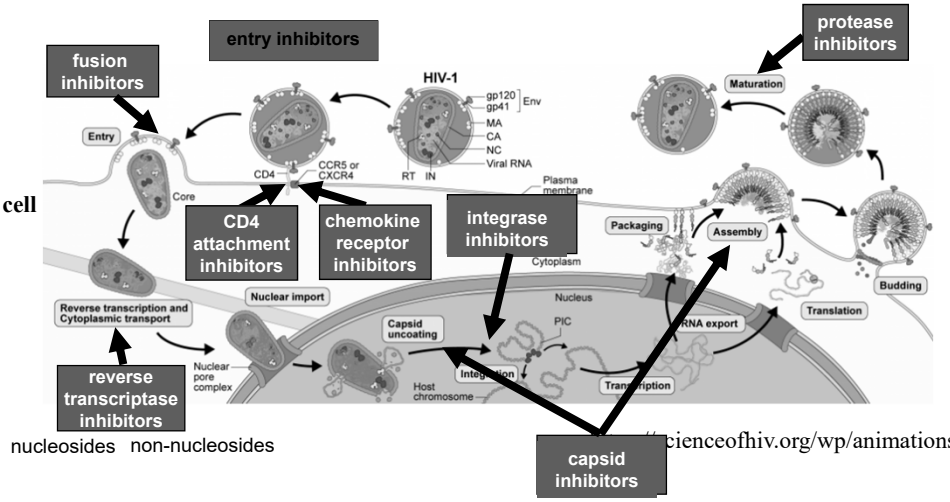
Life Cycle of HIV



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36

HIV Drug Resistance

Dr. Michael Saag

36 – HIV Drug Resistance

Speaker: Michael Saag, MD

IDBR INFECTIOUS DISEASE BOARD REVIEW AUGUST 19-23 2023

HIV Drug Resistance

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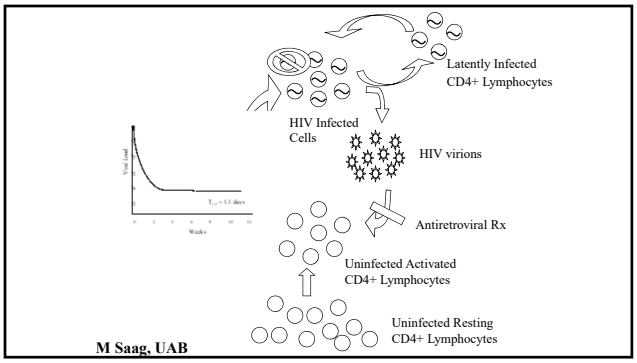
7/5/2023

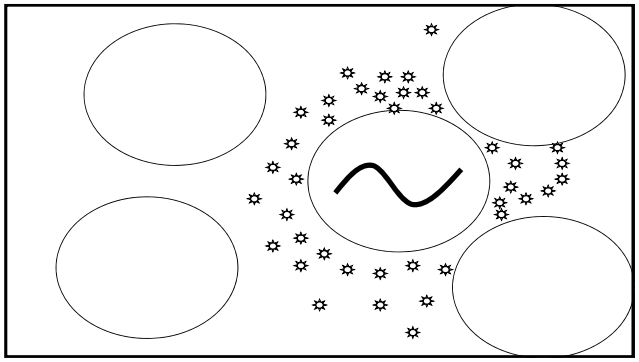
IDBR INFECTIOUS DISEASE BOARD REVIEW AUGUST 19-23 2023

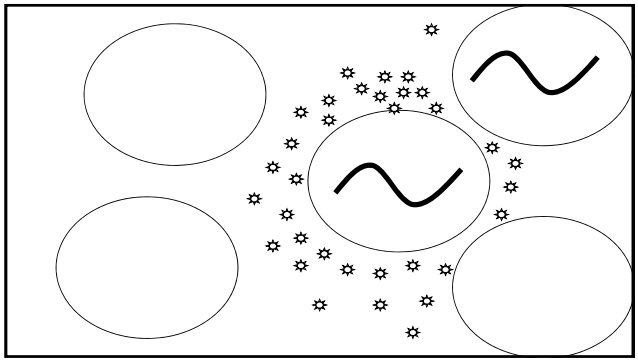
Disclosures of Financial Relationships with Relevant Commercial Interests

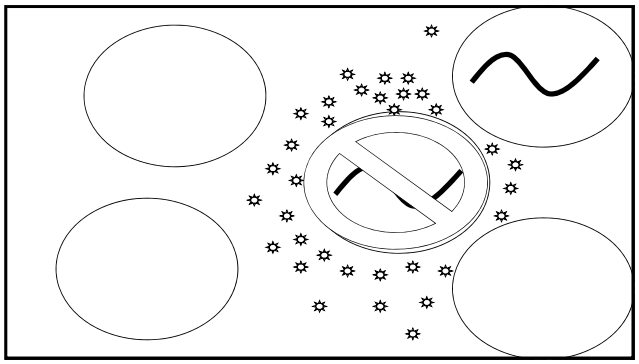
- **None**

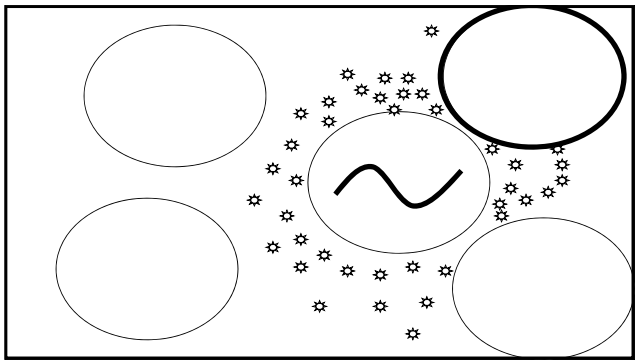
How does resistance happen?

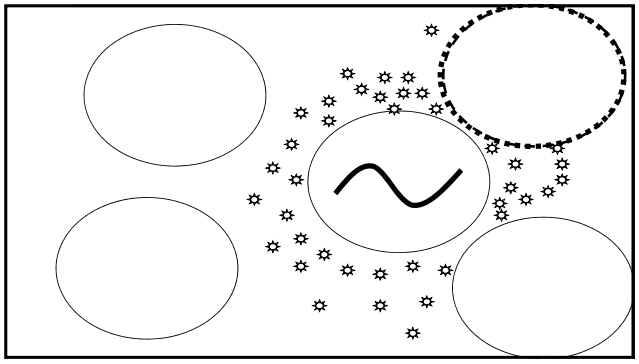


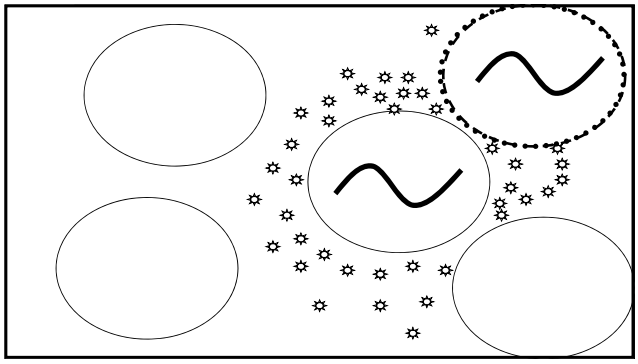












Resistance Testing

- Genotypic resistance test
  - Perform test that gives mutations in viral genes
- Phenotypic resistance test
  - Perform test that describes growth of virus in the presence of anti-HIV drugs
- Limitations:
  - Cannot detect minority species (< 10% of viral population)

Key Issues in HIV Resistance

Easily Tested

- Specific Mutations
- Cross – resistance
- Prevalence of resistance at baseline

Tough to Test

- Definition of Phenotypes
- Complex resistance patterns
- Genetic Barrier
- Nuances of Resistance
- Relationship between Pk and Pd

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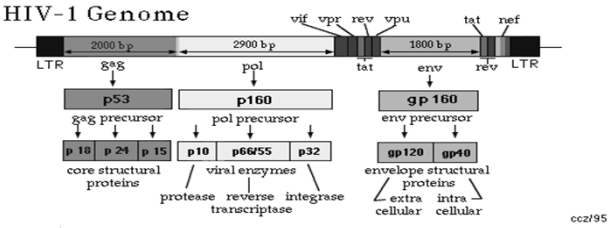
HIV Drug Resistance Testing

- Current guidelines recommend an HIV genotype as part of screening BEFORE ART is started.
- Following failure of 1st or 2nd regimens, HIV genotype is recommended to use with the history to choose the optimal next regimen.
- Following failure of 3rd and subsequent regimens, both HIV genotype AND HIV phenotype should be sent.
- If there is discordance between genotype and phenotype results, use the geno result (more sensitive).
- NOTE WELL: Resistance mutations accrued from an earlier regimen MAY NOT be detected by tests obtained at the time of the current failing regimen

HIV-1 Genome



Mutation Nomenclature

Codon (position)
PR = 1-99 amino acids
RT = 1-560 amino acids

M184V

Mutation Nomenclature

Codon (position)
PR = 1-99 amino acids
RT = 1-560 amino acids

M184V

Wild-type amino acid (consensus)

Mutant amino acid

Table 1. Amino acids and their abbreviations.

Alanine	A
Cysteine	C
Aspartate	D
Glutamate	E
Phenylalanine	F
Glycine	G
Histidine	H
Isoleucine	I
Lysine	K
Leucine	L
Methionine	M
Asparagine	N
Proline	P
Glutamine	Q
Arginine	R
Serine	S
Threonine	T
Valine	V
Tryptophan	W
Tryosine	Y

Everything You Need to Know About Nucleoside Analog Resistance in One Slide!

Mutation	Selected by	Effects on other NRTIs
184V	3TC, FTC	- Loss of susceptibility to 3TC, FTC - ↓ susceptibility to ABC, ddI (clinically insignificant) - Delayed TAMS and ↑ susceptibility to AZT, d4T, TDF
TAMs	AZT, d4T	- ↓ susceptibility to all NRTIs based on number of TAMs - More resistance with 41/210/215 than 67/70/219 pathway
151M, 69ins	AZT/ddI, ddI/d4T	- Resistance to all NRTIs - T69ins: TDF resistance
65R	TDF, ABC, ddI	- Variable ↓ susceptibility to TDF, ABC, ddI (and 3TC, FTC) - ↑ susceptibility to AZT
74V	ABC, ddI	- ↓ susceptibility to ABC, ddI - ↑ susceptibility to AZT, TDF
44D, 118I	AZT, d4T	-Increase NRTI resistance (with 41/210/215 pathway)

CASE 1

- 25 year old man presents with newly diagnosed HIV
- Had an episode c/w acute seroconversion syndrome 4 months ago
- Initial HIV RNA 40,000; CD4 443 cells/ul
- He wants to start ARV therapy

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Question #1

A baseline genotype is ordered that shows an M184V mutation. Which of the following drugs will have reduced susceptibility with this mutation?

A. Efavirenz
B. Zidovudine
C. Tenofovir
D. Etravirene
E. Emtricitabine

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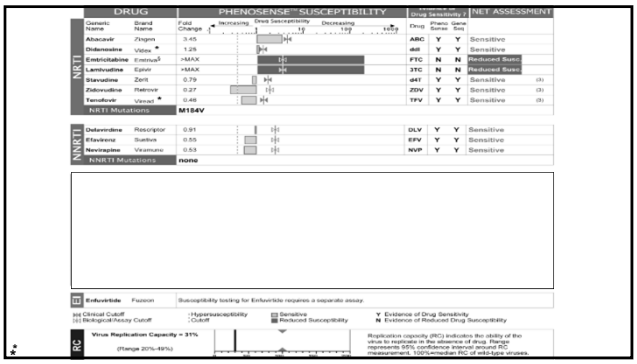


CASE 2

- 34 yo woman diagnosed with HIV 10 years ago
- Initially presented with PJP
- Initial Lab values
  - CD4 82 cells/uL
  - VL 106,000 c/mL
- Started on TDF / FTC / EFV (FDC)
- Did well for a while, then the regimen failed

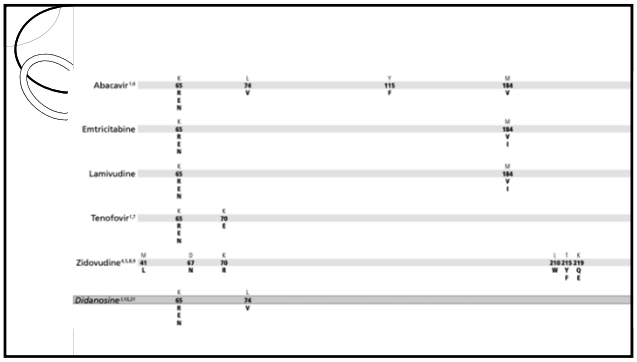
Question #2

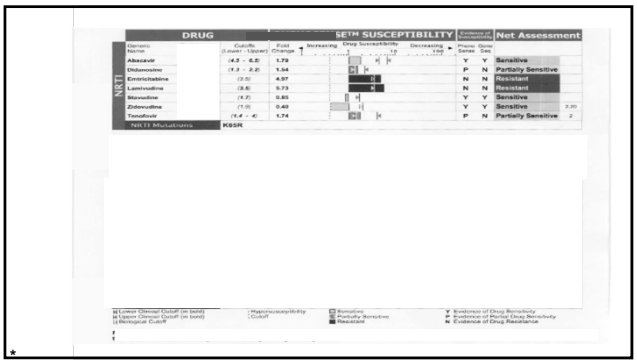
The genotype shows an M184V and K65R mutations. Which nRTI drugs would you include?

A. ZDV
B. TDF
C. ddI
D. ABC

The genotype shows a K65R mutation.
Which nRTI drugs would you include?

A. ZDV : Correct Answer
B. TDF :TDF won't work well
C. ddI : : Awful choice! (Sorry). The K65R pathway knocks this drug out…and the drug is pretty toxic over time
D. ABC : Abacavir activity typically reduced with a K65R mutation especially if M184V is also present





Non-nucleoside Reverse Transcriptase (NNRTI) Mutations

- K103N is the signature mutation for efavirenz (EFV).
- Y181C is the signature mutation for nevirapine (NVP).
- Older NNRTIs, efavirenz and nevirapine, have low genetic barriers (require only 1 mutation for resistance) and are **COMPLETELY** cross-resistant to one another.
- Newer NNRTIs, etravirine (ETR), rilpivirine (RPV), and doravirine (DOR) have higher barriers to resistance (require >1 mutation for resistance).
- K103N has no effect on etravirine susceptibility.
- Rilpivirine failure is associated with E138K, K101E, and/or Y181C and consequently, resistance to ALL NNRTIs.

CASE 3

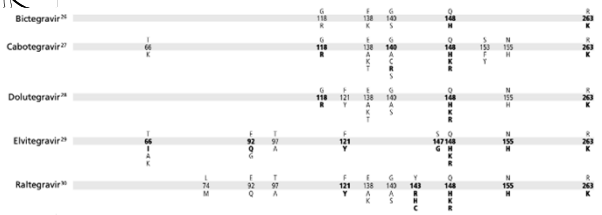
- 34 yo woman diagnosed with HIV three years ago
- Initially presented with PJP
- Initial Lab values
  - CD4 82 cells/uL
  - VL 106,000 c/mL
- She was treated with TDF / FTC / ELV/ Cobi (FDC)
- The regimen failed after 12 months

Question #3

Which of the following mutations indicate high level resistance to elvategravir ?

A. Q148R
B. L68I
C. L68V
D. K67N
E. K65R

InSTI Resistance Mutations



Question #4

Which of the following results would indicate the highest likelihood of maraviroc activity?

A. Pure R5 virus
B. Pure X4 virus
C. Mixture of R5 and X4 viruses
D. Dual Tropic (R5/X4) virus

CASE 4

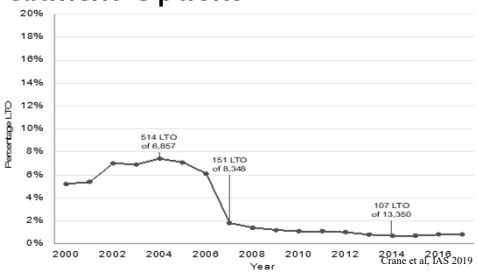
- 34 yo woman diagnosed with HIV 22 years ago
- Initially presented with PJP
- Initial Lab values
  - CD4 82 cells/uL
  - VL 106,000 c/mL
- Has been on multiple regimens over the years

Question #5

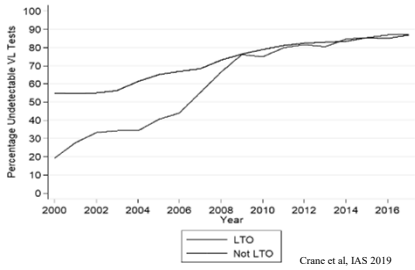
What is the likelihood she has high level resistance (< 2 active drugs available) ?

A. < 1 %
B. 1 - 5 %
C. 5 -10%
D. 10 - 20%
E. > 20%

Prevalence of Patients with Limited Treatment Options



Virologic Success in Those with or without LTO



Common Mutations To Memorize

• M184V/I	3TC and FTC
• M41L, D67N, K70R,L210W,T215Y, K219Q	"TAMS"
4 or more thymidine-analog mutations (TAMS) affect all approved nucleosides	
• K65R	tenofovir
• Q151M, 69SSS	multi-NRTI
• K103N	EFV (and NVP)
retains susceptibility to etravirine	
• Y181C	NVP and other NNRTI
• E138K, K101E	RPV and other NNRTI
• I50L	ATV
• N155H, Q148H/R/K	RAL and EVG
• Y143C	RAL
• R263K	DTG

Summary

- High concern about resistance testing on Board Exams
- Difficult to create test questions that do not require complex interpretation, have a single best answer, or are not 'multiple true-false'
- Knowing common mutations and their role is a good way to prepare for the exam

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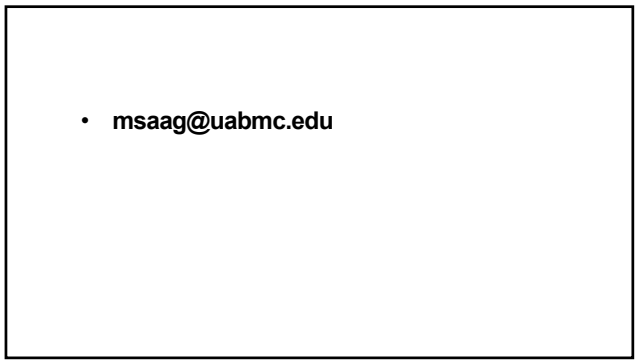
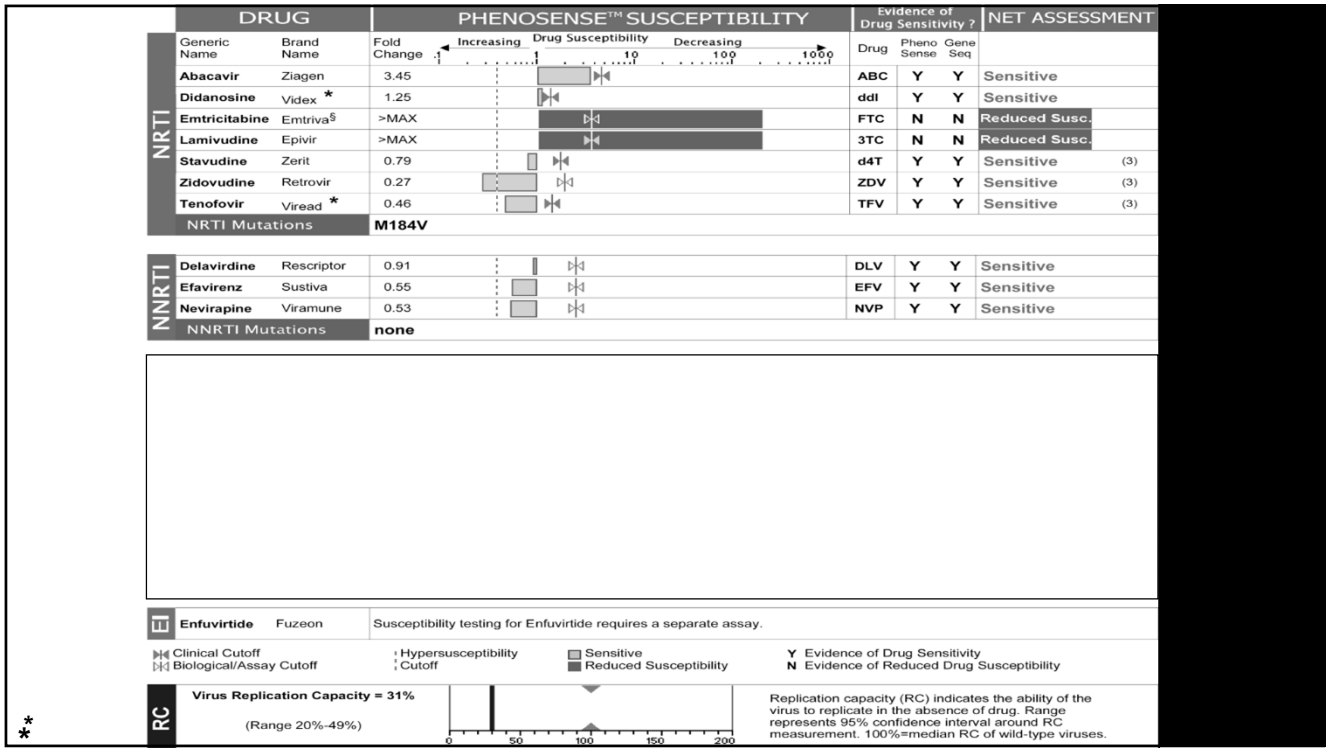
36 – HIV Drug Resistance

Speaker: Michael Saag, MD



36 – HIV Drug Resistance

Speaker: Michael Saag, MD



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Antiretroviral Therapy for Special Populations

Dr. Roy Gulick

37 – Antiretroviral Therapy for Special Populations

Speaker: Roy Gulick, MD

IDBR INFECTIOUS DISEASE BOARD REVIEW AUGUST 19-23 2023

Antiretroviral Therapy (ART) for Special Populations

Roy M. Gulick, MD, MPH
Rochelle Belfer Professor in Medicine
Chief, Division of Infectious Diseases
Weill Cornell Medicine

6/23/2023

IDBR INFECTIOUS DISEASE BOARD REVIEW AUGUST 19-23 2023

Disclosures of Financial Relationships with Relevant Commercial Interests

- **None**

Special Populations

- acute/recent HIV infection
- acute opportunistic infection
- tuberculosis
- HIV-HBV co-infection
- HIV-HCV co-infection
- pregnancy
- post-HIV exposure (PEP)
  - occupational
  - non-occupational
- pre-HIV exposure (PrEP)

Question #1

A 22-year-old man presents with fever, mouth pain, and skin rash. PE reveals 3 small oral ulcers and diffuse macular rash. Labs show WBC 3K, platelets 89K, monospot negative, RPR NR, HIV antibody negative, HIV RNA 1,876,000 cps/ml.

Which statement is correct?

A. ART should not be offered.
B. ART would decrease his symptoms.
C. ART has long-term virologic benefits in this setting.
D. ART has long-term clinical benefits in this setting.

Acute or Recent HIV

- ART is RECOMMENDED.
- ART reduces symptoms and signs and reduces transmission.
- No long-term virologic, immunologic, or clinical data available.
- Goal is full virologic suppression.
- Obtain genotype prior to ART.
- If ART is started prior to genotype results, use **bictegravir, dolutegravir,** or **boosted darunavir,** together with tenofovir (TAF or TDF) + emtricitabine.
- If patient was on IM cabotegravir for PrEP, use **boosted darunavir-based** regimen (rather than integrase inhibitor-based).
- Can modify regimen, if needed, when genotype results return.

DHHS Guidelines 5/23/23

Question #2

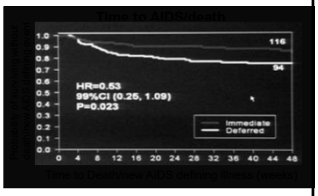
A 52-year-old woman is admitted for progressive SOB, is intubated, undergoes BAL and is found to have PCP. HIV Ab test is positive, CD4 103, HIV RNA 135,000 copies/ml. She is day 4 of IV trimethoprim-sulfa and corticosteroids and still intubated.

When should she start ART?

A. Immediately
B. In the next 2 weeks
C. After completing 21 days of trimethoprim-sulfa
D. At her first outpatient clinic visit

ACTG 5164: Immediate vs Delayed ART with an Acute OI

- 282 patients with treatable OI diagnosed within 14 days randomized to start ART within 48 hours vs. after 4 weeks
  - most common OI: PCP (63%)
- AIDS progression/death: immediate rx (14%) vs delayed rx (24%)
- No differences in safety/toxicity, IRIS, or week 48 responses
- Caution with CNS OI



Zolopa PLoS One 2009;4:e5575

HIV-TB Co-infection

- Treat active TB the same with or without HIV.
- All PLWH with TB should start TB meds immediately.
- In PLWH with TB, timing of starting ART depends on CD4 count:
  - For CD4 <50, start ART ASAP, within 2 weeks of TB rx
  - For CD4 ≥50, start ART within 8 weeks of TB rx
- Start pregnant women LWH with TB on ART as early as feasible.
- For TB meningitis, monitor closely.

DHHS Guidelines 5/23/23

Question #3

A 39-year-old man with HIV, CD4 298, HIV RNA 23,000 cps/ml, never on ART is diagnosed with pulmonary TB. The plan is to start INH, RIF, PZA, and ETH pending susceptibilities. He agrees to start ART and genotype is wild-type.

Which ART regimen do you recommend?

A. TDF/emtricitabine/efavirenz
B. TAF/emtricitabine + atazanavir (boosted)
C. TDF/emtricitabine + atazanavir (unboosted)
D. TAF/emtricitabine + darunavir (boosted)

HIV-TB Co-infection (2)

- Include a rifamycin in the regimen.
  - rifampin
    - significantly ↓ **TAF** – current FDA label: not recommended
    - significantly ↓ ALL **PIs** – cannot use together
    - ↓ **dolutegravir (DTG)** concentrations (need to ↑ DTG to 50 mg bid)
    - significantly ↓ **bictegravir (BIC)** – cannot use together
    - ↓ NNRTI concentrations: **efavirenz** (**EFV)** 600 mg daily is recommended
  - rifabutin: preferred; more manageable drug interactions with protease inhibitors
- For IRIS, continue both ART and TB meds while managing the syndrome.
- Treatment support, including DOT of TB rx is strongly recommended.

DHHS Guidelines 5/23/23

Question #4

IDSA 2023 PREVIEW QUESTION

A 55-year-old with HIV not previously on rx, CD4 320 and HIV RNA 67,000 cps/ml

Lab testing reveals: toxoplasma Ab+; CMV Ab+; HAV total Ab+; HBV surface Ag+, core Ab+, surface Ab-; HCV Ab-; RPR NR

Of the following, which ART regimen would you recommend?

A. abacavir/lamivudine/dolutegravir
B. abacavir/lamivudine + atazanavir (boosted)
C. dolutegravir/lamivudine
D. tenofovir (TAF or TDF)/emtricitabine + darunavir (boosted)

HIV-HBV Co-infection

- Some ART has activity against HBV
  - lamivudine (3TC), emtricitabine (FTC), tenofovir (TDF and TAF)
- Some HBV drugs have activity against HIV
  - entecavir (can select M184V) *McMahon NEJM 2007;356:2614*
- If treatment started, treat both optimally
  - 2 active agents for HBV (TAF or TDF) + (3TC or FTC)
  - + 3rd drug for HIV (preferred = BIC or DTG)
  - If tenofovir cannot be used, start a fully suppressive regimen and add entecavir

DHHS Guidelines 5/23/23

HIV-HCV Co-Infection

- Anyone with HCV should be screened for HIV.
- High-risk HIV+ patients should be screened for HCV annually.
- ART should be started in those with concomitant HCV.
  - Same initial regimens recommended, but caution with drug-drug interactions and overlapping toxicities.
- Patients with HIV and HCV should be evaluated for HCV therapy (including assessing liver fibrosis stage).
  - Also evaluate for HBV co-infection.
- HCV direct-acting antiviral regimens → high cure rates

DHHS Guidelines 5/23/23

Question #5

IDBR 2023 PREVIEW QUESTION

A 26-year-old woman with HIV on abacavir/lamivudine + efavirenz with CD4 630 and VL suppressed below detection becomes pregnant.

What do you recommend regarding ART?

A. Discontinue ART until 2nd trimester.
B. Change abacavir to zidovudine.
C. Change efavirenz to bictegravir.
D. Continue current regimen.

Antiretrovirals in Pregnancy

- ART recommended for all pregnant people, as early as possible, regardless of CD4 or VL level (rx and prevention of MTCT)
  - Perform drug-resistance testing if VL >500-1000 cps/ml and adjust regimen, based on results
  - ART does NOT increase the risk of birth defects
  - Start (or continue if safe/tolerated) standard 3-drug ART as early as possible:
    - 2 NRTIs + 3rd drug (PI, II, or NNRTI)
    - 2-drug regimens can be continued, if virologically suppressed
- Near delivery, if HIV RNA >1000 (or unknown), use intravenous zidovudine, and recommend Cesarean section at 38 weeks

DHHS Perinatal Guidelines 1/31/23 <www.clinicalinfo.hiv.gov>

ART in Pregnancy: NRTI

- Preferred:
  - abacavir/lamivudine
  - tenofovir (TAF or TDF)/(emtricitabine or lamivudine)
- Alternative:
  - zidovudine/lamivudine
- IV zidovudine recommended close to delivery if VL >1000

DHHS Perinatal Guidelines 1/31/23 <www.clinicalinfo.hiv.gov>

ART in Pregnancy: NNRTI

- Alternative:
  - efavirenz (birth defects reported in primate studies, NO evidence in human studies and extensive experience; screen for depression)
  - rilpivirine (NOT with baseline VL >100K or CD4 <200 or PPIs)
- Insufficient data: doravirine
- Not recommended:
  - etravirine (not for treatment-naïve pts)
  - nevirapine (toxicity, need for lead-in dosing, low barrier to resistance; could continue if on)

DHHS Perinatal Guidelines 1/31/23 <www.clinicalinfo.hiv.gov>

ART in Pregnancy: PI

- Preferred:
  - darunavir/ritonavir (need to use bid)
- Alternative:
  - atzanavir/ritonavir
- Not recommended:
  - cobicistat (↓ drug concentrations, limited experience)
  - lopinavir/ritonavir (side effects, need to use bid; could continue if on; may need to ↑ dose)

DHHS Perinatal Guidelines 1/31/23 <www.clinicalinfo.hiv.gov>

ART in Pregnancy: INSTI

- Preferred:
  - dolutegravir (neural tube defects not significantly ↑ vs. other ART)
- Alternative:
  - raltegravir (need to use bid)
- Insufficient data: bictegravir
- Not recommended:
  - elvitegravir/cobicistat (↓ drug concentrations)
  - IM cabotegravir + rilpivirine

DHHS Perinatal Guidelines 1/31/23 <www.clinicalinfo.hiv.gov>

ART in Pregnancy: Other

- Not recommended:
  - 2-drug regimens (e.g. dolutegravir/lamivudine, dolutegravir/rilpivirine; could continue if on)
  - cobicistat as a booster
  - enfuvirtide (not for treatment-naïve; could continue if on)
  - fostemsavir (limited data)
  - ibalizumab (no data)
  - maraviroc (tropism testing; not recommended in treatment-naïve; could continue if on)

DHHS Perinatal Guidelines 1/31/23 <www.clinicalinfo.hiv.gov>

Question #6

A 34-year-old nurse without HIV sustains a needlestick from a patient with HIV who has not taken ART for 2 years.

Which of these post-exposure (PEP) regimens do you recommend?

A. tenofovir (TDF)/emtricitabine
B. tenofovir (TDF)/emtricitabine + integrase inhibitor
C. tenofovir (TAF)/emtricitabine + integrase inhibitor
D. tenofovir (TDF)/emtricitabine + protease inhibitor

Antiretrovirals for PEP (1)

Postexposure prophylaxis (PEP) for **occupational** exposure:

- Assess nature of exposure:
  source fluid, volume of fluid, type of exposure, timing
- Assess exposure source; HIV and hepatitis testing
- Testing (baseline, 6 + 12 wks + 6 months with standard HIV Ab or 6 wks + 4 months if new HIV Ab/p24 test used) and counseling
- Offer 4 weeks of rx for recognized transmission risk
  - start ASAP (within 72 hours)
  - **tenofovir (TDF)/emtricitabine + dolutegravir** (not in women in early pregnancy or sexually active and not on birth control) or **raltegravir**
  - adjust regimen for possibility of resistance in source patient
  - f/u within 72 hours

PHS Guidelines updated 5/23/18

Antiretrovirals for PEP (2)

PEP for **non-occupational** exposure:

- Presentation ≤72 hours with substantial risk exposure from HIV+ or likely to be HIV+ – recommended
- Presentation >72 hours or no substantial risk of exposure – not recommended

- Testing: Do rapid HIV (Ag)/Ab test or if results not available, start PEP
- Prior to PEP: BUN/creatinine, LFTs, STI testing (CT, GC, syphilis), HBV/HCV testing, pregnancy testing

- Treatment: 4 weeks of
  - Preferred: **TDF/FTC + [dolutegravir** or **raltegravir]**
  - Alternative: **TDF/FTC + darunavir/ritonavir**

https://www.cdc.gov/hiv/clinicians/prevention/prescribe-pep.html#regimens

Question #7

23 year old man without HIV with a partner with HIV on ART with HIV RNA suppressed below detection asks about starting pre-exposure prophylaxis (PrEP).

In addition to safer sex counseling, which of these do you recommend?

A. Nothing – PrEP is not indicated.
B. PrEP with tenofovir (TDF)/emtricitabine daily.
C. PrEP with tenofovir (TAF)/emtricitabine "on demand".
D. PrEP with bictegravir/tenofovir (TAF)/emtricitabine daily.

CDC Guidance for PrEP:

https://www.cdc.gov/hiv/pdf/risk/prep/cdc-hiv-prep-guidelines-2021.pdf

- Inform all sexually active adults and adolescents about PrEP
- Before starting:
  - exclude acute and chronic HIV infection (by HIV testing and symptoms)
  - assess baseline CrCl, screen for STIs and HBV infection
- Prescribe PrEP for people with ongoing risk from sex or injecting drugs:
  - tenofovir (TDF)/emtricitabine for ♂ and ♀
  - tenofovir (TAF)/emtricitabine for ♂ ONLY
  - IM cabotegravir for ♂ and ♀
  - provide risk reduction, adherence counseling, condoms
- On PrEP:
  - HIV testing every 3-4 months, monitor CrCl every 6 (age >50 or CrCl <90) or 12 months
  - risk reduction, condoms, STI assessments/treatment
  - evaluate the need to continue PrEP

Conclusions

1. Acute (and recent) HIV – ART recommended.
2. Acute OI – ART within 2 weeks of diagnosis reduces mortality; caution with CNS opportunistic infections.
3. TB – Early ART prolongs survival; caution with rifamycin drug interactions.
4. Hepatitis B and C co-infection – Consider antiviral activity, drug-drug interactions, drug toxicities.
5. Pregnancy – Treat and reduce MTCT; modify ART recommendations based on safety and experience.
6. Post-exposure prophylaxis (PEP) – ART within 72 hours; give for 4 weeks; adjust for known drug resistance.
7. Pre-exposure prophylaxis (PrEP) – TDF/FTC (♂+♀), TAF/FTC (♂), IM CAB (♂+♀)

Acknowledgments

- **Cornell HIV Clinical Trials Unit (CCTU)**
- Division of Infectious Diseases
- Weill Cornell Medicine
- AIDS Clinical Trials Group (ACTG)
- HIV Prevention Trials Network
- Division of AIDS/NIAID/NIH
- The patient volunteers!

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BR4

Board Review Session 4

Drs. Gulick (Moderator), Bennett, Bloch, Dorman, Maldarelli, and Saag

BR4 –Board Review: Day 4

Moderator: Roy Gulick, MD

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

Board Review: Day 4

Moderator: Roy Gulick, MD, MPH
Faculty: Drs. Bennett, Bloch, Dorman, Maldarelli, and Saag

8/2/2023

BOARD REVIEW DAY 4 IDBR INFECTIOUS DISEASE BOARD REVIEW 2023

#46 A 62-year-old man with a history of hypertension has taken HIV PrEP with tenofovir DF/emtricitabine for 5 years.

His baseline creatinine clearance was 85 cc/min, but this has trended down with his latest creatinine clearance 55 cc/min (repeated at 60 cc/min).

He is in a monogamous relationship with his partner who has HIV and is taking a bictegravir-based regimen with HIV RNA <20 for years.

1 of 3

BOARD REVIEW DAY 4 IDBR INFECTIOUS DISEASE BOARD REVIEW 2023

#46 How would you manage his PrEP?

A) Continue tenofovir DF/emtricitabine, follow creatinine clearance monthly

B) Change to tenofovir AF/emtricitabine

C) Change to injectable cabotegravir every other month

D) Stop PrEP

2 of 3

BOARD REVIEW DAY 4 IDBR INFECTIOUS DISEASE BOARD REVIEW 2023

#47 A 60-year-old woman with a history of diabetes mellitus presented with a month of anorexia and nausea followed by 1 week of fever and right upper quadrant abdominal pain.

She had undergone an endoscopy with biopsy of a gastric ulcer 2 months before.

1 of 5

BOARD REVIEW DAY 4 IDBR INFECTIOUS DISEASE BOARD REVIEW 2023

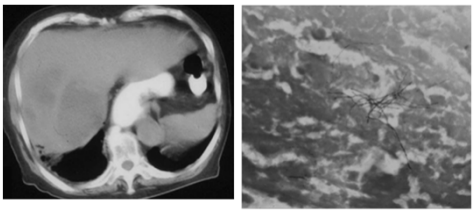
#47 On exam, she was febrile (101°F). She had RUQ abdominal tenderness. WBC count: 12,000.

Alkaline phosphatase: 195. An abdominal CT scan showed hypoattenuated lesions in the liver.

2 of 5

BOARD REVIEW DAY 4 IDBR INFECTIOUS DISEASE BOARD REVIEW 2023

#47 A Gram stain of the aspirate is shown.



3 of 5

BOARD REVIEW DAY 4 INFECTIOUS DISEASE BOARD REVIEW 2023

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

A) *M. tuberculosis*

B) *Nocardia*

C) *Streptococcus milleri* (anginosus group)

D) *Actinomyces*

E) *Aspergillus*

4 of 5

BOARD REVIEW DAY 4 INFECTIOUS DISEASE BOARD REVIEW 2023

#48 **A 40-year-old female is admitted with a 3-week history of daily fever accompanied by a non-pruritic skin eruption.**

She was initially seen at a walk-in clinic 5 weeks ago for cough and given a 7-day course of Augmentin for bronchitis with resolution of respiratory symptoms.

In the last 2 weeks she has developed diffuse arthritis of hands, knees, elbows, and ankles.

1 of 4

BOARD REVIEW DAY 4 INFECTIOUS DISEASE BOARD REVIEW 2023

#48 **Labs include WBC of 7.8 (82% seg, 15% lymph, 3% eos), platelets of 159, alkaline phosphatase of 454, ALT/AST 137/118 and bilirubin 1.9.**

CRP is 183.6, rheumatoid factor <10, ANA negative. Ferritin is 8622

CT scan of the abdomen shows hepatosplenomegaly and peri-portal lymphadenopathy.

2 of 4

BOARD REVIEW DAY 4 INFECTIOUS DISEASE BOARD REVIEW 2023

#48 **What is the most likely diagnosis for this patient?**

A) Adult-onset Still's disease

B) DRESS (drug associated rash with eosinophilia and systemic symptoms)

C) SLE (systemic lupus erythematosus)

D) HLH (hemophagocytic lymphohistiocytosis)

E) Acute CMV infection

3 of 4

BOARD REVIEW DAY 4 INFECTIOUS DISEASE BOARD REVIEW 2023

#49 **A 30-year-old female presents with a new diagnosis of smear-positive pulmonary TB.**

She is also found to have a new diagnosis of HIV.

Labs show mild anemia, normal liver enzymes, CD4 cell count=25 cells/uL.

1 of 3

BOARD REVIEW DAY 4 INFECTIOUS DISEASE BOARD REVIEW 2023

#49 **Which is most appropriate approach to therapy:**

A) Start HIV treatment immediately, defer TB treatment

B) Start TB treatment immediately, defer HIV treatment until after 6 months of TB treatment

C) Start TB treatment immediately, and start HIV treatment in 8-12 weeks

D) Start TB treatment immediately, and start HIV treatment within 2 weeks

E) Start HIV treatment immediately, and start TB treatment within 2 weeks

2 of 3

BOARD REVIEW DAY 4 INFECTIOUS DISEASE BOARD REVIEW 2023

#50 **A 37-year-old woman from New Jersey undergoes routine HIV testing with the following results:**

- **HIV 4th generation test: Reactive (antibody positive + p24 antigen negative)**
- **HIV-1/2 Supplemental Assay: HIV-1 antibody negative, HIV-2 antibody negative**
- **HIV-1 RNA: <20 copies/ml**

1 of 3

BOARD REVIEW DAY 4 INFECTIOUS DISEASE BOARD REVIEW 2023

#50 **What is the most likely interpretation of the results?**

A) She is a long-term non-progressor
B) She has acute HIV-1 infection
C) She has acute HIV-2 infection
D) She has a false negative viral test
E) She has a false positive 4th generation test

2 of 3

BOARD REVIEW DAY 4 INFECTIOUS DISEASE BOARD REVIEW 2023

#51 **A 36-year-old obese white man (BMI 34) recently diagnosed with HIV (CD4 560, HIV RNA 52,000) is recommended to start antiretroviral therapy but is concerned about weight gain.**

1 of 3

BOARD REVIEW DAY 4 INFECTIOUS DISEASE BOARD REVIEW 2023

#51 **Which is true of antiretroviral-induced weight gain?**

A) Raltegravir is associated with more weight gain than dolutegravir
B) Elvitegravir is associated with more weight gain than bictegravir
C) Tenofovir AF is associated with more weight gain than tenofovir DF
D) White men have the highest rates of weight gain on ART

2 of 3

BOARD REVIEW DAY 4 INFECTIOUS DISEASE BOARD REVIEW 2023

#52 **A 42-year-old woman newly diagnosed with HIV (CD4 425, HIV RNA 73,000, genotype with wild-type virus) starts tenofovir alafenamide/emtricitabine/bictegravir and has the following virologic response:**

1 of 4

BOARD REVIEW DAY 4 INFECTIOUS DISEASE BOARD REVIEW 2023

#52

Weeks of Therapy	HIV Viral Load
4 weeks	HIV RNA 9,400
8 weeks	HIV RNA 1,050
16 weeks	HIV RNA 105
24 weeks	HIV RNA 90
36 weeks	HIV RNA 67
48 weeks	HIV RNA 82

2 of 4

BOARD REVIEW DAY 4 INFECTIOUS DISEASE BOARD REVIEW 2023

#52 **In addition to reinforcing adherence, what would you recommend?**

A) Add darunavir/ritonavir
B) Add etravirine
C) Add darunavir/ritonavir and etravirine
D) Switch bictegravir to darunavir/ritonavir
E) Continue current regimen

3 of 4

BOARD REVIEW DAY 4 INFECTIOUS DISEASE BOARD REVIEW 2023

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

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

His absolute neutrophil count hovers between 750 and 1000 cell/μL.

1 of 5

BOARD REVIEW DAY 4 INFECTIOUS DISEASE BOARD REVIEW 2023

#53 **He is receiving prophylactic doses of trimethoprim-sulfamethoxazole.**

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

The micro lab reports that branched hyphae are present on wet mount of the BAL. No pneumocystis was seen.

2 of 5

BOARD REVIEW DAY 4 INFECTIOUS DISEASE BOARD REVIEW 2023

#53 **PCR on the BAL is positive for CMV. Liposomal amphotericin (5 mg/kg/day) is started.**

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

PCR of peripheral blood for CMV is undetectable.

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

3 of 5

BOARD REVIEW DAY 4 INFECTIOUS DISEASE BOARD REVIEW 2023

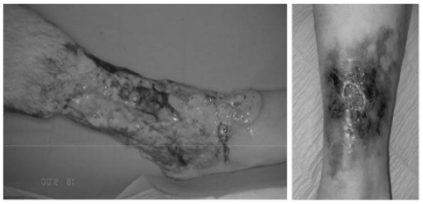
#53 **At this point, you would recommend:**

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

4 of 5

BOARD REVIEW DAY 4 INFECTIOUS DISEASE BOARD REVIEW 2023

#54 **A 55-year-old male is referred to you for evaluation of the leg lesions shown in the photo below.**



1 of 5

BOARD REVIEW DAY 4 INFECTIOUS DISEASE BOARD REVIEW 2023

#54 These lesions have been present for 3 months, and wax and wane. Several skin biopsies have been performed, with negative bacteria, fungus or mycobacteria stains and cultures.

A course of linezolid plus cephalexin for 3 weeks, and a course of fluconazole for 6 weeks had no effect.

The patient has reports recurrent episodes of abdominal pain and diarrhea in the past year and has lost 5 kg but denies fevers or other symptoms.

2 of 5

BOARD REVIEW DAY 4 INFECTIOUS DISEASE BOARD REVIEW 2023

#54 He was born in and lives in Chicago where he works as an accountant.

He has had unprotected anal intercourse with 3 male partners over the past year.

Laboratory studies show a high ESR and mild leukocytosis, and Hgb-8g/dl: his chemistries are normal.

3 of 5

BOARD REVIEW DAY 4 INFECTIOUS DISEASE BOARD REVIEW 2023

#54 He is most likely to have which one of the following?

A) Kaposi's sarcoma

B) Ulcerative colitis

C) Hepatitis C

D) *Haemophilus ducreyi*

E) Syphilis

4 of 5

BOARD REVIEW DAY 4 INFECTIOUS DISEASE BOARD REVIEW 2023

#55 A 56-year-old male with end-stage-renal disease due to hypertensive nephropathy is being evaluated for possible renal transplantation.

Routine pre-transplant serologies were obtained, which were notable for a positive Interferon-Gamma Release Assay (IGRA) for Mycobacterium tuberculosis. The patient is asymptomatic and has never been treated for TB.

1 of 4

BOARD REVIEW DAY 4 INFECTIOUS DISEASE BOARD REVIEW 2023

#55 Chest x-ray is normal.

The patient has a suitable living donor and the transplant team would like to proceed with transplantation as soon as possible.

2 of 4

BOARD REVIEW DAY 4 INFECTIOUS DISEASE BOARD REVIEW 2023

#55 Which one of the following would be the best course of action?

A) Inform the transplant team that patient is not a renal transplant candidate due to TB infection

B) Initiate treatment with isoniazid and vitamin B6 while proceeding with transplant; complete treatment for a total of 6-9 months

C) Initiate treatment with rifampin while proceeding with transplant; complete treatment for 4 months

D) Initiate treatment with once weekly isoniazid and rifapentine while proceeding with transplant; complete treatment for 12 weeks

E) Initiate treatment with isoniazid, rifampin, pyrazinamide and ethambutol for 6 months while proceeding with transplant

3 of 4

BOARD REVIEW DAY 4 | INFECTIOUS DISEASE BOARD REVIEW 2023

#56 **A 29-year-old man living with HIV on tenofovir alafenamide (TAF)/emtricitabine + dolutegravir (CD4 298, HIV RNA <20 cps/ml) develops pulmonary TB.**

The plan is to start empiric INH, RIF, PZA, and ETH pending mycobacterial susceptibilities.

1 of 3

BOARD REVIEW DAY 4 | INFECTIOUS DISEASE BOARD REVIEW 2023

#56 **How do you manage his ART regimen?**

A) Continue current regimen

B) Change dolutegravir to darunavir/ritonavir

C) Change dolutegravir to elvitegravir

D) Double the dose of dolutegravir

2 of 3

BOARD REVIEW DAY 4 | INFECTIOUS DISEASE BOARD REVIEW 2023

#57 **A 44-year-old man was diagnosed with Pneumocystis pneumonia as his AIDS-defining illness and begun on antiretroviral therapy with 2 nucleosides and an integrase inhibitor during his hospitalization.**

He stabilizes and follows up for repeated outpatient visits with an HIV RNA consistently <20 copies/ml and a CD4 cell count of 44 that increased to 163 (at 3 months), 232 (at 6 months), 242 (at 9 months), and was repeated at 243 (at 12 months).

1 of 4

BOARD REVIEW DAY 4 | INFECTIOUS DISEASE BOARD REVIEW 2023

#57 **His current medications are: tenofovir alafenamide/emtricitabine, dolutegravir, trimethoprim-sulfa double strength daily, and azithromycin 1200 mg once weekly.**

He says he's tired of taking pills and would like to stop some of them.

2 of 4

BOARD REVIEW DAY 4 | INFECTIOUS DISEASE BOARD REVIEW 2023

#57 **What do you recommend?**

A) Stop tenofovir alafenamide/emtricitabine

B) Stop trimethoprim-sulfa

C) Stop azithromycin

D) Stop trimethoprim-sulfa and azithromycin

E) Continue the current regimen

3 of 4

BOARD REVIEW DAY 4 | INFECTIOUS DISEASE BOARD REVIEW 2023

#58 **A 58-year-old HIV- negative gay man is evaluated for PrEP. His past medical history is notable for hypertension, treated for over 10 years with an ACE inhibitor. He is asymptomatic and weighs 145 lbs.**

He is sexually active with multiple partners but "usually" practices safe sex.

Lab studies reveal: HIV 4th generation test negative, HIV-1 RNA negative, CBC normal, creatinine 1.4 with a calculated creatinine clearance of 48 ml/min.

1 of 3

BOARD REVIEW DAY 4 INFECTIOUS DISEASE BOARD REVIEW 2023

#58 **What do you recommend for PrEP?**

A) No PrEP

B) Tenofovir disoproxil fumarate/emtricitabine 1 pill daily

C) Tenofovir disoproxil fumarate/emtricitabine 1 pill every other day

D) Tenofovir alafenamide/emtricitabine 1 pill daily

2 of 3

BOARD REVIEW DAY 4 INFECTIOUS DISEASE BOARD REVIEW 2023

#59 **A 43-year-old man is admitted with acute onset of right sided hemiplegia and dysarthria.**

He had been in excellent health until one month previously when he presented with shortness of breath and was diagnosed with acute pulmonary emboli and adenocarcinoma of the lung.

He was begun on eliquis and chemotherapy was deferred pending genetic testing.

1 of 4

BOARD REVIEW DAY 4 INFECTIOUS DISEASE BOARD REVIEW 2023

#59 **The patient lives with his wife and 2 children in Chicago. He works as a municipal bus driver. He denies pet or animal exposure.**

On presentation, he is afebrile. Exam is notable for poor dentition and dense right hemiplegia.

CT head confirmed a left middle cerebral artery infarct.

TTE confirms a 6x9 mm mass on the mitral valve.

Blood cultures x3 sets taken prior to initiation of antibiotics are no growth at 5 days.

2 of 4

BOARD REVIEW DAY 4 INFECTIOUS DISEASE BOARD REVIEW 2023

#59 **What is the most probable cause of endocarditis in this patient?**

A) *T whipplei*

B) *Mycobacterium chimaera*

C) *Bartonella henselae*

D) Hypercoagulable state

E) *Coxiella burnetii*

3 of 4

BOARD REVIEW DAY 4 INFECTIOUS DISEASE BOARD REVIEW 2023

#60 **A 24-year-old man presents with a fever, sore throat, myalgias, and vesicular rash following a trip to Europe.**

He has 3 lesions, one on his chest, one on his right shoulder, and one on his left buttock. One looks pustular, the others more vesicular, all have an erythematous base. There is no umbilication.

He is up to date with measles, mumps, rubella, and varicella vaccines. He reports anonymous sex with men and women in the past 4 weeks.

1 of 3

BOARD REVIEW DAY 4 INFECTIOUS DISEASE BOARD REVIEW 2023

#60 **The provider is concerned about mpox and asks you to advise on the best test. What do you recommend?**

A) Send a stool specimen for mpox PCR

B) Rub a swab on top of an intact vesicle and send for mpox PCR

C) Unroof a vesical with a needle, rub a swab over the lesion, and send for mpox PCR

D) Send a throat swab for mpox PCR

E) Send serum for mpox IgM and IgG

2 of 3

38

Syndromes that Masquerade as Infections

Dr. Karen Bloch

38 – Syndromes that Masquerade as Infections

Speaker: Karen C. Bloch, MD

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

Syndromes that Masquerade as Infections

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

7/5/2023

IDBR INFECTIOUS DISEASE BOARD REVIEW AUGUST 19-23 2023

Disclosures of Financial Relationships with Relevant Commercial Interests

- **None**

Special Thanks to Dr. Bennett Lorber!

ID Board Content

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

Mimics

- Many conditions masquerade as infections.
  - Fever almost universally present
  - Focal findings may be present
  - Examples:
    - Cellulitis vs stasis dermatitis
    - Viral vs Organizing Pneumonia
    - Lymphadenitis vs Lymphoma

VS

Test taking tip

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

Test taking tip

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

(pulmonary) TULAREMIA

Test taking tip

I say “Chitterlings” (aka chitlins, aka hog intestines)

You say…..

Test taking tip

I say “chitterlings”

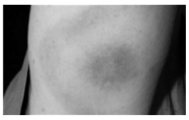
You say…..

YERSINIA (gastroenteritis)

Test taking tip

I say ”Bull’s-eye rash”

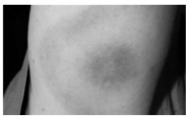
You say…..



Test taking tip

I say ”Bull’s-eye rash”

You say…..



Lyme disease
(or Erythema migrans or STARI)

My Approach to Mimics

- Think broadly, like an Internist
- The key is recognition, not treatment
- Goal for this talk is to cover lots of non-infectious diseases rather than in-depth discussion using buzz words for easy recognition!

Examples

Question 1

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

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

Question 2

PREVIEW QUESTION

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

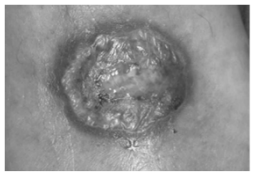
A. Ulcerative colitis
B. Adult-onset Still's Disease
C. Acute leukemia
D. Systemic lupus
E. Ankylosing spondylitis

Question 3

PREVIEW QUESTION

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

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



But this being boards…..

To optimize learning : CLOSE THE SYLLABUS

Case 4

- 26yo man presents with a 1-month h/o fever, night sweats and fatigue. He was evaluated by his PCP 2 weeks ago with a positive monospot.
- But, fevers have persisted and he has lost 10 lbs since the positive test.
- He lives in Indiana with his wife and 2 yo son, who are healthy. They have 2 cats.

Case 4

- Exam:
  - Vitals:
    - T=38.4ºC, HR=118 bpm
  - No cervical lymphadenopathy
  - Palpable spleen tip
  - No rash
- Labs
  - CBC
    - WBC=2.7, plt=53
    - Normal H/H
  - Normal Cr
  - AST/ALT=120/200
  - Alk phos=494, bili=1.9
  - Ferritin=**35,148** mg/ml

Question 4

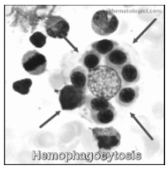
- What is the most appropriate next study?
  - A. Flow cytometry of whole blood
  - B. ANA profile
  - C. CMV PCR
  - D. Soluble IL-2 receptor level
  - E. Toxoplasma titer

Hemophagocytic Lymphohistiocytosis

- AKA HLH
- Immune activation syndrome
  - Primary (Peds): Familial due to genetic mutation
  - Secondary (adult or peds):
    - Infections (EBV or other herpes group viruses, HIV, histoplasmosis, *Ehrlichia*, COVID-19 etc)
    - Malignancy (lymphoma, leukemia)

HLH: Diagnostic Criteria

- At least **5** of the following:
  - Fever
  - Splenomegaly
  - Cytopenias (any line)
  - Hypertriglyceridemia (>3mmol/L)
  - Ferritin >500 mcg/mL
  - Elevated soluble IL-2 receptor (aka CD25)
  - Low NK cell activity
  - Hemophagocytosis on pathology



HLH Clues

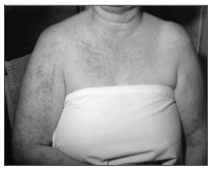
- EBV or other infection with progressive symptoms
- Massively elevated ferritin
- Cytopenia with negative ID evaluation

Case 5

- A 39-year-old woman is admitted with fever for 3 weeks, associated with diffuse arthralgias involving the knees, wrists and ankles.
- A severe sore throat was present during the first week of the illness, but has resolved.

Physical Exam

- T=104.2º F.
- Tender cervical LAN appreciated.
- Spleen tip is palpable.
- Both knees are swollen & painful.
- A rash is present on the trunk and extremities, most prominently under the breasts and in the area of her underwear waistband.



- Labs:
  - Ferritin 3600 ng/ml (nl 40-200)
  - WBC 32,200 (89% neutrophils)
  - AST and ALT 3x normal
  - ESR and CRP 5x normal
  - ANA and RF negative
  - Throat and blood cultures are so far negative
- On afternoon rounds with the attending, the fever has resolved with Tylenol and the rash is no longer present.

Question 5

- The most likely diagnosis is?
  - A. Lymphoma
  - B. Adult Onset Still's Disease
  - C. Acute Rheumatic Fever
  - D. Cryoglobulinemia
  - E. Kikuchi Disease

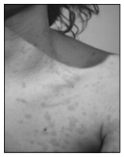
Adult Onset Still's Disease

Yamaguchi Criteria: (5 features with 2 major criteria)

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

Adult Onset Still's Disease

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

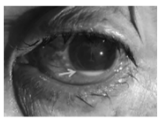
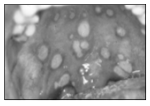
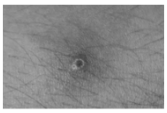

=


Koebner phenomenon (rash at pressure sites)

Case 6

- A 24-year-old man was referred by the ED for evaluation of ulcers of the mouth and penis. He was born and raised in Japan and is in the U.S. to attend graduate school.
- He has a history of recurrent painful oral ulcers for 3-4 years. Four days ago, he developed a painful ulcer on the penile shaft. He takes no medicines and denies sexual contact for the past 5 years.

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

Question 6

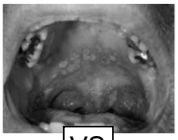
- The most likely diagnosis is?
  - A. Syphilis
  - B. Behçet's disease
  - C. Herpes simplex virus infection
  - D. Sarcoidosis
  - E. Cytomegalovirus infection

Behçet's disease

Pleomorphic vasculitis diagnosed clinically

- Recurrent oral ulcers (≥3 per year) PLUS 2 of the following
  1) recurrent genital ulcers
  2) eye (uveitis, retinitis, hypopyon)
  3) skin lesions, esp pathergy (red papule 24- 48 hours after needlestick)
- Less common manifestations (oral ulcers PLUS…)
  - GI disease (abdo. pain, bloody diarrhea)
  - Aseptic meningitis
  - Arterial and venous thrombosis

Behçet's disease



VS

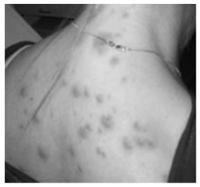
- Ulcers is the buzz word, but the trick is differentiation from infectious causes (HSV, coxsackie, etc)
- Additional Clues
  - Recurrence
  - Ocular findings
  - Pathergy (needle or IV site)

Case 7

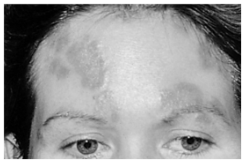
- A 38-year-old woman with AML is admitted with fever. She underwent induction chemotherapy 2 weeks prior, complicated by neutropenic fever that resolved with marrow recovery.
- She now presents with a 1-day history of fever without localizing symptoms.
- Exam: T 101.4; P 98, Otherwise unremarkable.
- CBC showed a white blood cell count of 12,250 with 20% bands.

Hospital Day 2:

- Fever persists despite broad spectrum antibiotics.
- Interval development of raised, red-purple, tender papules and nodules on her face, neck and the dorsum of her hands.



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



Hospital Day 4:
skin biopsy with dense perivascular neutrophilic infiltrate without evidence of vasculitis; stains for organisms negative.

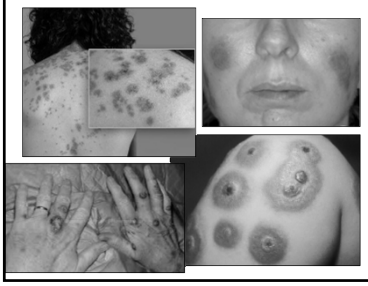
Question 7

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

Sweet Syndrome

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

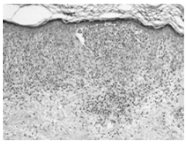
Skin Lesions in Sweet Syndrome



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

Sweet Syndrome

- Buzz words and associations:
  Fever and a rash
  Neutrophilia (peripheral and on path)

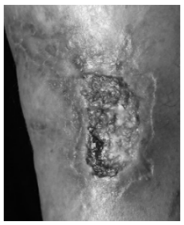


- Be suspicious in patients with malignancy (esp AML), IBD, recent URI, vaccination, pregnancy, or colony stimulating factor use in preceding 2 weeks

Case 8

- A 33-year-old recent immigrant from Central America is seen for a chronic ulcer of the leg.
- This has progressively enlarged after he bumped his leg on a table 3 months prior.
- There has been no response to oral antibiotics.
- For the past year he has had an "upset stomach".
- On further probing, he describes intermittent abdominal cramps, frequent diarrhea, and, on 2 occasions, blood in the stool.

- Exam:
  T 100.2
  Abdo pain to palpation
  Skin lesion



- Labs:
  WBC 11,150 (2% eos)
  ESR=79, CRP=110
  BMP normal
  Chest x-ray normal

Question 8

Which one of the following is the most likely diagnosis?

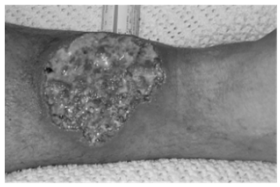
A. Ulcerative colitis
B. Cutaneous leishmaniasis
C. Amebic colitis
D. Cutaneous blastomycosis
E. Squamous cell cancer

Pyoderma gangrenosum

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

Pyoderma Gangrenosum

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



Case 9

- A 79-year-old woman is seen for 3 weeks of fever and fatigue.
- One week earlier she developed jaw discomfort when chewing food and had a brief episode of double vision.
- One month ago, she attended a luau and ate roast suckling pork prepared over an open fire.

- Exam:
  T 102.2, P 104, BP 124/84
  Slight tenderness over left scalp
  mitral regurgitant murmur
  rest of exam normal
- Labs:
  Hb 9.8; WBC 9800, normal diff
  UA normal
  basic metabolic panel normal
  sedimentation rate 147

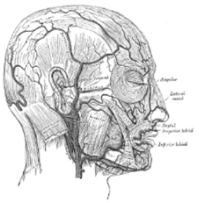
Question 9

Which of the following is most likely to be diagnostic?

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

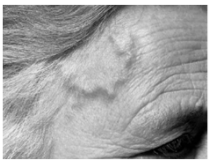
Giant Cell Arteritis

- Extracranial branches of the carotid.
- Clinical findings:
  - Fever (almost exclusively older adults)
  - Scalp or TA tenderness, jaw claudication
  - amaurosis fugax or sudden vision loss
- Marked inc ESR/CRP suggestive, TA biopsy diagnostic
- Immediate steroid therapy indicated if visual changes to prevent blindness



Giant Cell Arteritis

Buzz words & Associations:



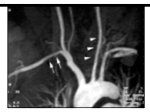
FUO in a patient >50 years PLUS

- scalp or TA tenderness
- Visual symptoms (diplopia or transient visual loss)
- jaw or tongue fatigue or pain while chewing
- ESR >100

Overlap of GCA and PMR

- ~50% patients with GCA have concomitant PMR
- Consider GCA in febrile patient with Buzz words for PMR….
  - morning stiffne**ss** in proximal muscles of shoulder and hip girdle
  - Gel phenomenon (stiffness with inactivity)

Takayasu Arteritis



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

Case 10

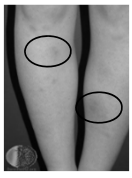
- A 37-year-old female presents with fever and joint pain. She is a long-distance runner and in excellent health.
- Three weeks prior she noted R knee pain after a long run. She was treated with a steroid injection with transient improvement, but subsequently developed bilateral ankle pain and redness.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

Exam:

T 100.5; Pulse 72; BP 110/70

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

Skin exam with painful pre-tibial nodules



Labs:

WBC 8.8 (76% segs)

CRP=167

Uric acid=4.4

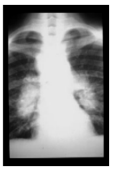
RF <15, Anti-CCP Ab negative

Question 10

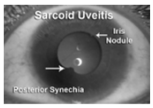
Which of the following is most likely to be diagnostic?

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

Sarcoidosis

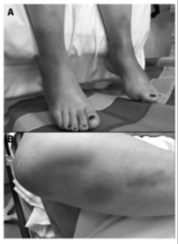


- Extra-pulmonary disease in ~1/3 of cases
- Lofgren Syndrome
  - Only form of sarcoid that is a clinical diagnosis
  - Triad of hilar LAN, acute arthritis, EN
  - Women, ankles (>90%), fevers common
- BUZZ WORDS
  - Hilar LAN, EN, uveitis, parotid enlargement
  - Non-caseating granulomas
  - Aseptic meningitis with basilar enhancement



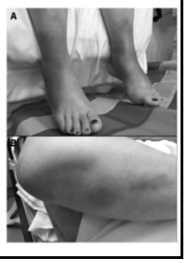
Erythema nodosum

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



Erythema nodosum

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



Case 11

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

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

Question 11

The most likely diagnosis is:

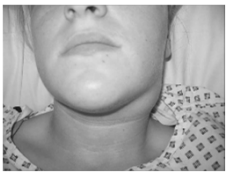
A. Hereditary angioneurotic edema
B. Familial Mediterranean fever
C. Systemic lupus erythematosus
D. Crohn's disease
E. Acute intermittent porphyria

Familial Mediterranean Fever

- Auto-inflammatory disease causing a periodic fever syndrome
  - Others: PFAPA, TRAPS, hyperimmunoglobulin D
- Recurrent attacks of fever & serositis (peritonitis, pleuritis, arthritis) manifesting as *pain*.
- Dx: Genetic testing
- Buzz words and associations:
  - Periodic fever episodes (PLUS…)
  - Serositis
  - Mediterranean ancestry

Case 12

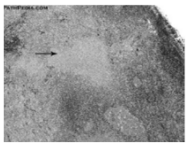
- A 26-year-old medical student presents with fever and cervical adenopathy.
- She was completely well until 9 days ago when she had the acute onset of fever and vague neck discomfort. She had no sore throat and no dental or scalp problems.



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

- Serologic studies:
  EBV IgM negative
  CMV, Toxo, *Bartonella* negative
  RF, ANA, ds-DNA negative
- Lymph node pathology:
  Necrotizing lymphadenitis with histiocytic infiltrate and phagocytosed debris.

  Stains for AFB and fungi negative.



Question 12

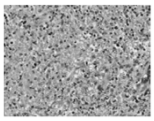
Which one of the following is the most likely diagnosis?

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

Kikuchi Disease

- AKA acute necrotizing histiocytic lymphadenitis
- Self-limited condition of unknown cause
- Typically occurs in young women
- Fever & cervical LAN (esp posterior, usually unilateral).
- Rarely: morbilliform rash, diffuse LAN, aseptic meningitis, uveitis.
- Leukopenia and atypical lymphocytes in 25% of cases.

Kikuchi Disease

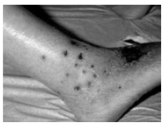


- Diagnosis by pathology:
  - necrotizing histiocytic infiltrate (not neutrophils) and fragments of nuclear debris.
- Buzz words and associations:
  - Acute onset fever and cervical adenopathy in young woman
  - Atypical lymphocytes (mono-like syndrome)
  - Path: necrotizing adenitis with histiocytosis

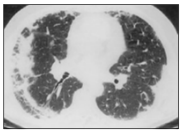
Case 13

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

- Exam: Temp 101.5; RR 24
- Diffuse wheezing; palpable purpura with nodules on elbows and legs.



- Labs: WBC 15,230 (22% eosinophils).
- CT scan: bilateral peripheral infiltrates.



- Skin nodule biopsy: granulomas

Question 13

Which one of the following is the most likely diagnosis?

A. Strongyloidiasis
B. Disseminated histoplasmosis
C. Sarcoidosis
D. Allergic bronchopulmonary aspergillosis
E. Eosinophilic granulomatosis with polyangiitis

EGPA

- AKA Churg-Strauss Syndrome
- Multisystem, small vessel vasculitis with allergic rhinitis, asthma, peripheral and lung eosinophilia.
- Most often involves lung and skin, but can involve heart, GI tract, and nervous system.
- Presence of blood eosinophilia and peripheral pulmonary infiltrate in setting of difficult to control asthma.
- Tapering of steroids often “unmasks” EGPA
- May be p-ANCA positive.

EGPA

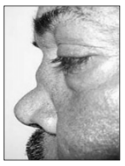
- Buzz words and associations:
  - Longstanding asthma
  - New infiltrates and eosinophilia (>10%) as steroids tapered.
  - Rash (tender nodules on extensor surfaces, purpura, ecchymosis, necrosis)
  - Fever UNCOMMON (until late)

Case 14

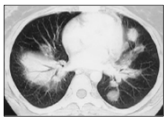
- A 38-year-old man is seen for a 6-week history of cough, intermittent fever and night sweats.
- He has had nasal stuffiness for 4-5 months with occasional epistaxis.
- He lives in Philadelphia, and 6 months ago traveled to Cincinnati on business.
- He has no pets and takes only an OTC decongestant.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

Exam:
- T 100.2; RR 18;

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



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

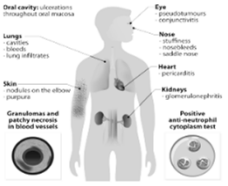


Question 14

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

Granulomatosis with polyangiitis (GPA)

- Systemic vasculitis of medium and small arteries.
- Primarily involves upper and lower respiratory tracts and kidneys.
- Variably involves joints, cartilage, eyes, skin, and nervous system.



Granulomatosis with polyangiitis

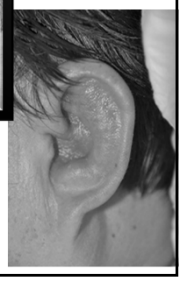
- Dx:
  Suggestive: Positive ANCA (~85% sensitivity)
  IFA: c-ANCA.
  ELISA: anti-proteinase 3 (PR3-ANCA)
  Diagnostic: Biopsy

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

Case 15

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

Case 15



Exam:

Afebrile

Left auricle is inflamed and tender, ear lobe is spared.

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

Labs: CBC normal

Question 15

The most likely diagnosis is?

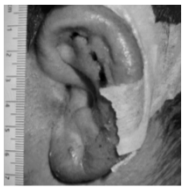
A. Malignant otitis externa
B. Leprosy
C. Granulomatosis with polyangiitis
D. Relapsing polychondritis
E. Congenital syphilis

Relapsing Polychondritis

--Immune-mediated condition.

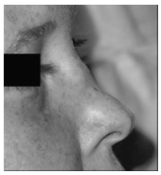
--Inflammation of cartilaginous structures, particularly ears, but also nose, eyes, joints, and airways.

--Clinical diagnosis.



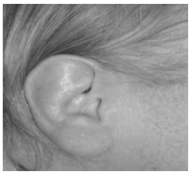
Saddle-nose Deformity

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



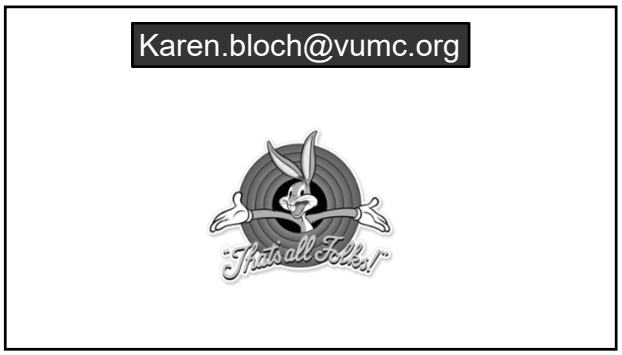
Relapsing Polychondritis

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



38 – Syndromes that Masquerade as Infections

Speaker: Karen C. Bloch, MD



39

Tuberculosis in Immunocompetent and Immunosuppressed Hosts

Dr. Susan Dorman

39 – Tuberculosis in Immunocompetent and Immunosuppressed Hosts

Speaker: Susan Dorman, MD

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

Tuberculosis in Immunocompetent and Immunosuppressed Hosts

Susan E. Dorman, MD
Professor of Medicine
Medical University of South Carolina

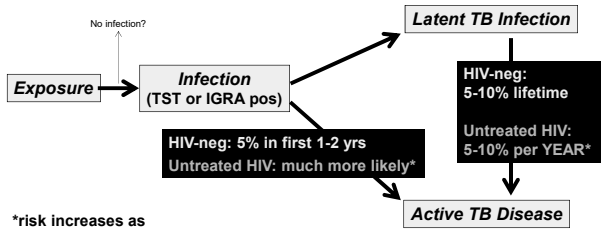
2/28/2023

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

Disclosures of Financial Relationships with Relevant Commercial Interests

- None

Overview of TB Epidemiology



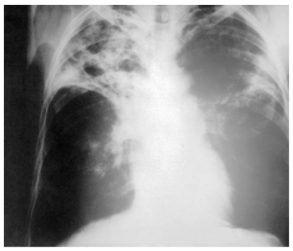
*risk increases as immunosuppression increases

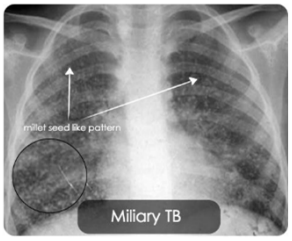
Risk Factors for Active TB Disease

Epi risk factors for TB INFECTION	Medical risk factors for PROGRESSION TO TB DISEASE	
Exposure to person w/ active TB	Recent TB infection	CXR fibrotic lesions c/w prior TB
From TB endemic area	HIV infection	Intestinal bypass, gastrectomy, chronic malabsorption
Homelessness	TNF-alpha inhibitors	CA head or neck, Hodgkins, leukemia
Incarceration	Immunosuppression	
Works healthcare, corrections	End stage renal dz	
Injection drug use	Diabetes	
	Silicosis	

Active TB disease: clinical presentations

- **Fever, sweats, wt loss**
- **Cough if pulmonary**
- **Subacute to chronic (wks to months)**
  - Can be acute in immunocompromised
- **Upper lobe/apical cavity is 'typical'**
  - With surrounding infiltrate
  - + / - adenopathy





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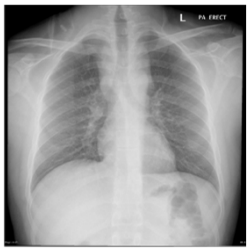


Tuberculous mediastinal lymphadenopathy

http://images.radiopaedia.org/images/5440907/ba7efaf8df7333e5eef8f4a964dd8e_jumbo.jpg

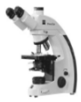
Active TB disease: clinical presentations

Extrapulmonary
- **CNS** (meningitis, focal tuberculomas)
- **Lymphadenitis** (cervical, thoracic, abdominal)
- **Bone and joint**
  - Vertebral (thoracic, lumbar, anterior wedging, +/- psoas abscess)
  - Consider TB in DDx of chronic osteomyelitis, arthritis
- **Pleural**
- **Abdominal/pelvic**
  - GU ('sterile' pyuria; obtain multiple cultures; can be associated with infertility)
  - GI (can mimic inflammatory bowel disease; obtain cultures/PCR, histopathology)

Obtain specimens from affected sites:
AFB smear
Mycobacterial culture
NAAT/PCR
Histopathology

Disseminated
- Advanced HIV, significant iatrogenic immunosuppression, d/o of IFN-gamma/IL-12/TNF axis
- Can present as sepsis
- Mycobacterial blood cultures, obtain respiratory specimens, other tissue specimens

Active TB disease: diagnosis

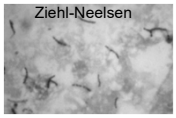
Smear microscopy	nucleic acid amplification tests	culture
		
LOD: 10,000 cfu/ml	100 cfu/ml	1-10 cfu/ml
Sensitivity: LOW	MEDIUM (currently)	HIGH

ADJUNCTIVE:
IGRA, TST: do not distinguish latent from active; NEG test does not rule out active TB
CXR, other radiology: can be suggestive of active TB; not specific
Histopathology: can be suggestive of active TB; not specific

Active TB disease: diagnosis

Smear microscopy for AFB

* ***NEG SMEARS DO NOT EXCLUDE A DX OF ACTIVE TB***
- Low sensitivity: takes 10,000 cfu/ml bacilli to make a smear pos
- Overall 50-60% sensitive for pulmonary TB
- Less sensitive in advanced HIV (30-50%)
- In pulmonary TB, the yield of smear microscopy increases if multiple specimens obtained
- Not specific for MTB (mycobacteria look alike)
- Good PPV in TB endemic settings



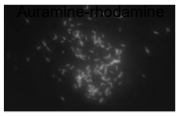


Image credits:
1. CDC/Dr. George P. Kubica
2. https://laboratoryinfo.com/auramine-rhodamine-staining-for-afb-principle-procedure-reporting-and-limitations/

Active TB disease: diagnosis

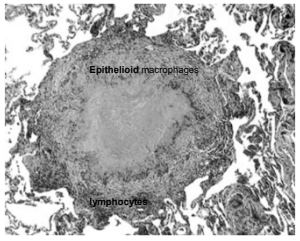
Nucleic Acid Amplification Tests

- E.g. 'Xpert MTB/RIF'
- Sensitivity of available NAATs 'in between' that of smear and culture
- **A negative NAAT does not rule out TB**
- **High specificity for *M. tuberculosis* (by design)**
- Xpert MTB/RIF detects MTB *&* rifampin resistance (NO info about INH)
- Procedures designed for, validated for sputum
  - Can use for other specimens but test can be falsely negative due to inhibitors

Active TB disease: diagnosis

Mycobacterial Culture

- The **most sensitive method** but SLOW (3-6 weeks)
- Once growth observed, lab performs additional tests:
  - Species identification
  - Growth-based DST
- Considered the gold standard, but not 100% sensitive
  - Pulmonary TB around 90-95% sensitive
  - Extrapulmonary TB much less sensitive



Typical caseating granuloma

Immunodeficient patients:
(e.g. advanced HIV; use of TNF alpha inhibitors)
- Caseation may not be apparent
- Granulomas may lack structure

Image credit: http://pathhsw5m54.ucsf.edu/overview/tb.html

Question 1

2023 PREVIEW QUESTION

38 y/o healthy physician; periodic travel to South Africa for work.
6 years ago: pos TST; poor adherence with isoniazid preventive therapy.
Now 5 weeks of fever, chills, night sweats, 10-lb wt loss, productive cough.
CXR RUL cavitary lesion.
Sputum Xpert MTB/RIF: "MTB detected" & "Rifampin resistance not detected".
HIV negative, LFTs normal. What is the best course of action?

A. Prescribe 9 months of isoniazid for presumed latent TB infection
B. Do nothing pending culture results
C. Start TB treatment with rifampin, isoniazid, PZA, ethambutol
D. Start TB treatment with rifampin, isoniazid, PZA
E. Start TB treatment with a regimen for multidrug-resistant TB

Active TB disease: treatment

1st line tx = RIPE

- **Rifampin, Isoniazid, PZA, Ethambutol x 2 months then**
- **rifampin plus isoniazid x 4 more months (continuation phase)**
- Use pyridoxine (vitamin B6) to prevent neuro toxicity of INH

Always start with daily treatment

- Daily more efficacious than intermittent
- In HIV-pos, intermittent tx associated with emergence of RIF resistance

Active TB disease: treatment

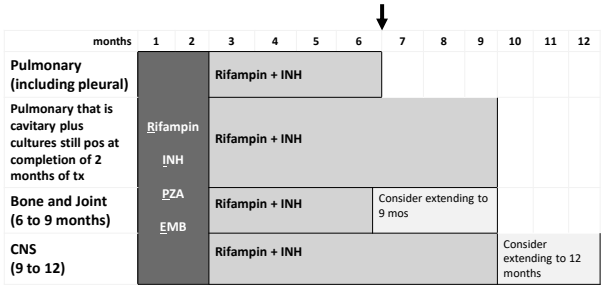
Extend continuation phase therapy for

- Pulmonary dz if cavitation & cx pos at end of tx month 2 (9 months total)
- CNS TB (9-12 months total duration)
- Bone and joint TB (6-9 months total duration)

Corticosteroids: indicated for TB meningitis

- Pericardial TB: previously universally recommended BUT recent placebo controlled randomized trial showed no difference in outcomes overall

Active TB disease: treatment durations



Question 2

The 38 y/o physician is started on rifampin, isoniazid, PZA, ethambutol (plus pyridoxine) for presumed pulmonary TB.
3 weeks later the culture grows *M. tuberculosis*, susceptible to those drugs.
4 weeks into TB treatment develops nausea, anorexia, abdominal pain.
ALT 380, AST 270. He reports no alcohol consumption or acetominophen.
Which drug is **least** likely to be associated with liver toxicity?

A. Rifampin
B. Isoniazid
C. PZA
D. Ethambutol

Active TB disease: treatment

Drug adverse effects

- **Hepatotoxicity: isoniazid = PZA > rifampin**
- **Peripheral neuropathy: isoniazid (use pyridoxine = Vit B6)**
- **Retrobulbar neuritis: ethambutol (acuity, color vision)**
- Arthralgias: PZA

RIFAMPIN CHEWS UP SOME OTHER DRUGS*

Oral anticoagulants	HIV PIs
Hormonal contraceptives	HIV NNRTIs
Methadone	HIV INSTIs
Corticosteroids	HIV CCR5 inhibitors
Fluconazole	TAF*

*Induces hepatic cytochromes & uridine diphosphate gluconyltransferase, resulting in increased metabolism (and decreased serum levels, potential decreased efficacy, potential need for increased doses) of other drugs metabolized by those enzymes

**intracellular TFV-DP levels higher with TAF+RIF c/w TDF alone, but clinical outcomes not well-studied – if TAF+RIF used then monitor HIV VL*

Drug-resistant TB

- Risk factors for:
  - Contact with drug-resistant TB case
  - Prior h/o TB treatment, esp if non-adherent with tx
- **MDR=resistance to isoniazid plus rifampin**
- **XDR=MDR plus resistance to fluoroquinolones plus at least one of the injectable 2nd line drugs** (amikacin, kanamycin, capreomycin)
- Treat with multiple agents against which the isolate is susceptible
- Do not add single drug to a failing regimen
- **Bedaquiline (Sirturo™): novel drug, novel target (MTB ATP synthase),** FDA-approved for pulm drug-R TB when effective tx cannot otherwise be provided; **QT prolongation; half-life 4 months**

Question 3

IDBR 2023 PREVIEW QUESTION

24 y/o M from Zambia, in U.S. for community college, recently tested HIV-positive, CD4 400, not yet on ART.

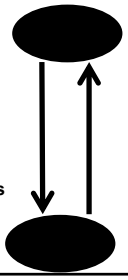
Prominent anterior cervical lymph node but well-appearing, normal BMI, normal liver and renal chemistries, mild anemia.

Lymph node biopsy grows *M. tuberculosis* in culture.

Best course of action regarding timing of TB therapy and HIV therapy?

A. Start ART immediately, defer TB tx
B. Start TB tx immediately, defer ART until completes 6 months TB tx
C. Start TB tx immediately, and start ART within about 8 weeks
D. Start both TB tx AND ART immediately

Active TB disease: Special considerations w/ respect to HIV



HIV:
Increases risk of progression from latent to active TB

CD4 influences severity & clinical manifestations of TB

TB:
Can increase HIV viral load

Associated with more rapid progression of HIV

Active TB disease: Special considerations w/ respect to HIV

Clinical Presentation

- Lung cavitation may be absent in advanced immunosuppression
- Negative CXR does not exclude TB
- With advancing immunosuppression, risk for
  - 'Smear-negative' pulmonary TB
  - Extrapulmonary TB (with or without pulmonary involvement)
  - CNS TB
  - Widely disseminated TB including mycobacteremia

Active TB disease: Special considerations w/ respect to HIV

A rifamycin-based TB regimen is recommended despite drug-drug interactions

Drug-drug interactions

- **RIFAMPIN (RIF)**
  - Accelerates clearance of PIs, NNRTIs, INSTIs, CCR5 inhibitors
    - INSTIs: rifampin + (DTG 50 mg **BID** or RAL **800** BID) OK for selected patients
    - TAF: intracellular TFV-DP levels higher with TAF+RIF than with TDF alone but clinical outcomes not well-studied. If TAF+RIF used then monitor HIV VL.
    - Good virologic, immunologic, clinical outcomes with rifampin + standard dose EFV regimens
    - PI-based regimens: Do not use rifampin
    - Cabotegravir (oral or LAI): Do not use any rifamycin
- **RIFABUTIN (RBT)**
  - Weaker enzyme inducer than rifampin
  - A CYP450 substrate (rifabutin metabolism affected by NNRTIs and PIs)
  - PI-based ART: decrease rifabutin to 150 mg daily, or 300 mg every other day

Active TB disease: Special considerations w/ respect to HIV

When to start ART

- **CD4 < 50: within 2 weeks of starting TB tx**
- **CD4 ≥ 50: within 8 weeks of starting TB tx**

- HIV-infected pregnant women with active TB should be started on ART as soon as feasible (for maternal health and PMTCT)

- **TB meningitis: be cautious** (high rates of AEs and death in RCT); guidelines recommend not starting ART within first 8 weeks

Question 4

30y/o F with HIV, CD4=20, viral load >1 million copies/mL (new dx).
Microbiologically confirmed pulmonary TB (new dx).
RIPE TB treatment started immediately; tolerated well.
12 days later starts DTG-based ART with appropriate bid dosing of DTG.
Four weeks after ART started she reports new headaches, RUE paralysis.
Which is most appropriate:

A. Stop TB tx immediately since this is likely a side effect of a TB drug
B. Obtain a brain MRI immediately
C. Perform a lumbar puncture immediately
D. Change TB treatment to cover drug-resistant TB
E. Stop ART immediately

Active TB disease: Special considerations w/ respect to HIV

Immune reconstitution inflammatory syndromes (IRIS)

PARADOXICAL WORSENING of TB when ART started after TB treatment initiated

UNMASKING of TB when ART started in setting of not-yet-recognized active TB

- Typically 2 weeks to 3 months after starting ART
- Risk factors: CD4<50, high pre-ART VL, severe TB, short interval between initiation of TB tx and ART
- Protean manifestations (fever, new lesions, extension of prior lesions)

Active TB disease: Special considerations w/ respect to HIV

Immune reconstitution inflammatory syndromes (IRIS)

- General clinical approach
  - Deal promptly with any 'limited space' issues (CNS inflammation, obstructing adenopathy, etc): corticosteroids; surgery if indicated
  - Consider in DDx: malignancy, other OI, wrong original dx of TB, drug-resistant TB; clinical eval is patient-specific
  - NSAIDs if mild; corticosteroids if more severe/refractory signs/sx (prednisone 1.5 mg/kg/d x 2 wks then 0.75 mg/kg/d x 2 wks - Meintjes et al AIDS 2010;24:2381)
  - **Continue TB treatment plus ART**

Active TB disease: Transplant recipients

- **Transplantation-associated immunosuppression increases risk of active TB disease if the person is infected with MTB**
- **'atypical' presentations leading to delayed dx**
  - 1/3 to 1/2 is disseminated or extrapulmonary
  - 4% of cases thought to be donor derived
- High mortality
- **RIFAMPIN DDI** with calcineurin inhibitors (e.g. cyclosporine, tacrolimus), mammalian target of rapamycin inhibitors (e.g. sirolimus/everolimus), corticosteroids…….at risk for graft rejection
  - Monitor drug levels of calcineurin inhibitors, mTORs
  - Use rifabutin instead of rifampin

Active TB disease: People on TNF-alpha inhibitors

- ***TNF-alpha inhibitors markedly increase the risk of active TB if infected***
  - Can present with atypical TB (e.g. non-cavitary pulm dz, extrapulmonary, disseminated)
  - Increased TB morbidity, mortality
  - Full monoclonal IgG1 mabs most potent (ie infliximab, adalimumab, golimumab)

- ***Test for latent TB infection (TST or IGRA) prior to starting anti-TNF agents***
  - If LTBI, then initiate LTBI tx prior to starting anti-TNF
  - Limited data on optimal duration of delay between initiating LTBI treatment and initiating anti-TNF treatment (some say 2-8 weeks)

Question 5

24 y/o U.S. born man; wife recently diagnosed with smear-pos pulmonary TB. Contact investigation: the 24 y/o man has strongly positive IGRA assay. He has no other known TB contact and reports a neg TST many years ago. What is the most appropriate next course of action for the 24 y/o M?

A. Start preventive therapy immediately using daily isoniazid
B. Start preventive therapy immediately using weekly isoniazid plus rifapentine
C. Repeat the IGRA assay
D. Start RIF, INH, PZA, EMB (Vit B6) immediately for active TB
E. Obtain medical history, perform TB symptom review and CXR

Latent TB infection (LTBI): diagnosis

Tuberculin skin test

- A mix of antigens; can have 'false-pos' test due to prior BCG vaccination, NTM
- Intradermal inoc, measure induration at 48-72 hours (pos rxn lasts a few days)
- Cut-offs based on likelihood of true exposure, risk of progression to active TB if infected (5 mm; 10 mm; 15 mm)
- Adjunctive in diagnostic eval for active TB
- Booster effect (recall of waned CMI):
  - Some people infected with MTB may have neg rxn to a TST if many years have passed since Mtb infection. However, the TST PPD stimulates immune response to Mtb antigens, and a subsequent TST can be positive.
  - "Booster effect" can be mistaken for TST conversion
  - Use 2-step TST for individuals who may be tested periodically (e.g. HCW)

Latent TB infection (LTBI): classification of tuberculin skin test results

≥ 5 mm is POS	≥ 10 mm is POS	≥ 15 mm is POS
HIV-infected Recent TB contact CXR with fibrotic changes Transplantation Prednisone ≥ 15 mg/d x 1 month or more TNF-α antagonists	Recent arrival (w/in 5 years) from TB high prevalence area Injection drug use Residents & employees of high-risk settings (HWC, corrections, homeless shelters) Mycobacteriology lab staff Children < 5 years old Medical conditions: diabetes, silicosis, end-stage renal dz, gastrectomy or small bowel resection, CA head & neck	Persons with no known risk factors for TB infx or progression

Latent TB infection (LTBI): diagnosis

Interferon gamma release assays (IGRAs)

- QuantiFERON-TB tests; T-SPOT.TB
- Blood-based; in vitro stimulation of WBC with protein antigens specific for *M. tuberculosis*
- **No cross-reactivity with BCG**
  - *M. kansasii, M. marinum, M. szulgai* can cause false pos IGRA
- Sensitivity approx same as that of TST
  - Can be negative in immunosuppressed
- As for TST, adjunctive in diagnostic eval for active TB
- 'issues' around performance in clinical care; not fodder for board Q's

Latent TB infection (LTBI): diagnosis

Excluding active TB is a key component of the diagnosis of latent TB infection

- **ROS** (fever, wt loss, cough, night sweats, focal signs/sx that could be assoc with extrapulmonary TB)
- **Chest X-ray** to exclude occult pulmonary TB

Latent TB infection (LTBI): treatment

Preferred

- Isoniazid plus rifapentine once weekly x 12 doses (3HP)
- Rifampin daily for 4 months (4R)
- Isoniazid plus rifampin daily for 3 months (3HR)

Alternative

- Isoniazid daily for 6 months (or 9 months)

Notes:

- Rifampin + PZA NOT recommended (hepatotoxicity)
- No age cut-off for LTBI treatment

Latent TB infection (LTBI): treatment

- Perform LFTs prior to tx in adults with risks for hepatotoxicity (etoh, risk for viral hepatitis, other hepatotoxic meds)
- Monthly ROS for adverse effects
  - Peripheral neuropathy (numbness/tingling extrems) if on INH (use Vitamin B6=pyridoxine)
  - Hepatotoxicity (N/V, abd discomfort, jaundice)
  - LFT monitoring as clinically indicated

Bacille Calmette-Guerin (BCG)

- Attenuated live vaccine (from *M. bovis*)
- ***Neonatal vaccination***
  - Decreases incidence of severe forms of childhood TB
  - No/very limited impact on adult TB
  - Regional lymphadenitis can occur after vaccination; typically no treatment needed
  - Disseminated infection can occur in immunocompromised (treatment indicated)

Bacille Calmette-Guerin (BCG)

Immunotherapy for bladder cancer

- Intravesicular administration
- Complications
  - granulomatous prostatitis or hepatitis, epididymo-orchitis, spondylitis, psoas abscess, miliary pulmonary, dissem/sepsis
  - Contemporaneous with BCG tx or up to years later
- Treatment
  - Inherent resistance to PZA
  - Treat with rifampin + INH + ethambutol

Thank YOU & Good luck!

Susan Dorman [DORMAN@MUSC.EDU]

40

Non-AIDS-Defining Complications of HIV/AIDS

Dr. Michael Saag

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

Non AIDS-Defining Complications of HIV/AIDS

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

7/5/2023

IDBR INFECTIOUS DISEASE BOARD REVIEW AUGUST 19-23 2023

Disclosures of Financial Relationships with Relevant Commercial Interests

- **None**

CASE 1

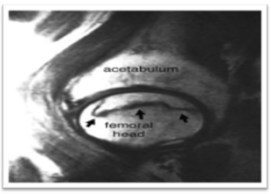
- 55 year old man presents with R hip pain
- H/o COPD requiring steroids frequently
- HIV diagnosed 17 years ago
- On TDF / FTC / EFV for 10 years; originally on IND / AZT / 3TC
- Initial HIV RNA 340,000; CD4 43 cells/ul
  - Now HIV RNA < 50 c/ml; CD4 385 cells/ul
- Electrolytes NL; Creat 1.3; Phos 3.5 Ca 8.5
- Mg 2.1, alk phos 130; U/A neg
- R Hip film unremarkable

QUESTION #1

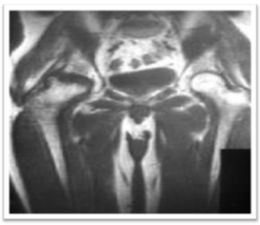
Which if the following is the most likely underlying cause of his hip pain?

A. Osetonecrosis of Femoral Head
B. Fanconi's syndrome
C. Vitamin D deficiency
D. Tenofovir bone disease
E. Hypogonadism

Osteonecrosis



This image demonstrates a classic segmental area of osteonecrosis with a dark line denoting the border between dead bone and living bone.



M. Levine. Ostoenecrosis of the hip- emedicine.com

Avascular necrosis in HIV

- Reported prior to the HAART era; increasing in HAART era.
- Rates of AVN 4.8/1000 person years >> general population.
  - Age ~ 35 yrs
  - Male predominance
  - H/o IDU
  - Increased duration of HIV
  - Low CD4
  - Elevated lipids
  - Glucocorticoid steroid use
  - Alcohol use

Monier et al, CID 2000;31:1488-92, Moore et al, AIDS 2003

CASE 2

PREVIEW QUESTION

- 46yowf c/o (CD4 582, VL <50 c/ml) c/o 1 week cramps in calves, tingling in hands, feet
- Today awoke and can't move except hands/feet
- No F/C, chest pain, SOB, incontinence
- + chronic diarrhea 4x/day
- Chronic fatigue, poor appetite
- Meds
  - TDF/FTC/EFV (2008), on TDF/FTC/Elv/cobi since 2014
  - zoloft, buproprion, norco, prilosec, trazodone, pravachol ibuprofen

CASE 2: Exam

PREVIEW QUESTION

- VS: T 98.2 P 79 BP 112/73
- RR 16, 02 sat 97%
- Pertinent findings
- Neuro: CNII-XII intact, strength 1+ all extremities except 4+ hand/wrist and ankles.
- NI reflexes. Alert, oriented.

CASE 2: Labs

PREVIEW QUESTION

137 | 116 | 5 Gluc 83
1.6 | 18 | 1.0 AG 3

Ca 8.3 Phos 1.8 Mg 2.1
Lactate 1.5 CK 186
UDS +cocaine/benzo/opiate
UA: 1.015 pH 6.5 2+ pro
Neg: gluc/ketones

QUESTION #2

PREVIEW QUESTION

Which of the following is the most likely diagnosis?

A. Cocaine toxicity
B. Nucleoside-induced myopathy (ragged red fiber disease)
C. Serotonin Syndrome
D. Statin toxicity
E. Fanconi's syndrome

CASE 3

PREVIEW QUESTION

- 35 year old man presents with complaints of increasing fatigue, headache, SOB / DOE
- HIV diagnosed 4 mos ago with PCP; intolerant to TMP/SMX
- Now on TAF / FTC / BIC + PCP Prophylaxis with Dapsone
- Claims adherence to all meds;
  "Doesn't miss a dose!"
- Normal PE
- Pulse Ox 85%; CXR no abnormalities
- ABG: 7.40 / 38 / 94/ 96% (room air)

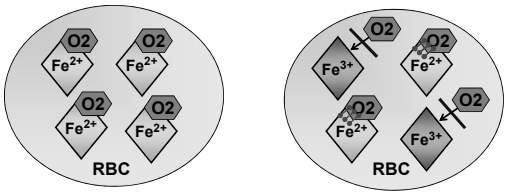
QUESTION #3

PREVIEW QUESTION

Which of the following is the most likely underlying cause of his symptoms?

A. Recurrent PCP
B. IRIS Reaction
C. Drug toxicity
D. Pulmonary Embolus
E. Patent Foramen Ovale

Hemoglobin and Methemoglobin



CASE 4

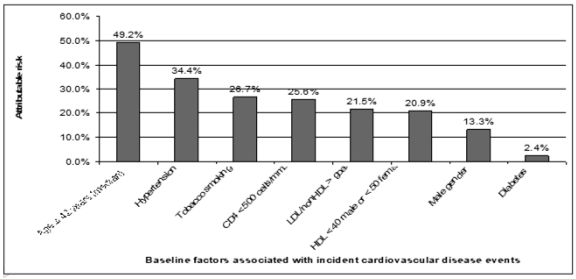
- 55 year old man presents with complaints of crushing chest pain
- HIV diagnosed 10 years ago
- Initial HIV RNA 340,000; CD4 43 cells/ul
  - Now HIV RNA < 50 c/ml; CD4 385 cells/ul
- Initally Rx with ZDV/3TC / EFV;
  now on ABC/3TC/ EFV
- On no other medications / smoker
- ECG shows acute myocardial infarction

QUESTION #4

Which of the following is the highest relative risk for his Acute MI?

A. Cigarette smoking
B. Lipid levels (LDL level of 180 / HDL 30)
C. Abacavir use
D. Lack of use of aspirin
E. HIV infection

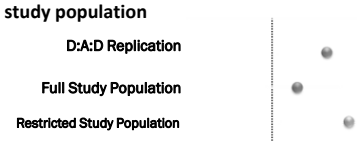
Low CD4⁺ T Cell Count Is a Risk Factor for Cardiovascular Disease Events in the HIV Outpatient Study



Clin Infect Dis 2010;51 (15 August)

Abacavir and Risk for Myocardial Infarction- Analysis of NA-ACCORD

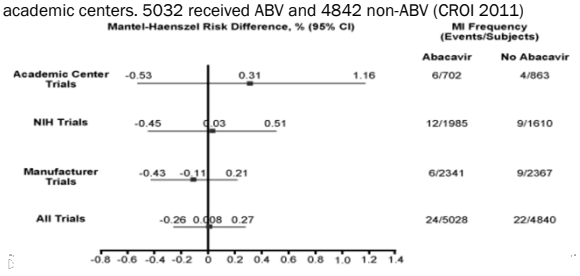
Adjusted hazard ratios of MI among persons with recent ABC use (vs. no recent ABC use): replication of the D:A:D model, NA-ACCORD model in the Full study population, and NA-ACCORD model in the Restricted study population



Palella FJ *et al*, Abstract 749 CROI Seattle 2015

FDA meta-analysis

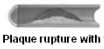
26 randomized, controlled ART trials of abacavir. 16 GSK studies, 5 NIH, 5 academic centers. 5032 received ABV and 4842 non-ABV (CROI 2011)



MI Classification Protocol

Universal Definition of MI:

Primary MI (Type 1 'traditional' MI atherosclerosis)



Plaque rupture with thrombus

Secondary MI (Type 2 supply-demand mismatch)

Vasospasm

Secondary MIs common in HIV-infected individuals before age 50

Causes of Secondary MI in HIV-infected Individuals*	N (%)
Sepsis/bacteremia	100 (35%)
Cocaine induced/illicit drug	39 (14%)
Hypertensive urgency/emergency	28 (10%)
Respiratory failure	26 (9%)
Non-coronary cardiac	23 (8%)
Hypotension	15 (5%)
Procedure related	12 (4%)
GI bleed	11 (4%)
Neurologic	6 (2%)
Overdose	5 (2%)
Other/unknown	23 (8%)

***Crane et al. *Am J Epidemiol* Apr 15 2014**

Bonus Question #1:

In a 40 yo male PWH non-smoker, non-diabetic with LDL cholesterol 125 mg/dl, HDL 45 mg/dl, with an ASCVD score of 1.5%, should he be started on a statin ?

A. Yes
B. No
C. Not sure

REPRIEVE Study (started in 2015)

- 7769 HIV$^+$ men and women (30%) age 40 – 70 yo
- Low to moderate risk for statin use
- All patients on ARV Rx with CD4 > 100 cells / ul
- Randomized to pitavastatin vs placebo
- Study stopped by DSMB
- Findings:
  - 35% reduction in CV events

CASE 5

- 25 year old black woman presents with fatigue
- History of IV Heroin use; intermittently takes TDF/FTC PreP
- Exam no edema
- Work up in ER shows creatinine 8.4 BUN 79; mild anemia; mild acidemia
- In ER 10 weeks earlier; normal renal function
- U/A high grade proteinuria
- US of kidneys: Normal to increase size; no obstruction
- Rapid HIV test positive

QUESTION #5

Which of the following is the most likely cause of her renal failure?

A. Volume depletion / ATN
B. Heroin Associated Nephropathy
C. HIVAN
D. Membranous glomerulonephritis
E. Tenofovir Toxicity (PrEP)

Bonus Question #2:

In a patient with HIV Associated Nephropathy, which of the following is the most effective intervention to prevent progression to ESRD?

A. An ACE inhibitor
B. Corticosteroids
C. High Molecular Weight Dextran
D. Antiretroviral Therapy
E. A calcium channel blocker

CASE 6

- 55 year old man presents with complaints of fever / volume depletion
- HIV diagnosed in ER on rapid test
- Lymphadenopathy / splenomegaly / few petechiae / Oriented X 3
- HIV RNA 340,000; CD4= 3 cells/ul
- On no medications

Hb 8.2 gm/dl; Plt count 21,000; Creatinine 2.0

Rare schizocytes on peripheral blood smear

QUESTION #6

Which of the following is the most effective intervention to increase the platelet count?

A. Splenectomy
B. Corticosteroids
C. Plasmapheresis
D. Ethambutol + Azithromycin
E. Antiretroviral Therapy

CASE 7

- 45 year old recently diagnosed with HIV
- HIV RNA 140,000; CD4= 230 cells/ul
- Baseline labs:
- Hb 11.2 gm/dl; AST 310 / ALT 120

  140 | 101 | 5 Gluc 100

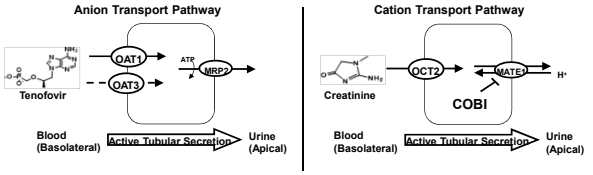
  4.2 | 28 | 1.1 eGFR = 65 ml/min
- Started on TAF/FTC+ Dolutegravir; No other medications
- Returns 4 weeks later, labs unchanged except creatinine now 1.3 mg/dl (eGFR 55)

QUESTION #7

Which of the following is the most likely cause of her increased creatinine / reduced eGFR?

A. Glomerular lesion
B. Proximal Tubule damage
C. Proximal Tubule inhibition
D. Distal Tubule damage
E. Distal Tubule inhibition

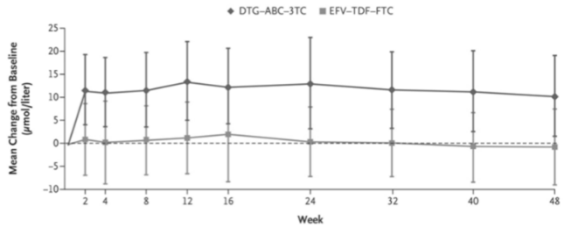
Tenofovir and COBI Interact with Distinct Renal Transport Pathways



The active tubular secretion of tenofovir and the effect of COBI on creatinine are mediated by distinct transport pathways in renal proximal tubules

Ray A, et al. Antimicro Agents Chemo 2006;3297-3304
Lepist E, et al. ICAAC 2011; Chicago. #A1-1724

Changes in eGFR



Walmsley, et al. N Engl J Med. 2013;369:1807-18.

CASE 8

- 26 year old presents with cryptococcal meningitis and newly diagnosed HIV (Rx with AMB +5FC; to fluconazole)
- HIV RNA 740,000; CD4= 23 cells/ul
- Baseline labs:
- CSF: 2 lymphocytes / protein 54 / glu 87 (serum 102)
  OP = 430 mm H_20
  Started on TAF/FTC /Bictegravir at week 2
- Returns 6 weeks later, Fever 103 and a mass in supra-clavicular region (3 x 4 cm)

QUESTION #8

Which of the following is the most likely cause of the new mass?

A. B Cell Lymphoma
B. Multicentric Castleman's Disease
C. IRIS reaction to cryptococcus
D. Mycobacteria Avium Complex
E. Bacterial Abscess from prior PICC line

IRIS

- Immune Reconstitution Inflammatory Syndrome
- Occurs 4 – 12 weeks after initial ARV administration
- Most often in patients with advanced HIV infection
- High viral load / low CD4 count
- TB, MAC, crypto, PML, KS are most common OIs
- Is **NOT** related to type of ARV therapy

CASE 9

- 48 yo Male presents with newly diagnosed HIV infection
- Asymptomatic
- **Initial: HIV RNA 160,000 c/ml**
  CD4 count 221 cells/ul
- Other labs are normal; Started on ARV Rx with DTG + TAF/FTC
- Returns for a 3 month follow up visit
- **HIV RNA < 20 c/ml; CD4 390 cells/ul**

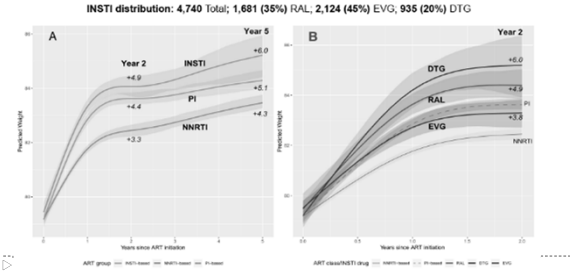
QUESTION # 9

Which of the following will most likely be present on his 3 month visit from use of dolutegravir:

A. Morbilliform skin rash (extremities)
B. 3 kg weight gain
C. Mild cognitive impairment
D. Depression
E. Anemia

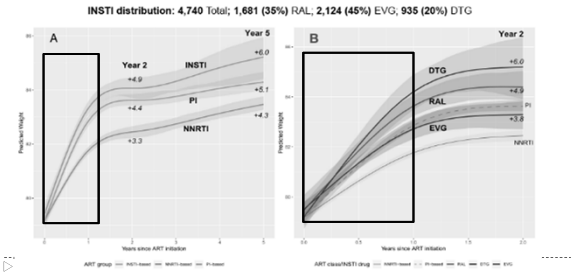
Change in Weight Overtime – NA-ACCORD

Bourgi et al CROI 2019



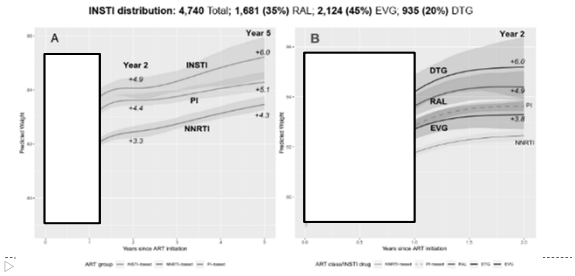
Change in Weight Overtime – NA-ACCORD

Bourgi et al CROI 2019



Change in Weight Overtime – NA-ACCORD

Bourgi et al CROI 2019



CASE 10

- 48 yo Male presents with newly diagnosed HIV infection
- Asymptomatic except for weight loss / fatigue
- **Initial: HIV RNA 160,000 c/ml**
  CD4 count 221 cells/ul
- Other labs are normal; Started on ARV Rx
- Returns for a 3 month follow up visit
- **HIV RNA < 20 c/ml; CD4 390 cells/ul**

QUESTION # 10

Assuming he remains undetectable, you tell him that his risk of transmitting HIV to his seroneg partner via sex is:

A. Virtually zero risk (< 0.2%)
B. Very low risk (< 2%)
C. Possible (<10 %)
D. It depends on which ARV regimen he's on

PARTNERS Study

- 548 heterosexual and 972 discordant gay couples followed up to 8 years
- Seropositive partner had VL < 200 c/ml
- 77,000 sexual acts without condoms
- Zero transmissions (from seropositive partner)
- Upper bound of 95% CI: 0.23 /100 CYFU
- **Sexual Transmission from a person with Undetectable Viral Load is Effectively Zero**

Rodger AJ, et al. Lancet 393: 2428-38, 2019

U=U: Undetectable=Untransmittable

Dear Colleague: September 27, 2017

https://www.preventionaccess.org/about
https://www.health.ny.gov/diseases/aids/general/the_opinion.htm
https://www.cdc.gov/hiv/library/dcl/dcl0927117.html

CASE 11

- 58 yo MSM Male presents for routine evaluation
- On ARV Rx:
- **HIV RNA < 20 c/ml; CD4 590 cells/ul**
- **He is sexually active with 3 to 4 different partners / year**
- **Receptive and insertive anal intercourse**
- **A routine annual anal PAP is collected and shows LSIL**

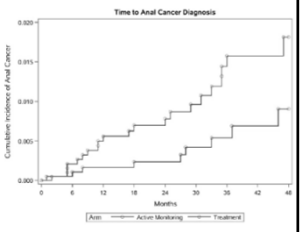
QUESTION # 11

Which of the following should be performed?

A. High Resolution Anoscopy with Biopsy
B. Digital Rectal Exam; if negative monitor for 1 yr
C. Sigmoidoscopy
D. Colonoscopy
E. Monitor only; repeat anal PAP in 6 months

Treatment of HSIL reduces risk of anal cancer by 57%

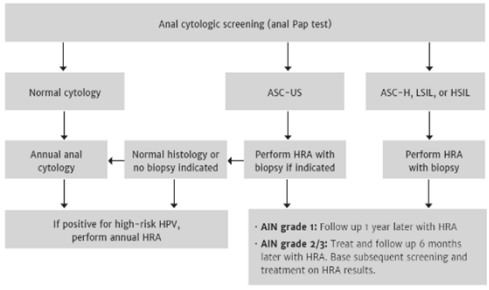
- **30 anal cancers diagnosed** in median f/u of 25.8 months
  - 9 in Treatment arm (173/100,000 PY)
  - 21 in Active Monitoring arm (402/100,000 PY)
- 8 study-related serious AEs:
  - 7 in treatment arm (3 pain, 3 abscess, 1 skin ulceration)
  - 1 in monitoring arm (infection)



Anal dysplasia

Palefsky J, et al. N Engl J Med 2022; 386:2273-2282

Figure 1. Follow-up of Anal Cytologic Screening Results



Recommendations: Screening

- ☑ Clinicians should promote smoking cessation for all patients with HIV, especially those at increased risk for anal cancer. (A3)
- ☑ For all patients aged ≥35 years with HIV, clinicians should recommend and perform DARE annually to screen for anal pathology (B3)
- ☑ Clinicians should evaluate any patient with HIV who is <35 years old and presents with signs or symptoms that suggest anal dysplasia. (A3)
- ☑ Clinicians should conduct or refer for HRA and histology (via biopsy) in any patient with abnormal anal cytology. (A2)
- ☑ Clinicians should refer patients with suspected anal cancer determined by DARE or histology to an experienced specialist for evaluation and management. (A3)

8/2/2023 NYSDOH AIDS Institute Clinical Guidelines Program

Contact me:

msaag@uabmc.edu

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HIV-Associated Opportunistic Infections II

Dr. Henry Masur

41 – HIV-Associated Opportunistic Infections II

Speaker: Henry Masur, MD

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

HIV-Associated Opportunistic Infections II

Henry Masur, MD, FIDSA, MACP
Clinical Professor of Medicine
George Washington University

6/2/2023

IDBR INFECTIOUS DISEASE BOARD REVIEW AUGUST 19-23 2023

Disclosures of Financial Relationships with Relevant Commercial Interests

- **None**

Question #1

A 50-year-old male has HIV (CD4=40 cells/uL and HIV viral load =600,000 copies/uL) has central nervous system toxoplasmosis documented by a compatible CT of the head and a positive CSF PCR for toxoplasma.

The patient also has cryptosporidiosis with 4 stools per day plus considerable nausea and thus has limited food intake.

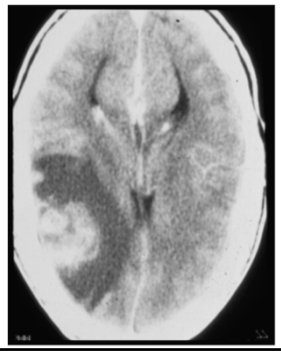
The pharmacy cannot obtain sulfadiazine or pyrimethamine.

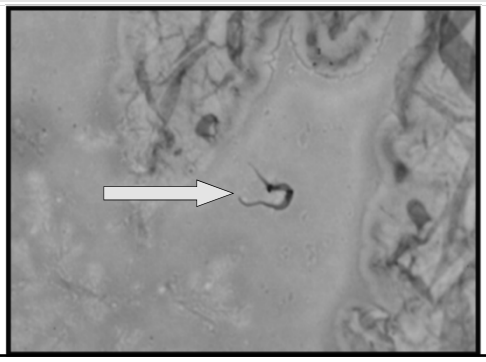
The best option for therapy of the toxoplasmosis would be:

A. Atovaquone
B. Clindamycin plus primaquine
C. Trimethoprim-Sulfamethoxazole
D. Azithromycin plus Doxycycline
E. Nitazoxanide

Question #2

- **A 39-year-old female from Brazil presents to an ER with a seizure.**
  - **Her CT scan is shown**
  - **Her HIV serology is positive**
  - **CD4 = 20/µL**
  - **VL = 100,000 copies/µL**
- **It is thought to be unsafe to perform an LP.**
- **She is started on sulfadiazine and pyrimethamine.**
- **ARVs are held until her acute problem is under control.**
- **After 10 days, she has not improved and a brain biopsy is performed (see image).**



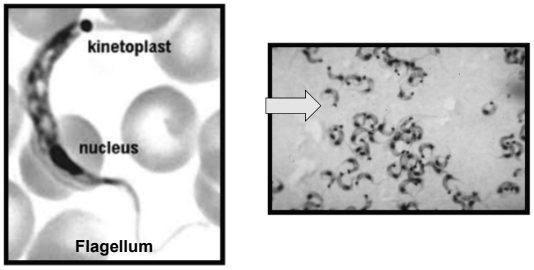


Question #2

What is the most likely diagnosis?

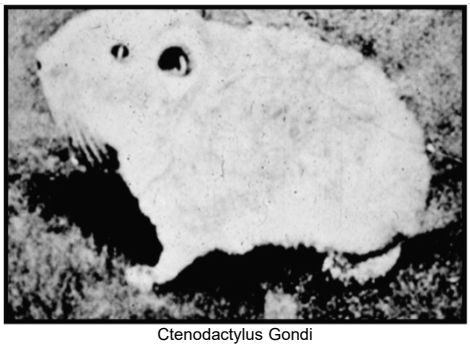
A. Toxoplasmosis
B. Cysticercosis
C. Leishmaniasis
D. Trypanosomiasis
E. Acanthamoeba

Trypanosoma cruzi
Blood Smear and CSF

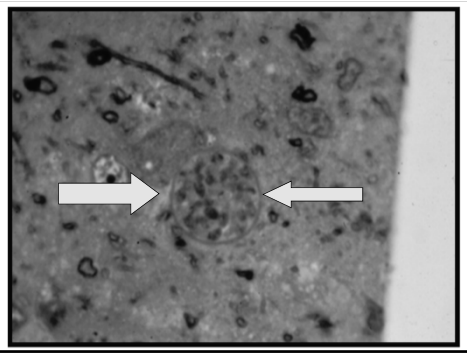


Badero et al, AIDS THERAPY, 4th Ed

Toxoplasmosis



Ctenodactylus Gondi



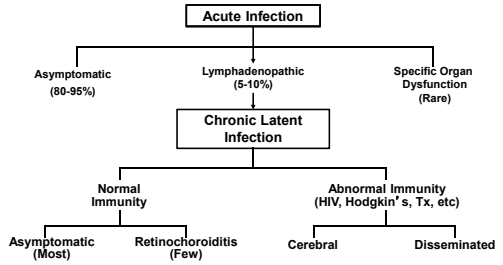
Incidence of Toxoplasmosis

- **Seroprevalence in General Population**
  - **US-20%**
  - **Parts of Europe, Africa: 80%**
- **Clinical disease common (30%) before era of ART and chemoprophylaxis**
- **Disease "never" occurs in seronegative patients except**
  - **Acute infection**
  - **Insensitive assay**
  - **Loss of ability to make antibody**

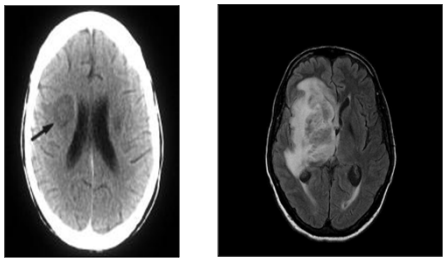
Transmission of Toxoplasma

- **Feline feces (cats, but also lions etc)**
  - Oocysts begin to be excreted 20 - 24 days post infection
  - Excretion persists 7 - 21 days
- **Rare Meat (Lamb>Beef>Pork)**
- **Unusual**
  - Raw shellfish, goat milk (reported 2009-2010)
  - Iatrogenic
    - Transfusion/Needle injury/transplant
- **Congenital**
  - Acute acquisition by mother during gestation
  - Chronic infection in immunosuppressed mother

Clinical Manifestations of Toxoplasmosis when Acquired Post-Partum



CNS Toxoplasmosis



Non Contrast CT | Flair MRI

Evaluation of CNS Mass Lesions in Patients with HIV/AIDS

- Toxoplasmosis
- Lymphoma
- Tuberculosis
- Fungus
- Nocardia
- Bacterial
- Syphilis
- Kaposi
- Chagoma
- Glioblastoma

Radiologic Results
- Non-specific although certain features suggestive
- Look for Extra CNS lesions for biopsy

Laboratory Studies to Perform
- Serology: Toxo IgG, Toxo PCR
- Serum Crypt Ag and Histo ag
- Blood culture - AFB, fungus
- CSF - Crypt Ag
  - PCR (EBV, CMV, Toxo)
- Urine - Histo Ag

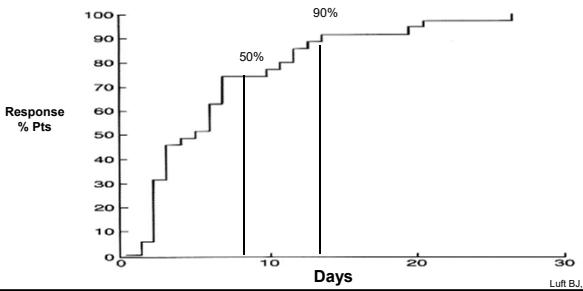
Response to Empiric Therapy

Empiric Diagnosis of CNS Toxo

- **When Initiating Therapy**
  - **Compatible CT or MR *plus***
  - **CD4 Count <100 cells/uL *plus***
  - **Toxo IgG antibody positive *plus***
  - **Not on TMP-SMX prophylaxis**
- **Post Initiation of Therapy**
  - **Radiologic and Clinical Response within 2 weeks**

Time to Neurologic Response for CNS Toxo

35 CNS Toxo Patients Treated with Clindamycin - Pyrimethamine



Luft BJ, NEJM 1993

Definitive Diagnosis of Cerebral Toxoplasmosis

- **Brain biopsy**
- **Serum PCR**
- **CSF PCR**

Therapy for Cerebral Toxoplasmosis

- **Preferred Regimen**
  - Sulfadiazine plus pyrimethamine plus leucovorin (PO only)
    - Expensive, not universally available
  - **Trimethoprim-sulfamethoxazole (PO or IV)**
- **Alternative Regimens**
  - Clindamycin plus pyrimethamine
  - Atovaquone +/- Pyrimethamine

Note:
Sufladiazine and Pyrimethamine may be unavailable or unrealistically expensive

Adjunctive Therapies for CNS Toxoplasmosis

- **Corticosteroids**
  - Not routine
  - Only if increased intracranial pressure/symptoms/signs
- **Anticonvulsants**
  - Not routine
  - Only after first seizure

Could The Exam Test on Obstetrical Toxoplasmosis?

Drugs Are Probably A "Look Up"

- **Initial therapy of Mother**
  - Acquisition <18 weeks: Spiramycin 1g PO TID
  - Acquisition ≥ 18 weeks: Pyrimethamine + sulfdiazine and folinic acid
- **Fetal Assessment**
  - Amniocentesis for toxo PCR to be done at 18 weeks gestation or later
  - Fetal ultrasonography every 4 weeks until delivery
- **Fetal Management**
  - Amniotic fluid PCR positive and/or fetal ultrasounographic findings suggestive of congenital toxo
    - Pyrimethamine + sulfadaiazine + folinic acid until delivery
    - Is fetus viable and what is risk consideration by parents
  - No evidence of fetal infection (negative AF PCR, no fetal ultrasonographic abnormalities)
    - Continue initial therapy

Primary Prevention of Toxoplasmosis in Patients with HIV

- **Indication**
  - Positive IgG and CD4<100 cells/uL
- **Drugs**
  - First Choice
    - TMP-SMX (one ds qd)
  - Alternatives
    - Other dosing regimens for TMP/SMX
    - Dapsone-Pyrimethamine
    - Atovaquone +/- Pyrimethamine

Primary Prevention of Toxoplasmosis in PLWH

- **For patients with CD4<200 who are on TMP-SMX or atovaquone for PCP prophylaxis**
  - Nothing more is needed
- **For patient on Aerosol Pentamidine or Dapsone for PCP prophylaxis**
  - If on dapsone: add pyrimethamine
  - If on Aerosol pentamidine: not protected-
    - Consider switching to atovaquone if seropositive for toxo

Mycobacteria Species

- **M. tuberculosis***
  - M. bovis
  - M. africanum
- **Mycobacteria Other Than TB (MOTT)**
  - M. avium complex*
  - M. kansasii
  - M. hemophilum
  - M. genavense
  - M. terrae
  - M. scrofulaceum
  - M. xenopi

Question #4

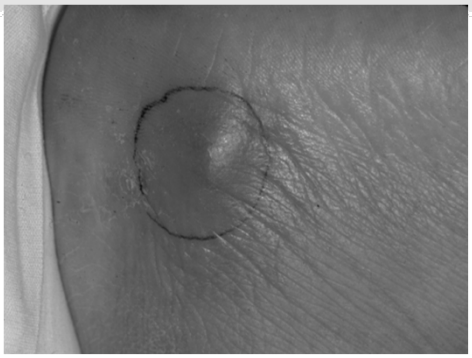
A 45-year-old male with HIV (CD4<10 cells/cc3, VL> 100k) has been taking TMP-SMX and Efavirenz-Tenofovir-Emtricitabine only intermittently.

For the past 3 weeks he has had a low grade fever, mild weight loss, and a lesion which is shown on the next slide.

Aspiration of the lesion showed many AFB rods, non branching, but after 6 weeks nothing grew.

The lesion is to be aspirated again.

See next slide



Question #4

What advice do you give the lab and hospital epi?

A. This should grow at 37°C
B. This should grow on conventional TB culture media
C. This most likely was acquired by acupuncture or some other manipulation.
D. This is treatable with trimethoprim-sulfamethoxazole
E. This can be cultured only at 32°C with iron enriched medium

Tuberculosis and HIV

Susan Dorman has reviewed this in detail

- **Major Issues for Boards**
  - **Most of US cases were acquired outside of US**
  - **Positive PPD = 5mm for PWH**
  - **Two indications for prophylaxis, not one**

TB Prophylaxis in PWH

- **There Are <u>TWO</u> Indications for PWH**
  - Positive screening test for LTBI, and
    - No evidence of active TB disease, and no prior history of treatment for active disease or latent TB infection
  - Close contact with a person with infectious TB
    - <u>Regardless of screening test result</u>

TB Prophylaxis In Pregnancy in US

- **When to Treat**
  - Probably defer if indication is positive PPD or IGRA until post delivery
    - Especially if on effective ART
  - Give if exposed to active case
- **What to Treat**
  - Too controversial for exam
    - Controversy over safety of INH
      - Especially important to give pyridoxine
    - Rifapentine probably contraindicated

Prevention of TB

- **Options**
  - **3HP: Weekly INH/Pyr plus Rifapentine x 12w**
  - **3HR: Daily INH/Pyr plus rifampin x 3 months**
  - **INH: Daily x 6-9 months**
  - **4R: Daily rifampin x 4 months**
  - **1HP: Daily INH/Pyr plus Rifapentine x 4 w**
- **Recommendations are In Flux**
  - **CDC, WHO, and NIH Guidelines Are Not Fully Harmonized and each regimen has advantages/disadvantages**
  - **INH alone can be used for any ART regimen**
    - **its never a "wrong" regimen for an exam but…adherence and hepatotoxicity are problems**
  - **Look up compatibility of other drugs with specific ART regimens**
- **For Exam**
  - **None are wrong as long as drug interactions and ART regimens are considered**
  - **Many prefer the shorter regimens**

One Question They Could Ask Whether Pregnant or Non Pregnant…..

- **If the serum ALT or AST levels increase to**
  - greater than five times the upper limit of normal without symptoms or
  - Greater than three times the upper limit of normal with symptoms
    - (or greater than two times the baseline value for patients with baseline abnormal transaminases)

LTBI treatment should be stoppend

Therapy for HIV Positive Patients With Active TB

- **Always start TB therapy first, and then start ART later depending on CD4 count and severity of disease**
  - **If CD4<50, or if pregnant at any CD4, start ART within 2 weeks**
  - **If CD4 >50, start within 8 weeks**
- **Only use regimens to treat active TB if the drugs are DAILY**
- **Failing Therapy?**
  - **Consider IRIS vs drug resistance or non adherence**
- **Treatment of Drug Resistant TB**
  - **Too complicated for exam!**

Active TB disease: Treatment Durations Regardless of HIV Status

Review from Susan Dorman

months	1	2	3	4	5	6	7	8	9	10	11	12
Pulmonary (including pleural)	"RIPE"		Rifampin + INH									
Pulmonary that is cavitary plus cultures still pos at completion of 2 months of tx	Rifampin INH PZA EMB		Rifampin + INH									
Bone and Joint (6 to 9 months)			Rifampin + INH				Consider extending to 9 mos					
CNS (9 to 12)			Rifampin + INH							Consider extending to 12 months		

Active TB disease: Treatment Durations Regardless of HIV Status

Review from Susan Dorman

2022 Update: 4 Month-119 Doses for TB Likely To Be Drug Sensitive

4 Month Regimen Recommended for HIV-TB if CD4>100 and ART is Efavirenz Based

- **INH + Rifapentine + Moxifloxacin + Pyrizinamide** **Months 1+2**
- **INH + Rifapentine + Moxifloxacin** **Months 3+4**

5 of 7 weekly doses should be DOT (Directly Observed Therapy)

Bone and Joint (6 to 9 months)	EMB	Rifampin + INH	Consider extending to 9 mos	
CNS (9 to 12)		Rifampin + INH		Consider extending to 12 months

Non Tuberculous Mycobacterial Infections in HIV Infected Patients

You Need Microbiologic or Epidemiologic Clue on Exam!

• Avium complex	Dissemination
• Hemophilum	Cutaneous abscesses
• Bovis	Adenitis, Dissemination
• BCG (Bovis)	Dissemination
• Genovense	Dissemination
• Scrofulaceum	Adenitis, Dissemination
• Xenopi	Lung nodules or infiltrates
• Malmoense	Cavitary lung, CNS ring lesions
• Chelonei	Skin, Soft Tissue, Joint, Bone

Mycobacterium Avium Complex

Confusing Terminology: Some Labs Are Identifying MAC Species Not Clear If There Is Clinical Benefit in Identifying

- **M. avium**
- **M. intracellulare**
- **M. chimaera**
- **M. colombiense**
- **M. arosiense**
- **M. marseillense**
- **M. timonense**
- **M. vulneris**
- **M. yongonense**

Question #3

An HIV-infected patient is admitted to the hospital with three weeks of cough, fever, 25 lb weight loss, and anorexia. He is found to be HIV infected and to have a CD4 count =10 cells/uL and VL =500k

- **His chest x-ray shows diffuse interstitial infiltrates**
- **BAL =PCP by immunofluorescence**

Two weeks later while the patient is still in the hospital due to disposition issues, the lab reports

- **Three blood cultures and the BAL are growing a mycobacterium**
- **Probe = Mycobacterium avium complex**

What type of isolation is appropriate?

A. None
B. Droplet
C. Respiratory
D. Contact
E. Contract and droplet

Mycobacterium Avium Intracellulare Complex

- **Epidemiology**
  - Ubiquitous in dirt, animals etc
- **Transmission**
  - Respiratory via dust
  - GI via food, water
  - Person-to-person unlikely
  - Environmental isolates correlate poorly with human isolate

Mycobacterium Avium Intracellulare

- **Risk factors**
  - CD4 < 50 or High VL
  - Colonization: GI / respiratory
- **Incidence pre ART: 20-40% (North America)**
  - Now declining with ART and probably non-ART related factors
- **Acute Disease: Clinical manifestations**
  - Fever, wasting, nodes, liver, spleen
  - Rare as cause of lung disease
  - Lab: Alk Phos, Hg, Albumen

Mycobacterium Avium Intracellulare Diagnosis

- **Source of Isolates**
  - **Blood**
    - **Bactec (7-14 days),**
  - **Sputum/Stool/Urine**
    - **Low predictive value**
- **Lab Identification**
  - **Specific DNA Probes for specimens/ cultures**
  - **MALDI-TOF**

MAC: Susceptibility Testing

Recommended for primary isolates

- Validated CLSI (Clinical Laboratory Standards Institute)
  - Clarithromycin
  - Amikacin
- Other drug susceptibility results not clearly associated with clinical outcome

Treatment for MAC

- Antiretroviral Therapy
  - Start as soon as possible after diagnosis/within 2 weeks
- Specific Therapy
  - Clarithro (or Azithro) + Ethambutol
    - Rifabutin optional 3rd drug: use if severe disease ("high burden of organisms")
    - Beware drug interactions with clari or rifabutin

Treatment for MAC

- Response:
  - Fever should decline within 2-4 weeks
  - Blood cultures should be negative in 2-4w
  - Repeat blood cultures only if symptoms
- Stop chronic suppression:
  - CD4 > 100 x 6M, asx and therapy >12 m

Salvage Therapy for MAC Not For Boards

- No evidence-based standard
- Logical to be guided by in vitro susceptibility testing
  - Not standardized for MAC other than macrolides and amikacin
  - Options
    - Amikacin, Ciproflox, Moxiflox, Mefloquine, Linezolid, Bedaquiline

~~Primary MAC Prophylaxis 2021~~

- Primary prophylaxis against disseminated MAC disease is **NOT** recommended if ART initiated immediately
  - Primary MAC prophylaxis, if previously initiated, should be discontinued if person is on ART

What Is This?

Immune Reconstitution Inflammatory Syndrome

- Definition
  - Worsening manifestations or abrupt /atypical presentation of infection or tumor when ART started
    - Paradoxical-exacerbation of pre-existing infection or tumor
    - Unmasking-exacerbation of previously occult infection/tumor
- Timing
  - Few days to 6 months after ART initiated
  - Viral load drop more relevant than CD4 rise
    - (better lymphocyte function>number)

Immune Reconstitution Inflammatory Syndrome

- Predictors
  - Pre therapy low CD4 or high VL
  - Prior OI or short therapy for OI
  - High pathogen load
- Outcome-Morbidity Can Be Severe
  - Obstructed bowel, biliary tract, ureter, bronchus
  - Myocarditis, meningeal inflammation/increased ICP, serositis (pleura, peritoneum, pericardium)

Pathogens Commonly Associated with IRIS

- Mycobacterium avium complex
- Mycobacterium tuberculosis
- Cryptococcus neoformans
- Many others
  - CMV retinitis, HBV
  - Mucocutaneous HSV and VZV
  - PCP, Histo
  - PML
  - KS

Examples of IRIS

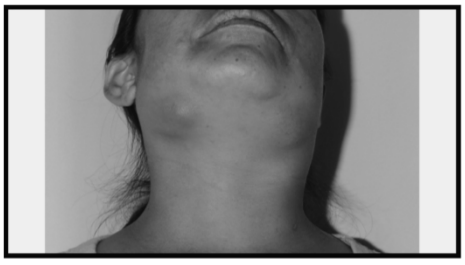
PATHOGEN	NOMENCLATURE	TYPICAL/CHARACTERISTICS OF THE DISEASE
Mycobacterium tuberculosis	TB-IRIS	Paradoxical exacerbation of TB
Nontuberculous mycobacteria (NTM)	NTM-IRIS	Mainly lymphadenitis, also pulmonary and abdominal diseases
Bacille Calmette-Guérin (BCG)	BCG-IRIS	Necrotizing regional lymphadenitis
Mycobacterium leprae	Leprosy-associated IRIS	Borderline and type 1 reactional state
Cryptococcus neoformans	C-IRIS	Mainly meningitis, also lymphadenitis
Pneumocystis jiroveci	Pneumocystosis-associated IRIS	Paradoxical exacerbation of pneumonitis
Cytomegalovirus (CMV)	CMV retinitis after ART or immune recovery uveitis	Acute retinitis after commencing ART or uveitis
JC polyomavirus	PML-IRIS	Multifocal leukoencephalopathy
Human herpesvirus 8	KS-IRIS	Rapid progression of existing and/or new KS lesions
Hepatitis B or C virus	Hepatitis B or C virus-associated IRIS (that may mimic DILI)	Hepatitis flare and/or liver enzyme elevation
Varicella-zoster virus		Dermatomal or multidermatomal zoster and rarely myelitis after ART
Herpes simplex virus		Herpes Lesions with exaggerated inflammation and rarely myelitis or encephalitis after ART
Molluscum contagiosum virus	Inflammatory molluscum contagiosum	Inflamed molluscum lesions
* **Malassezia spp.**	Inflammatory seborrheic dermatitis	Abnormally inflamed seborrheic dermatitis

Cecil Textbook French and Meintjes)

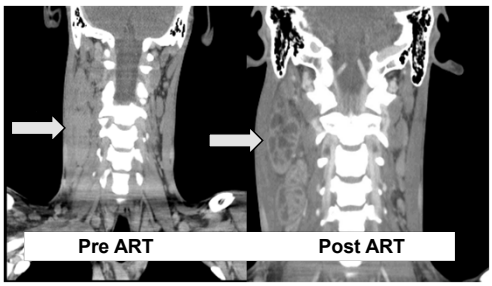
Management of IRIS

- Reassess Diagnosis
  - Evaluate for concurrent, additional OIs and tumors
- Treat IRIS
  - Continue ART
  - Treat identified pathogen-usual practice without data
  - NSAIDS or Corticosteroids
    - Prednisone 20-40mg qd x 4-8 weeks

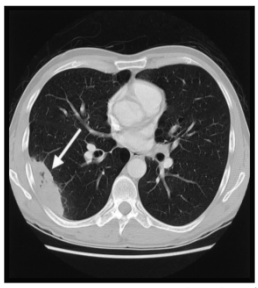
Immune Reconstitution Inflammatory Syndrome (Mycobacterium avium complex)



MAC IRIS in Patient with HIV



CT Scan: Pleural-Based MAC



Phillips P et al. Clin Infect Dis 2005;41:1483

Questions?

Examples of IRIS

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* Cecil Textbook French and Meintjes)

42

Pharyngitis Syndromes Including Group A Strep Pharyngitis

Dr. Karen Bloch

42 – Pharyngitis Syndromes and Group A Strep Pharyngitis

Speaker: Karen C. Bloch, MD

IDBR INFECTIOUS DISEASE BOARD REVIEW AUGUST 19-23 2023

Pharyngitis Syndromes
Including Streptococcal Pharyngitis

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

7/5/2023

IDBR INFECTIOUS DISEASE BOARD REVIEW AUGUST 19-23 2023

Disclosures of Financial Relationships with Relevant Commercial Interests

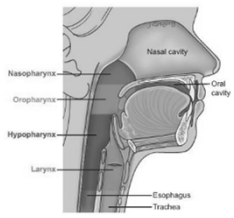
- **None**

Special Thanks to Dr. Bennett Lorber!

Think Like a Realtor

Think Like A Realtor

Pharyngitis

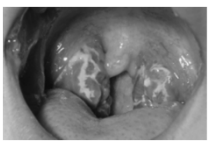


- Small square footage
- Micro-neighborhoods
- Regional differences

Case 1

IDBR INFECTIOUS DISEASE BOARD REVIEW AUGUST 19-23 2023 PREVIEW QUESTION

38yo female with 1 day of sore throat and fever.
Childhood history of anaphylaxis to penicillin.
Physical exam
- T=102.3
- HEENT-tonsillar purulence
- Neck-Tender bilateral anterior LAN



Labs:
- Rapid strep antigen test negative

42 – Pharyngitis Syndromes and Group A Strep Pharyngitis

Speaker: Karen C. Bloch, MD

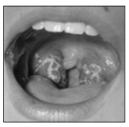
Question 1

2023 PREVIEW QUESTION

What is the most appropriate antimicrobial treatment?

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

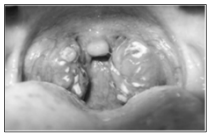
Group A streptococcus

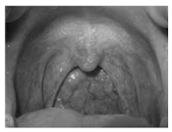


- AKA *Streptococcus pyogenes*
- 5-15% sore throats in adults
- Usually *self-limited* infection (even untreated)

Differentiating Pharyngitis

GAS VS **Viral pharyngitis**





Differentiating Pharyngitis

GAS	Viral pharyngitis
• Acute onset • Fever • Lymphadenopathy • Exposure to contact with streptococcal pharyngitis	• The 3 C's – Conjunctivitis – Coryza – Cough • Other symptoms – Diarrhea – Ulcerative stomatitis – Hoarseness

How Specific are Clinical Findings?

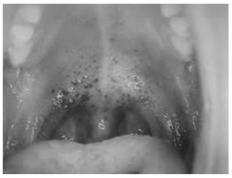
- Modified CENTOR score
  - Can't cough
  - Exudate
  - Nodes
  - Temperature
  - OR age <15 yr (+1) or >44 years (-1)

Points	Strep probability
0 or 1	< 10%
2	11 -17%
3	28 -35%
4 or 5	35-50%

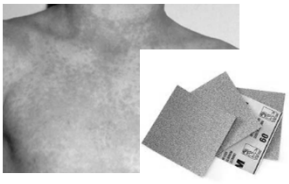
IDSA guidelines recommend antibiotics only following a RADT positive testing.

Streptococcal Clues

- Palatal petechia



- Scarletina

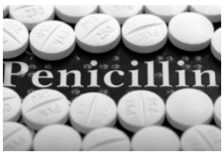


Laboratory Diagnosis

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

Treatment for GAS Pharyngitis

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

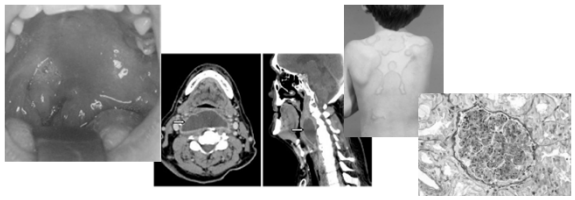


PCN Allergic:

- cephalosporin, clindamycin, macrolides (+/-)
- Not recommended: tetracyclines, sulfonamides, fluoroquinolones

Secondary Complications

- Infectious complications
- Immunologic complications



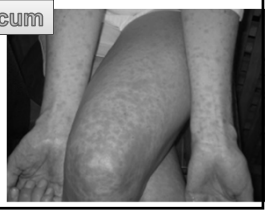
Pharyngitis and….

Pharyngitis & Rash

- Young adult with fever, sore throat, tonsillar exudate, scarletinoform rash BUT…Negative RADT and culture

Arcanobacterium haemolyticum

- Gram positive rod
- Rash in >50%, mimics strep
- Rarely life-threatening sequelae



Pharyngitis & Rash

- Acute HIV

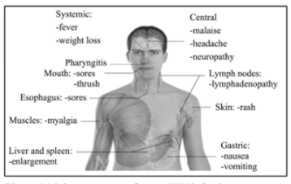
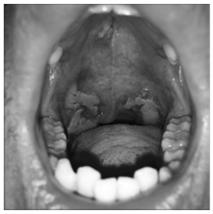


Figure 1 Main symptoms of acute HIV infection

- Secondary syphilis



42 – Pharyngitis Syndromes and Group A Strep Pharyngitis

Speaker: Karen C. Bloch, MD

Pharyngitis after Receptive Oral Intercourse

Neisseria gonorrhoeae	Herpes simplex virus
• Diagnose by nucleic acid amplification test of pharyngeal swab	• HSV-2 • Usually with initial infection • Tonsillar vesicles • Labial or genital ulcers variably present

Pharyngitis & Conjunctivitis

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

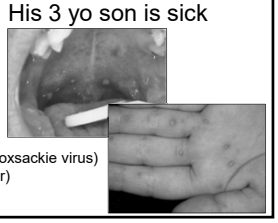
Adenovirus

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

Pharyngitis and Vesicles

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

Hand, Foot, and Mouth disease



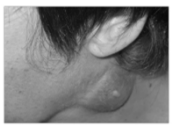
- Caused by enteroviruses (most common Coxsackie virus)
- More common in kids (often serve as vector)

Case 2

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

Case 2

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



CMAJ 2014;186:E62

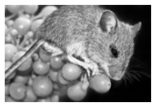
Question 2

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

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

Oropharyngeal Tularemia

- Uncommon in the US
- Transmission through ingestion (or rarely inhalation)
  - Inadequately cooked game
  - Contaminated water
  - Rodent contamination
- Exudative tonsillitis, suppurative LAN
- Treatment: streptomycin or gentamicin, with doxycycline or quinolone 2nd line

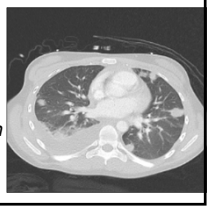


Pharyngitis and Chest Pain

- 20 yo college student with sore throat, fever and chills with a positive RADT for GAS. Despite oral amoxicillin, develops new onset of cough and pleuritic CP; CT below

Lemierre syndrome

- Septic phlebitis of internal jugular vein
- Often follows GAS pharyngitis or mono (EBV)
- Classic cause is *Fusobacterium necrophorum*
- Causes septic pulmonary emboli

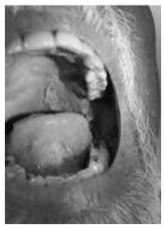


Pharyngitis & TNF-alpha inhibitors

- 69yo man on infliximab presents with 2 months of painful oral ulcer and 20 lb wt loss

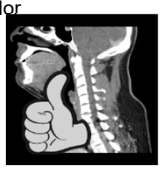
Oropharyngeal Histoplasmosis

- Can mimic oral malignancy
- Denotes disseminated disease



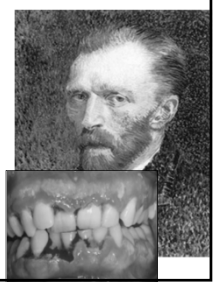
Extra-Tonsillar Infections: 1

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



Extra-Tonsillar Infections: 2

- Vincent Angina
  - AKA Trench mouth
  - AKA acute necrotizing ulcerative gingivitis
  - Bad breath (mixed anaerobes)
  - Painful
  - Sloughing of gingiva



Extra-Tonsillar Infections: 3

- Ludwig Angina
  - Cellulitis of floor of the mouth
  - Often starts with infected molar
  - Rapid spread with potential for airway obstruction
  - Fevers, chills, drooling, dysphagia, muffled voice, woody induration of neck
  - Mixed oral organisms

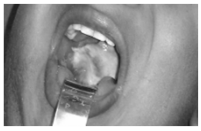
Case 3

PREVIEW QUESTION

- A 32-year-old woman is seen for a sore throat and fever for 4 days
- Recently returned from her sister's wedding in Kazakhstan
- She c/o odynophagia, and a low-grade fever. Today, she noted a choking sensation, prompting medical evaluation.

PREVIEW QUESTION

- Exam:
  - HEENT: Submandibular swelling with gray exudate coating posterior pharynx.
  - An S3 gallop is heard.



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

Question 3

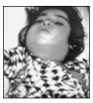
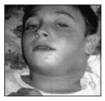
PREVIEW QUESTION

The most likely diagnosis is?

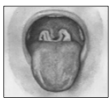
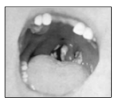
A. Streptococcal pharyngitis
B. Kawasaki disease
C. Vincent angina
D. Diphtheria
E. Candida

Buzz words and Visual Associations

Bull neck:

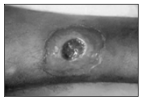




Grey pseudomembrane: extends onto palate or uvula; bleeds when scraped

Other clues

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



Noninfectious Mimics

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

42 – Pharyngitis Syndromes and Group A Strep Pharyngitis

Speaker: Karen C. Bloch, MD

43

Photo Opportunities: Images You Should Know for the Exam

Dr. John Bennett

43 – Photo Opportunities: Images You Should Know for the Exam

Speaker: John Bennett, MD

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

Photo Opportunities: Images You Should Know for the Exam

John E. Bennett, MD
Bethesda, Maryland

7/23/2023

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

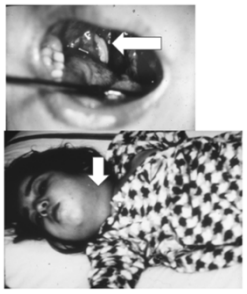
Disclosures of Financial Relationships with Relevant Commercial Interests

- **None**

Question 1: pharyngitis

A family of Syrian refugees had just arrived in the USA when their 8 yr old daughter fell ill with a sore throat so severe she was having trouble swallowing and had a gray membrane over one tonsil and submental edema. Unless treated appropriately, this child may develop which of the following complications

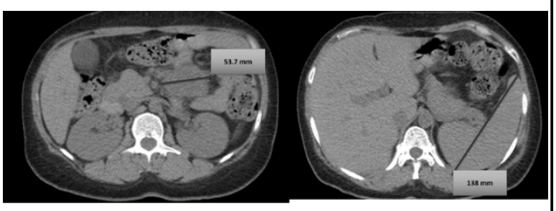
A. Bell's palsy
B. Toxic shock
C. Cardiac valve vegetations
D. Cardiomyopathy
E. Pulmonary septic emboli.



Question 2 Abnormal abdominal CT

38 yr female presented to ER with week of fatigue and muscle cramps. Ten year history of multiresistant HIV. Variable compliance.Meds past month: darunavir/cobicistat, zidovudine, dolutegravir. Born in Ethiopia and visited one week last year. Has kitten at home.
Lived in USA 15 yr
WBC 3.5, plt 150k, Hgb 9, CD4 33, viral load undetectable.
IGRA indeterminate.
Exam: afebrile. Unremarkable exam.
CXR: right midlung infiltrate
Abdominal CT : mesenteric mass, splenomegaly

Large mesenteric mass, splenomegaly



Which of the following is most likely

- A. Kaposi's sarcoma
- B. Diffuse large B cell lymphoma
- C. Visceral leishmaniasis
- D. Mycobacterium avium complex
- E. Bartonella henselae

43 – Photo Opportunities: Images You Should Know for the Exam

Speaker: John Bennett, MD

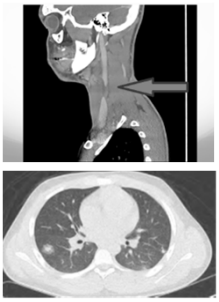
Question 3: skin and lung lesion

A 40 yr old male farmer from Birmingham, Alabama presented with a leg lesion of several years duration with he attributed to a rough seat on his tractor. He also complained of a chronic "cigarette" productive grayish sputum. He lived on a farm with his aunt, who was healthy and a stray cat he has adopted. He drank well water . He was talking no medications. He had no history of recent travel, alcohol or drug abuse. He was afebrile and had normal lab work. A PAS of his skin biopsy and his chest ray is shown.

- The most likely source of his skin lesion was
- Pigeon droppings
- Moist soil
- Well water
- Coughing by an infected person
- His cat

Question 4: bacteremia

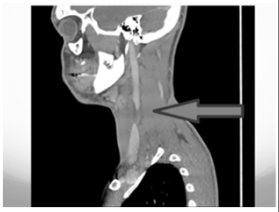
An 18-year-old male had the acute onset of sore throat, followed in two days by high fever. On presentation in the emergency room he was acutely ill, with a temperature of 105°F. Chest x-ray, followed by the CT shown here, showed a nodule in the left lower lung field. Swelling and tenderness in the right anterior cervical triangle led to the CT with IV contrast shown here.



Question #4

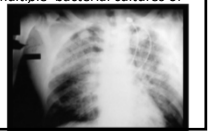
Blood cultures were likely to reveal which of the following:

A. Aerobic Gram positive rod
B. Aerobic Gram negative rod
C. Anaerobic Gram positive rod
D. Anaerobic Gram negative rod
E. Endemic mycosis



Question 5: pneumonia

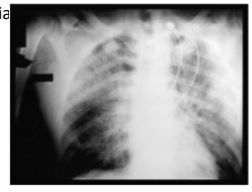
- A 22-year-old previously healthy hiker presented with a 4 day history of malaise, and myalgias, dry cough and progressive dyspnea. Admission temperature was 39.2°, pulse 110, respirations 28 and BP110/70. On exam, diffuse crackles were heard at the posterior chest. Hematocrit was 52; WBC was 9,800; platelets 110,000,.Because of increasing respiratory distress, the patient was intubated. Over the next 24-48 hours, the patient produced scanty respiratory secretions, and multiple bacterial cultures of secretions obtained through the endotracheal tube were negative , as was a respiratory panel PCR.



Question 5 continued

The patient had just returned from a hiking trip in Idaho and had been camping out in a cabin and lean-tos where he saw numerous mice. The cabin had the odor of mouse feces. The most likely cause of the pneumonia

A. Sin nombre virus
B. Legionella
C. Bartonella quintana
D. Francisella tularensis
E. Borrelia hermsii

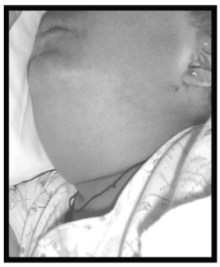


43 – Photo Opportunities: Images You Should Know for the Exam

Speaker: John Bennett, MD

Question 6: neck swelling

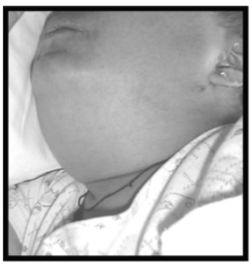
This 25-year-old woman from Guatemala had been given antithymocyte globulin and cyclosporine for her aplastic anemia but had as yet not responded and remained profoundly aplastic when she was observed to have over 24 hours to develop this swelling underneath her chin.



Question 6 continued

There no lesions visible in the front of her mouth but she couldn't open very wide because that caused pain. She took sips of fluid without discomfort but was very nauseated and drinking very little.

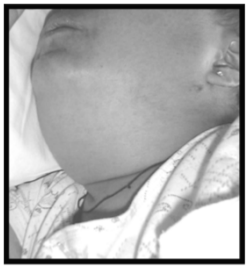
The swelling was firm and not apparently red or painful. She could speak softly without obvious hoarseness.



Question 6 continued

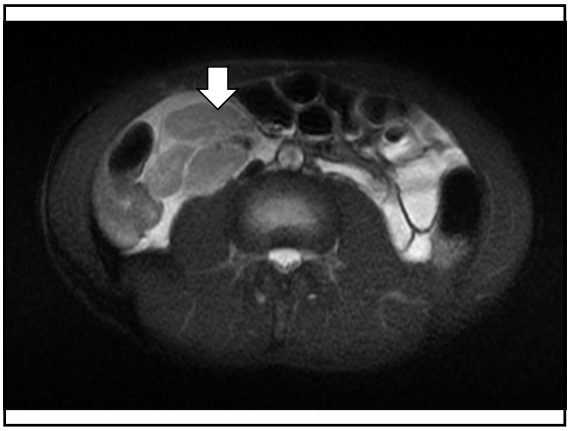
The most likely source of this infection is which of the following:

A. Herpetic stomatitis
B. Dental abscess
C. Retropharyngeal abscess
D. Vincent's angina
E. Lemierre's syndrome



Question 7: mesenteric adenitis

- 12 year old boy in Washington, DC presents with the acute onset of right lower quadrant pain and fever. No pets. No recent travel. Private school. Vaccinations up to date.
- Exam: Temp 102. RLQ tenderness and rebound. Good bowel sounds. WBC 12, 500
- MRI: large mesenteric nodes
- Chest xray: normal



Question 7

- The most likely organism causing this infection is:
- A. Mycobacterium tuberculosis
- B. Yersinia pseudotuberculosis
- C. Salmonella typhi
- D. Mycobacterium avium-intracellulare
- E. Mumps

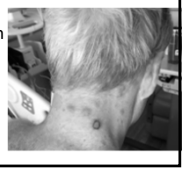
43 – Photo Opportunities: Images You Should Know for the Exam

Speaker: John Bennett, MD

Question 8: skin lesions and fever

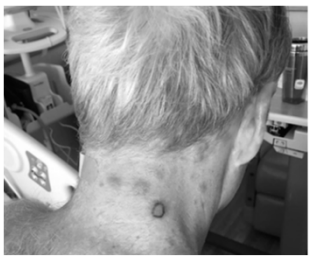
- A 52-year-old male in prior good health presented with increasing fatigue over the past month and was found to have myelodysplastic syndrome with excessive blasts.
- Hemoglobin was 7.0, platelets 70,000 and ANC 598/cu mm.
- He was transfused with four units of packed red blood cells and started on cefepime because of fever up to 38.5C.
- Routine chest xray was normal, as were admission blood and urine cultures. On the third hospital day, multiple slightly tender, painless red skin lesions appeared on his neck, trunk and lower extremities.

Note that in the photo, a black circle has been drawn around one of the lesions.



Question 8

The most likely diagnosis is
A. Cryptococcosis
B. Ecthyma gangrenosum
C. Pyoderma gangrenosum
D. Leukemia cutis
E. Sweet syndrome

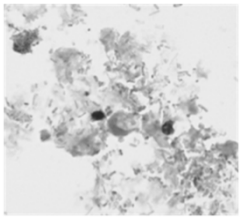


Question 9: outbreak of diarrhea

- Owners of an aquatic park were notified by the Public Health Department that 8 children had developed diarrheal disease in the week following their visit to the park. The children had profuse, watery diarrhea, abdominal cramping, and low-grade fevers. The illnesses were all self limiting. The children all reported eating hot dogs with catsup and various flavors of "slurpies" (shaved ice drinks) at the park.
- Parasitology examination of their stool specimens was positive with acid-fast organism, 4-6 µm in diameter.

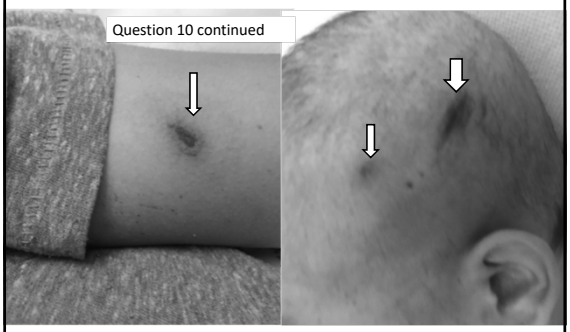
Question 9

The most likely source of the outbreak was:
A. Shaved ice
B. Hands of a food server
C. Hot dogs
D. Contaminated water
E. Syrups on the shaved ice



Question 10: skin lesions and fever

- 21 yr male with ALL diagnosed 14 months prior, multiple relapses after chemotherapy and after CD19 CAR T cell therapy 4 months ago, followed by cytokine release syndrome. Relapsed. Retreated with alemtuzumab, etoposide , ifosfamide, remained pancytopenic. On transfer he arrived with temp 38.4C then afebrile, with 4 skin lesions on his head and arms. WBC 0.05K, plt 17K, ALT 77. CT of chest, abdomen, head negative. Sinuses: fluid in some sinuses. Vancomycin, meropenem, GCSF, plt tx, RBC tx started. Liposomal amphotericin B started . Skin biopsy obtained. Routine blood culture is growing a fungus.



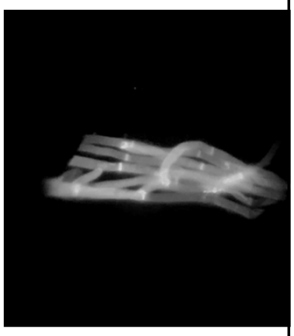
43 – Photo Opportunities: Images You Should Know for the Exam

Speaker: John Bennett, MD

Question 10 continued

Calcofluor white stain of skin biopsy impression smear showed hyphae. The most likely diagnosis is:

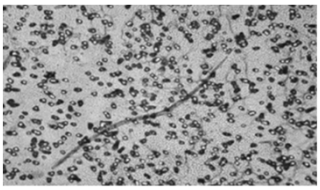
a. Aspergilllosis
b. Mucormycosis
c. Fusariosis
d. Scedosporiosis
e. Candidiasis



Question 11: abnormal blood smear

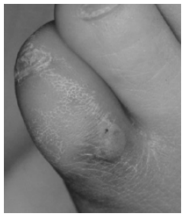
The 35 yr year old recent immigrant from Nigeria has this organism found in his blood smear. He is at risk of having which of the following if untreated:

1. Blindness
2. Lymphedema
3. Cardiomyopathy
4. Encephalopathy
5. Hepatic cirrhosis



Question 12: fever and skin lesions

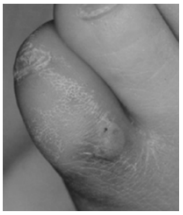
A 38-year-old marine sergeant reported to sick bay a week after shore leave with the acute onset of fever, malaise and five pustular skin lesions including the one shown here.
He is acutely ill but his vital signs (other than temperature) are normal. He had pain on flexion and slight swelling in the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



Question 12

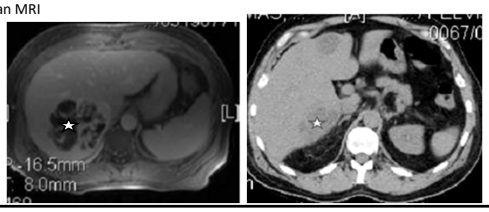
The most likely organism to grow from his blood culture in 2-3 days is which of the following:

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



Question13: liver lesion

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



Question 13

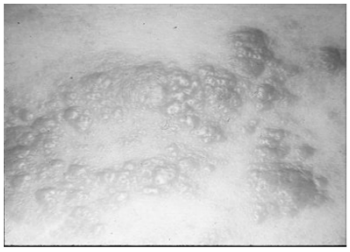
Which of the following is the most likely cause of his liver lesion?

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

43 – Photo Opportunities: Images You Should Know for the Exam

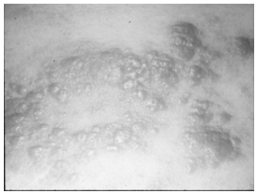
Speaker: John Bennett, MD

Question 14: skin lesion
A 38-year-old Mexican migrant worker in California reported this painless lesion had been present for almost a year. It was insensitive to light touch.

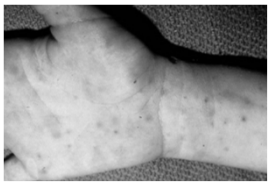


Question 14
WHICH OF THE FOLLOWING IS LIKELY THE MOST USEFUL DRUG?

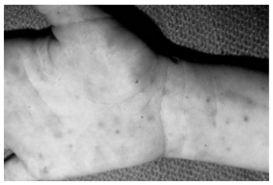
A. Thalidomide
B. Clarithromycin
C. Amikacin
D. Dapsone
E. Liposomal amphotericin B



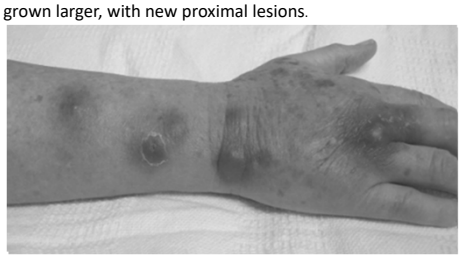
Question 15: fever and skin lesions
This 19-year-old girl from a dairy farm near Frederick, Maryland had the sudden onset in July of fever, severe headache, nausea, vomiting and muscle aches. On the fourth day, she developed the rash shown here on her wrists, palms, ankles, and soles.



She should immediately receive which of the following:
A. Ceftriaxone
B. Ampicillin
C. Levofloxacin
D. Doxycycline
E. Meropenem

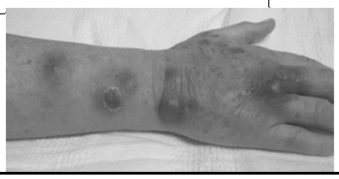


Question 16: skin lesions
This 55-year-old microscope repairman has an aquarium at home with tropical fish. This very slightly tender nodule appeared on the dorsum of his hand a week ago and has grown larger, with new proximal lesions.



Question 16
You need to be sure the micro lab does which of the following to culture the organism:

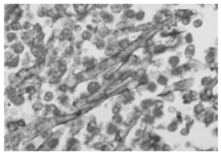
A. Addition of ferric citrate to mycobacterial agar
B. Use of fresh chocolate agar
C. Sabouraud's agar without antibiotics
D. Incubation on mycobacterial agar at 30°C
E. NNN medium



43 – Photo Opportunities: Images You Should Know for the Exam

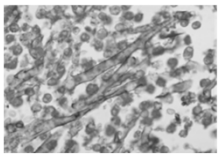
Speaker: John Bennett, MD

Question 17: histology of lung lesion
A 42-year-old patient received a stem cell transplant 4 months ago for treatment of refractory lymphoma. He had received multiple courses of chemotherapy for his lymphoma. He has not engrafted, and has been neutropenic for 4 months, receiving broad spectrum antibacterials and voriconazole.
Because of a new lung lesion with cavitation, he had a bronchoalveolar lavage. A Gomori silver stain of the lavage shows a mold, below.

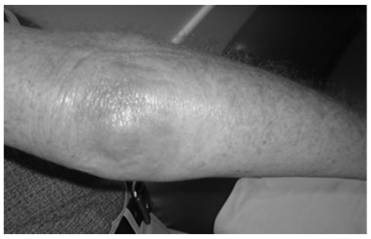


Question 17
What is the likely organism?

A. Rhizopus
B. Alternaria
C. Talaromyces
D. Fusarium
F. Aspergillus



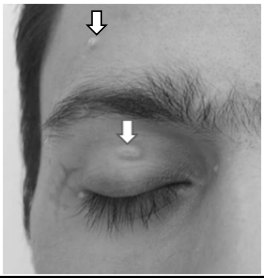
Question 18: sore elbow
This 40-year-old dentist presented with pain and swelling in his elbow of three days duration. He had full range of motion in the elbow despite discomfort on motion. He was afebrile. He has never had such episodes before, and is in good health, having recently finished a marathon.



Question 18
WHAT IS THE LIKELY CAUSE OF THIS LESION?

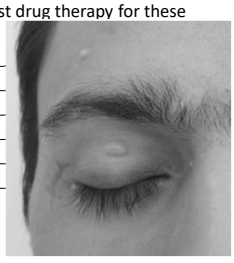
A. Olecranon bursitis
B. Streptococcal cellulitis (erysipelas)
C. Septic arthritis
D. Tophaceous gout

Question 19: skin lesions
The following lesions were seen in an asymptomatic male presenting for the first time for evaluation of HIV (CD4 = 125 cells, VL = 1 million). Lesions have been present for months, but are increasing in size and number



Question 19
Which of the drugs listed is the best drug therapy for these lesions:

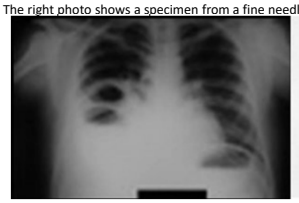
A. Acyclovir
B. Valganciclovir
D. Voriconazole
E. Amphotericin B
F. Antiretroviral therapy alone



43 – Photo Opportunities: Images You Should Know for the Exam

Speaker: John Bennett, MD

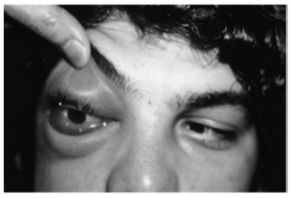
Question 20: lung lesion is Greek sheep herder
A 42-year-old Greek man visiting family in the USA was seen in clinic for cough. He had been employed for over a decade herding sheep in the mountains of northern Greece. He had been living and cooking his meals outdoors, drinking spring water and eating an occasional fish he caught from streams.
The left photo is his chest x-ray, showing a right lower lobe cavity.
The right photo shows a specimen from a fine needle aspirate of a lung lesion.



Question 20
WHAT IS THE LIKELY CAUSE OF THIS CONDITION?

A. Spring water
B. Dog stool
C. Undercooked lamb
D. Undercooked pork
E. Undercooked fish

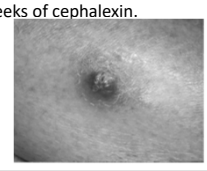
Question 21: orbit inflammation
A 23-year-old previously healthy (HIV negative) male presents with a two day history of a progressively red and painful right eye and low grade fever. His vision is slightly blurred. He has no history of local trauma or recent surgery, and is aware of no other recent illness. On physical examination he is febrile to 38.3°C, he has a moderate ophthalmoplegia involving cranial nerves III, IV, and VI.
His pupil reacts sluggishly to light. There is marked chemosis, periocular edema and proptosis.
His laboratory examination is normal except for WBC = 17000 (90% neutrophils).



Question 21
The most likely process which led to this ocular presentation is:

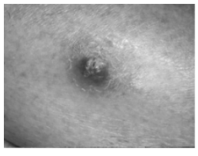
A. Preseptal cellulitis
B. Gonococcal conjunctivitis
C. Hematogenous bacterial endophthalmitis
D. Ethmoidal sinusitis
E. Herpetic keratitis

Question 22: skin lesion
This 55-year-old woman from Honolulu had been receiving prednisone in doses of 20-60 mg for uveitis when she developed a series of indolent red lesions on her right arm, left arm and right shin. They were not painful, occasionally drained a drop of serosanguineous fluid and enlarged over the course of several weeks.
She was afebrile and had a normal physical exam except for uveitis and the lesions. Her chest CT scan is normal.
There was no response to two weeks of cephalexin.



Question 22
WHAT IS THE LIKELY CAUSE OF THIS CONDITION?

A. Sporotrichosis
B. Erythema Nodosum
C. Leprosy
D. Non tuberculous Mycobacterium
E. Nocardiosis

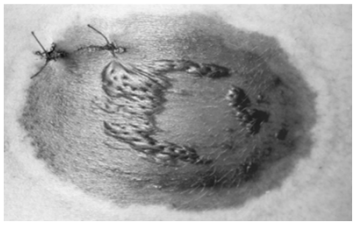


43 – Photo Opportunities: Images You Should Know for the Exam

Speaker: John Bennett, MD

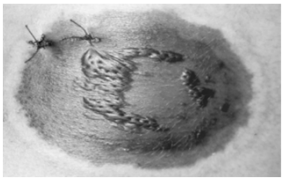
Question 23: skin lesion

This lesion developed over days on the abdomen of a neutropenic febrile 20 year old man under treatment for acute myelocytic leukemia. Sutures are from a skin biopsy.



Question 23
The appearance is most consistent with which of the following?

A. Erythema marginatum
B. Purpura fulminans
C. Impetigo
D. Pyoderma gangrenosum
E. Ecthyma gangrenosum



The end

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

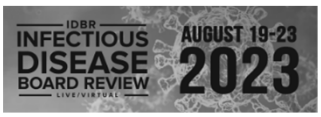
44a

Infections in the Neutropenic Cancer Patient and Hematopoietic Stem Cell Recipients

Dr. Kieren Marr

44a – Infections in the Neutropenic Cancer Patient and Hematopoietic Stem Cell Recipients

Speaker: Kieren Marr, MD



Infections in the Neutropenic Cancer Patient and Hematopoietic Stem Cell Recipients

Kieren Marr, MD
Adjunct Professor of Medicine, Oncology and Business
Johns Hopkins University School of Medicine
Carey School of Business

7/12/2023

Disclosures of Financial Relationships with Relevant Commercial Interests

- **Consultant: Cidara Therapeutics**
- **Employment: Sfunga Therapeutics**
- **Ownership Interests: Pearl Diagnostics, Sfunga Therapeutics**

Goals of This Review

- Focus on testable complications specific to the immunocompromised host
  - Types of immune – suppressing drugs and diseases
  - Recognition of specific "neutropenic syndromes"
    - Skin lesions
    - Invasive fungal infections
    - Neutropenic colitis

Fundamentals: Underlying disease risks

- Immune defects associated with underlying malignancy (and prior therapies)
  - AML and myelodysplastic syndromes (MDS)
    - Qualitative and quantitative neutropenia
  - Lymphoma
    - Functional asplenia
  - CLL and multiple myeloma
    - Hypogammaglobulinemia
  - Aplastic anemia
    - Severe, prolonged neutropenia

Fundamentals: Therapeutic risks

- Recognize risks with cytotoxic therapy (neutropenia)
  - Prolonged (>10 days) and profound (< 500 cells / mm3) leads to high risks for severe bacterial and fungal infections
    - Bacteremia, pneumonia, candidemia, aspergillosis
    - Outcomes tend to be poor – preventative therapies important
- Recognize infectious risks with other biologic therapies that immunosuppress
  - T cell suppressing agents and 'targeted' biologics
    - Viral and fungal infections

Immune modulating anti-cancer drugs

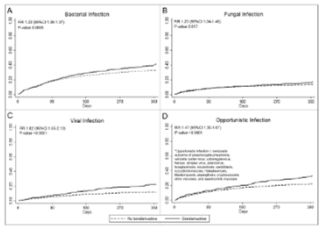
- Drugs that impact neutrophils
  - Many cytotoxic agents
    - Bacterial infections, fungal infections
- Drugs that impact T cells
  - Purine analogs (fludaribine, cladribine, clofarabine) and temozolomide
    - CD4+ T cell dysfunction: Herpes viruses (CMV, VZV), intracellular bacteria, fungi (PJP, Aspergillus)

44a – Infections in the Neutropenic Cancer Patient and Hematopoietic Stem Cell Recipients

Speaker: Kieren Marr, MD

Bendamustine

- Nitrogen-based alkylating agent and antimetabolite
- Indolent non-Hodgkins lymphomas, CLL
- Neutropenia *and lymphopenia* (months - years)
- Higher risks for infections (bacterial, CMV, PJP, histoplasmosis)



Fung et al. Clin Infect Dis 68(2): 247-55

Immunotherapies

- Targeted therapies (mAb, small molecule enzyme inhibitors, immune checkpoint inhibitors)
- Non-specific immunotherapies
- CAR T-cell therapy

Table 1. Novel targeted therapies: immune sequelae.

Target	Agents	B-Cell Depletion	T-Cell Depletion	HGG [1]	Neutropenia
CD20	Rituximab Ofatumumab Obinutuzumab	+++	-	+	++ [2]
CD52	Alemtuzumab	++	+++	+	+ [3]
CD38	Daratumumab	+	+	-	+
SLAMF7	Elotuzumab	-	-	-	-
CD19/CD3	Blinatumomab	+++	+	++	++
BTK	Ibrutinib Acalabrutinib Zanubrutinib	++	-	+	+
PI3K	Idelalisib Copanlisib Duvelisib	++	+	-	+
JAK	Ruxolitinib	-	+	-	-
BCL-2	Venetoclax	-	-	-	++

Plus signs indicate relative effect (e.g., mild, moderate, significant). [1] Hypogammaglobulinemia. [2] Late neutropenia may occur (median time 175 days, Dunleavy et al.). [3] Neutropenia typically resolves in 2–4 weeks.

*

Little et al. J Fungi 7, 1058

Key anti-CD Monoclonal Abs

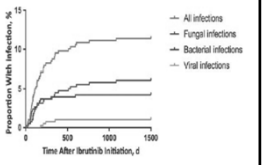
- Common antibodies that impact B and T cells
  - Rituximab (anti-CD20)
    - B cell depletion: CLL, lymphoma
    - Prolonged B cell (6 – 9 mo.); neutropenia can occur
    - Loss of vaccine responses, responses to encapsulated bacteria (pneumonia). Hepatitis B reactivation, PML, PJP
  - Alemtuzimab (anti-CD52)
    - T and B cell depletion for a long time (about 6 months): lymphoma, leukemia, BMT (graft vs. host disease treatment)
    - Herpes viruses (esp. CMV), fungal infections (PJP, Aspergillus)

Tyrosine kinase inhibitors

- BCR – ABL Tyrosine – kinase inhibitors
  - Inhibit signal transduction through BCR-ABL oncogene (ex. imatinib, dasatinib, nilotinib)
    - CML. Think T and B cells (VZV, Hep B reactivation)
    - Autoimmune pneumonitis and colitis (infection mimic), steroids
    - Aspergillosis and other IFI

Bruton's tyrosine kinase inhibitors

- Ibrutinib
- B cell development, macrophage phagocytosis
- Lymphoid malignancies (ex. CLL, lymphomas)
- Single-center review: 11%
- Fungal, bacterial infections
  - Aspergillosis (including CNS)
- Autoimmune – idiopathic drug "toxicities": colitis, pneumonitis



Varughese et al. Clin Infect Dis 2018; 67(5): 687-92
Bercusson A. Blood 2018 132(18): 1985-88
Blez et al. Haematologica 2019 (in press)

44a – Infections in the Neutropenic Cancer Patient and Hematopoietic Stem Cell Recipients

Speaker: Kieren Marr, MD

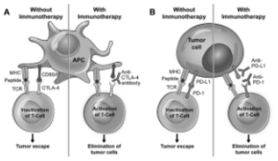
Phosphoinositide 3-kinase (PI3K) inhibitors

- Selective small molecule inhibitors of the B-cell receptor pathway (idelalisib)
- Decreased T-reg, inhibition NK, neutropenia
- Possibly increased IFI (esp. with combo)
- HBV screening, consider antiviral prophylaxis in HBsAg negative or anti HBc-positive patients

Maschmeyer et al. Leukemia 33, 844-62 (2019)

Checkpoint inhibitors

- Block immune checkpoints that regulate T cell activation / function – multiple tumors
- Targeting PD-1 on T cells (pembrolizumab, nivolumab, cemiplimab) or PD-L1 on tumor cells (atezolizumab, avelumab, durvalumab)
- Targeting CTLA-4 on T cells (ipilumumab)
- Induce colitis, pneumonitis
- Increased risks for infection in people receiving concurrent steroids, TNF-α targeting agents for above



Soularue et al. BMJ gut 2018

JAK inhibitors

- Janus kinase inhibitor (Ruxolitinib)
- Inhibit DC, CD4+ function, decreased T-reg, NK
- HBV: screening, prophylactic entecavir in HBsAg - / anti-HBc-positive
- Tb screening

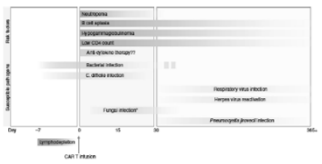
Maschmeyer et al. Leukemia 33, 844-62 (2019)

Venetoclax

- Inhibits anti-apoptotic BCL2 – family proteins (AML, lymphoid malignancies)
- Sometimes given with hypomethylating agents for AML (ex. azacytidine)
  - Severe, prolonged neutropenia – bacterial, fungal infections
  - Drug interactions may limit use of azole prophylaxis
    - Cyp3a inhibition requires VEN dose decrease / toxicities
    - Aspergillosis increasingly recognized

CAR T-cell Therapy

- Used to treat hematologic malignancies
- CAR = chimeric antigen receptor
  - T cells removed from body and processed to add specific receptors (proteins to recognize Ag's on cancer cell and activate T cells)
- Infectious risks associated with early lymphodepletion, cytokine release syndrome (and therapies for CRS)



Wudhikarn & Perales, BMT 2022 57: 1477-88

Neutropenic "syndromes"

44a – Infections in the Neutropenic Cancer Patient and Hematopoietic Stem Cell Recipients

Speaker: Kieren Marr, MD

Question #1

PREVIEW QUESTION

35 year old woman with AML day 15 after induction therapy.

Fever, chills, diffuse erythematous rash. Blood culture + GPC in chains

Exam – 100/62, HR 120, grade 2 oral mucositis, and a diffuse, blanching, erythematous rash. CXR - bilateral diffuse infiltrates. She is receiving levofloxacin and acyclovir.

This is most consistent with infection with which of the following organisms?

A. *Streptococcus pneumoniae*
B. Coagulase-negative *Staphylococcus*
C. *Enterococcus faecalis*
D. *Streptococcus mitis*
E. *Stomatococcus mucilaginosus*

Viridans Streptococci

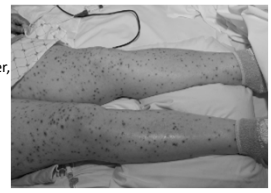
- Key points: neutropenia, mucositis, high-dose cytosine arabinoside, fluoroquinolone
- Can present with fever, flushing, chills, stomatitis, pharyngitis
- VGS shock syndrome:
  - After 24-48 hours, hypotension in 1/3 of cases
  - Rash, shock, ARDS in 1/4 of cases (similar to toxic shock)
- Endocarditis unusual (<10%)
- *S. mitis*, *S. oralis*
- Vancomycin
- Mortality high (15-20%)

Testable contexts: Breakthrough Bloodstream Infections

- Typical patient- neutropenic, progressive sepsis
- Recognize holes in protection, specific syndromes
  - ARDS, rash, quinolones, mucositis → viridans Streptococci
  - Sepsis with β-lactams → Stenotrophomonas, ESBL
  - Sepsis with carbepenems → KPC
  - Lung and skin lesions → *P. aeruginosa*, Fungi
  - Skin lesions, gram + → *Corynebacterium jeikeium*
  - Mucositis (upper, lower tract) → *Fusobacterium* spp., *Clostridium spp., Stomatococcus mucilaginosis*

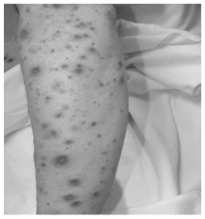
Question #2

59 year old woman with AML with neutropenia for 25 days. She has been febrile for 6 days, and is receiving meropenem, vancomycin, and acyclovir. New skin lesions that are small, papular, and tender, with no central ulceration.

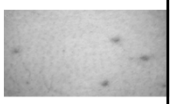


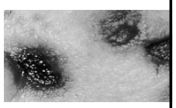
A. *Rhizopus* spp.
B. Varicella zoster virus
C. *Cryptococcus neoformans*
D. Vancomycin resistant Enterococci
E. *Candida tropicalis*

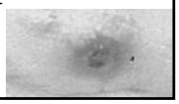
Skin Lesions



- Candidiasis
  - Small, tender papules
- Herpes
  - vesicular
- *Aspergillus*
  - ulcerative, necrotic
- Other filamentous fungi (*Fusarium, P. boydii*)
  - Multiple, erythematous, different stages
- *P. aeruginosa*
  - Ecthyma gangrenosum

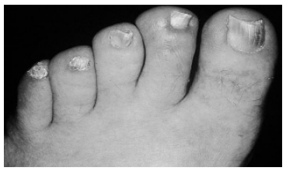






Fusarium

- Invasive pulmonary disease with skin lesions
- Locally invasive infections in neutropenic patients
  - Keratitis
  - Onychomycosis



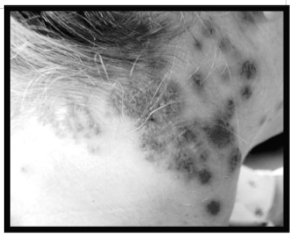
44a – Infections in the Neutropenic Cancer Patient and Hematopoietic Stem Cell Recipients

Speaker: Kieren Marr, MD

Question #3

50-year-old woman with newly diagnosed AML developed tender, pruritic papules and plaques on her neck. She had been febrile 38.7°C for the past several days and had received a dose of G-CSF 3 days earlier, with rapid WBC increase (900 ANC). Most likely etiology:

A. *Candida albicans*
B. Sweet's syndrome
C. *Aspergillus niger*
D. Varicella Zoster Virus
E. *Pseudomonas aeruginosa*



Haverstock, C. et al. Arch Dermatol 2006;142:235-b-240-b.

Sweet's syndrome

- Acute febrile neutrophilic dermatosis
- Variants: classic (idiopathic), malignancy-associated, drug induced
- Tender erythematous plaques and nodules typical; also bullous, cellulitic, necrotizing lesions
- Classic stem: neutropenia resolving with GCSF assist, fever, skin lesions, cultures - negative
- Steroids

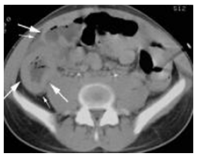
Question #4

IDBR 2023 PREVIEW QUESTION

70 yr old woman with AML, neutropenic for 15 days, s/p induction chemotherapy develops fever, diarrhea, and abdominal pain. Exam - decreased bowel sounds and tenderness with deep palpation in her RLQ. CT shows inflammation in cecum. Levofloxacin and fluconazole prophylaxis. 4 days prior to her admission for chemotherapy, she ate Chinese food with fried rice.

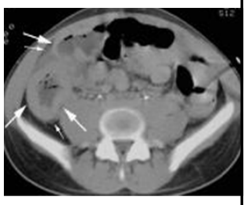
Which is the most likely etiology?

A. Norovirus
B. *Clostridioides (Clostridium) difficile*
C. Mixed anaerobic and aerobic bacteria
D. *Candida albicans*
E. *Bacillus cereus*



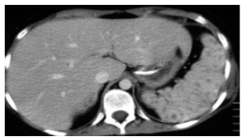
Neutropenic Enterocolitis

- Neutropenic enterocolitis (typhlitis)
  - Necrotizing inflammation with transmural infection of damaged bowel wall
  - Mixed infection with gram-negative, gram-positive, anaerobic bacteria, fungi
  - Can be accompanied by bacteremia
    - Hint: mixed, anaerobic (*C. septicum, C. tertium, B. cereus)*
  - Medical and (less often) surgical management



Hepatosplenic Candidiasis

- Inflammatory response to fungi invaded by portal vasculature
- Presentation after engraftment: abdominal pain, increased LFTs (alk phosph), fever, leg / flank pain
- Differential: other fungi, bacteria, lymphoma
- *C. albicans* most common
  - Amphotericin B primary therapy followed by prolonged fluconazole, echinocandins



Summary: PEARLS

- Recognize typical infections associated with neutropenia and/or other immune suppression (biologic inhibitors of cellular defenses)
- Predict breakthrough bloodstream pathogens based on therapy
- Know specific syndromes
  - *S. viridans* sepsis – ARDS
  - Differential of skin lesions
  - Neutropenic patients - IFI
    - Pulmonary
    - Bloodstream
    - Hepatosplenic candidiasis
  - GI tract enterocolitis

44a – Infections in the Neutropenic Cancer Patient and Hematopoietic Stem Cell Recipients

Speaker: Kieren Marr, MD

Thank you

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44a – Infections in the Neutropenic Cancer Patient and Hematopoietic Stem Cell Recipients

Speaker: Kieren Marr, MD

Table 1. Novel targeted therapies: immune sequelae.

Target	Agents	B-Cell Depletion	T-Cell Depletion	HGG [1]	Neutropenia
CD20	Rituximab Ofatumumab Obinutuzumab	+++	-	+	++ [2]
CD52	Alemtuzumab	++	+++	+	+ [3]
CD38	Daratumumab	+	+	-	+
SLAMF7	Elotuzumab	-	-	-	-
CD19/CD3	Blinatumomab	+++	+	++	++
BTK	Ibrutinib Acalabrutinib Zanubrutinib	++	-	+	+
PI3K	Idelalisib Copanlisib Duvelisib	++	+	-	+
JAK	Ruxolitinib	-	+	-	-
BCL-2	Venetoclax	-	-	-	++

Plus signs indicate relative effect (e.g., mild, moderate, significant). [1] Hypogammaglobulinemia. [2] Late neutropenia may occur (median time 175 days, Dunleavy et al.). [3] Neutropenia typically resolves in 2–4 weeks.

*

Little et al. J Fungi 7, 1058

44b

Selected Syndromes in Stem Cell Transplant Recipients

Dr. Kieren Marr

44b – Selected Syndromes in Stem Cell Transplant Recipients

Speaker: Kieren Marr, MD

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

Selected Syndromes in Stem Cell Transplant Recipients

Kieren Marr, MD
Adjunct Professor of Medicine, Oncology and Business
Johns Hopkins University School of Medicine
Carey School of Business

7/12/2023

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

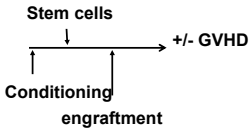
Disclosures of Financial Relationships with Relevant Commercial Interests

- **Consultant: Cidara Therapeutics**
- **Employment: Sfunga Therapeutics**
- **Ownership Interests: Pearl Diagnostics, Sfunga Therapeutics**

PEARLS

- **Fundamentals – risks (temporality)**
  - **Early – mucositis, neutropenia**
  - **Late – GVHD (steroids, asplenia, T cell dysfunction)**
- **Syndromes**
  - **Early pulmonary syndromes**
    - **Bacterial, fungal pneumonia**
    - **Non-infectious: Alveolar hemorrhage, IPS**
  - **Late pulmonary syndromes**
    - **CMV, respiratory viruses, IFI**
    - **Non-infectious: BOOP**
- **Hemorrhagic cystitis**
  - **BK**
  - **Non-infectious: conditioning**
- **Diarrhea – colitis – hepatitis**
  - **Herpes viruses**
  - **Non-infectious: GVHD**
- **Neurologic syndromes**
  - **Herpes viruses (+HHV-6), west nile, angio-invasive, toxoplasmosis, PML (JCV)**
  - **Non-infectious: PRES, antibiotics**

Fundamentals of BMT



- Immune risks for infection are temporal
  - Neutropenia (early, w/in 30 days)
    - Bacterial infections
    - Fungal infections
  - Impaired cellular and humoral immunity (later, post-engraftment)
    - Bacterial infections
    - Fungal infections
    - Viral infections

Fundamentals of BMT

- Autologous (self) vs. allogeneic (other)
- Types of allogeneic donors
  - Related, HLA – matched (MR)
  - Related, HLA - mismatched (haploidentical)
  - Unrelated, HLA – matched (MUD) or Unrelated, HLA – mismatched (MM-URD)
- Types of stem cells
  - Bone marrow
  - Peripheral blood
  - Cord blood
- Types of conditioning regimens
  - Myeloablative
  - Nonmyeloablative

Approach for the boards

- Know common infections and non-infectious mimics
- Approach stems in context
  - Patient's age, disease, history impact risks after BMT
  - What kind of BMT did the patient have?
  - Is the patient early vs. late after BMT?

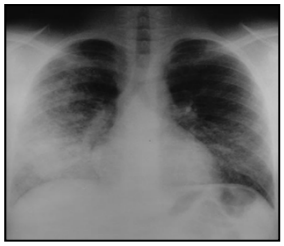
Type of BMT and timeline impacts immunity, drugs and exposures

44b – Selected Syndromes in Stem Cell Transplant Recipients

Speaker: Kieren Marr, MD

Case #1

42 year old M AML 20 days after a matched unrelated donor BMT (nonmyeloablative) develops fever, cough, pulmonary infiltrates.
Pre-transplant: HSV+, VZV+, CMV D+/R-
Exam– 98% sat on 2L nc, T 38.3, crackles RLL
Labs- Cr 2.2, WBC 1200 cells/mL, plt 122
He's currently receiving acyclovir and fluconazole for prophylaxis.



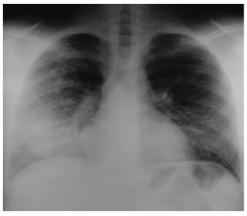
Case #1

What is the most likely cause of his current process?

A. *Candida albicans*
B. *Klebsiella pneumoniae*
C. CMV
D. Parainfluenza virus
E. Hemorrhage

Pulmonary Complications

- Bacterial pathogens
  - *P. aeruginosa, Streptococci*, Legionella, *S. aureus*
  - Aspiration events with severe mucositis early after BMT
  - Encapsulated sinopulmonary pathogens late after BMT
- Filamentous fungi early and late (*A. fumigatus)*



Pulmonary Complications (Con't)

- Respiratory virus infection follows seasonal epidemiology
  - Increased risk for lower tract involvement
  - Influenza, RSV, Parainfluenza 3, Human metapneumovirus
  - Adenovirus: reactivation and acute infection (particular issue with kids)
- Herpes viruses
  - CMV with prolonged impairment in cellular immunity
  - HSV classically described with prior airway manipulation

Early non-infectious lung injury

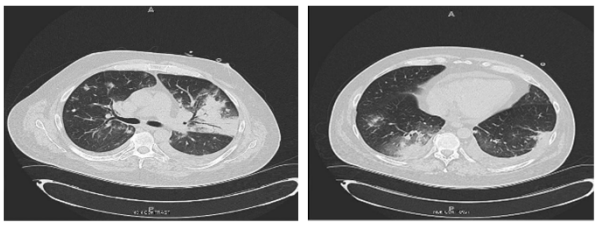
- Diffuse alveolar hemorrhage
  - Bleeding in alveolar space, heterogeneous etiology
    - Vasculitis, drug-induced injury, cancer-chemotherapy / thrombocytopenia
- Idiopathic pneumonia syndrome
  - Within 1st 120 days of BMT, non-infectious
  - Risks: conventional ablative conditioning, acute GVHD (inflammatory pathogenesis?)

Case #2

A 46 year old male 18 months s/p HLA mismatched BMT. History of GVHD skin, GI tract, and BOOP 3 months ago, treated with steroids. One month s/p Parainfluenza 3 URI, with chest CT - tree-in-bud opacities in LLL. Received levofloxacin for 10 days.

He now has increasing shortness of breath and cough.

Case # 2 (con't.)



Case # 2 (con't.)

Blood cultures no growth. Sputum – LF GNR. Serum galactomannan is negative. What is the most likely cause of his current process?

A. *Cryptococcus neoformans*
B. *E. coli*
C. MRSA
D. *Aspergillus fumigatus*
E. *Fusarium* spp.

DDx of Late pulmonary syndromes

- Infectious
  - CMV disease
  - Respiratory virus infections
  - PJP
- Non-infectious
  - Bronchiolitis obliterans syndromes

CMV Infection after BMT

- Reactivation occurs in seropositive patients (R+).
  - Reactivation alone triggers cytokine storm, GVHD, disease
  - Risk for *disease* dependent on immunity
    - Highest risk group for disease after BMT: D- / R+
      - No transferred immunity to CMV
      - This is different than SOT, where highest risk group is D+ / R-
- Primary infection in seronegative patients (R-) from community, positive graft (D+) or blood products (rare)

CMV Disease

- Pneumonitis
  - Indolent cough, fever, SOB, interstitial infiltrates
- Gastrointestinal disease
  - Esophagitis, colitis, hepatitis (rare)
- Encephalitis, retinitis less frequent

CMV Disease after BMT (con't.)

- Treatment concepts
  - Pre-emption with ganciclovir driven by PCR
    - Not prophylaxis (SOT) with ganciclovir (toxicities)
    - Prophylaxis of R+ patients with letermovir
  - Induction therapy with maintenance GCV
  - Resistance to GCV is *rare* (as opposed to SOT)
    - Most failures are due to steroids, T cell depletion
    - Recipe for GCV – resistance: long exposure to suboptimal doses of GCV in a patient with poor cellular immunity
    - Refractory disease can be due to Res and intolerance (neutropenia)
      - Miribavir (inhibits UL-97 kinase) approved for refractory treatment

Pneumocystis Pneumonia

- Common late after BMT
  - Steroid receipt, T-cell depletion
- Prophylaxis at least 6 months
  - Bactrim
  - Toxicities
    - Dapsone, atovaquone, aerosolized pentamidine
      - Less effective, other infections occur**
- Late diagnoses occur
  - BAL DFA less sensitive

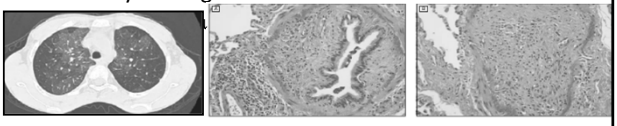
Toxoplasmosis

- Clusters of disease reported in BMT patients
  - T-depleted BMT
  - Some early. Acquisition vs. reactivation?
- Regions with high seroprevalence screen for disease with pre-emptive therapy
- Pneumonia, encephalitis, fever

Isa et al, ID Week 2014
Meers et al. Clin Infect Dis, 2010 Apr 15;50(8):1127-34

Bronchiolitis Obliterans

- Chronic GVHD of lung
  - Allorecognition of lung antigens
- Circumferential fibrosis of terminal airways ultimately leading to airflow obstruction



Williams JAMA 2009

A. Obliteration of bronchiolar lumen
B. Inflammation between the epithelium and the smooth muscle

Case #3

35 yr old F, 80 days after allogeneic BMT with 5 days of anorexia, nausea, epigastric pain, and diarrhea. CMV D-/R+, HSV+, VZV+.
Exam: faint maculopapular rash on upper body. Afebrile.
Meds: acyclovir, TMP-SMX and fluconazole.
ANC 1000, ALC 250. LFTs normal.

What is the most appropriate initial work-up and management?

A. Perform serum VZV PCR
B. Empiric corticosteroid treatment
C. Send C. diff toxin and start oral vancomycin
D. CMV PCR, stool C. diff, bacterial culture
E. #D *and* upper, lower endoscopy

Graft vs. Host Disease (GVHD)

- Acute (early after HSCT)
  - Fever
  - Rash
  - GI: hepatic, colon
- Chronic (later after HSCT)
  - Skin changes (lichen planus, sceroderma)
  - Hepatic (cholestatic)
  - Ocular (keratoconjunctivitis)
  - GI (oral, dysphagia)
  - Pulmonary syndromes

DDx of GI Disease in BMT

HEPATITIS

- GVHD
- Herpes viruses (CMV, VZV)
- Hepatitis B virus
  - Increased viral replication and liver damage
  - Hepatitis not common during neutropenia

DIARRHEA

- GVHD
- CMV
- C. difficile
- Norovirus (chronic diarrhea mimicking GVHD)
- Adenovirus

Adenovirus Infection after BMT

- More common in children, high risk BMT
  - Severe GVHD and steroids
- Enteritis, cystitis, upper respiratory infection, pneumonia, encephalitis, hepatitis
- No controlled treatment studies
  - Taper immunosuppression
  - Cidofovir most active in vitro
  - Ribavirin not effective in larger studies

Case #4

53 year old F 7 yrs s/P allo BMT presents with fever, chills, rigors. H/O severe chronic GVHD skin. PE – T 39.2. tachycardia, tachypnea, hypotension. Skin thick, cracked (Sjogren-like). Social- dog and two cats, no recent exposures. Labs- WBC 8200 / mm3, platelet 43,000/mm3. CT of her chest, abdomen, pelvis - splenic atrophy. Blood cultures positive for gram-negative rods after 5 days.

Most likely cause of her current condition:

A. Fusobacterium nucleatum
B. Eikenella corrodens
C. Capnocytophaga canimorsus
D. Acinetobacter baumannii

Case #5

IDBR 2023 PREVIEW QUESTION

40 year old M day 60 after allogeneic BMT from unrelated donor, with bloody urine for 6 days. Has skin GVHD, receiving a prednisone taper (1 mg/kg/day). Exam, faint diffuse erythematous rash. Cr 1. LFTs normal. CMV pcr negative.

The most likely etiology is:

A. Cyclophosphamide
B. CMV
C. EBV
D. BK
E. JC virus

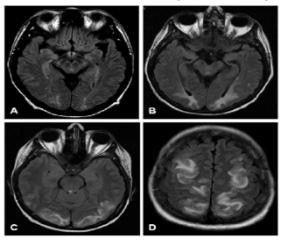
DDx of Hemorrhagic Cystitis

- Conditioning related (early)
  - Cyclophosphamide
- BK virus (later)
- Adenovirus (later)

DDx of Neurologic Syndromes

- Infection
  - Herpes viruses: HSV, CMV, HHV6*
  - West nile virus
  - JCV – PML (especially with T-depleting Abs)
  - Pulmonary – CNS lesions
    - Invasive fungal infections
    - Nocardia
    - Toxoplasmosis
- Drugs: carbapenems, cefepime, PRES*

Posterior reversible encephalopathy (PRES)



- Usually early after HSCT (within 1st 3 months)
- Calcineurin inhibitors: Cyclosporin*, tacrolimus
- Seizures, visual changes, MS changes

44b – Selected Syndromes in Stem Cell Transplant Recipients

Speaker: Kieren Marr, MD

HHV-6 after BMT

- HHV-6 seroprevalence > 95% after age 2
  - Early reactivation common after BMT 38-60% SCT (type B)
  - Clinical correlates reported: rash, marrow suppression, delayed platelet engraftment, idiopathic pneumonitis
- Meningoencephalitis**
  - Nonspecific presentation (confusion, memory loss, EEG / MRI: temporal)
  - Early - within 60 days of BMT
  - RFs: MM/URD or UCB SCT, anti-T-cell
- Diagnosis: PCR of CSF
- Chromosomal integration
- ACV-resistant. Treat with ganciclovir, foscarnet, cidofovir

VZV Infection after BMT

- Multidermatomal lesions
- Primary viral pneumonia
- Encephalitis
- Hepatitis
  - Classic: abd pain, transaminitis late
  - Can occur without skin lesions
- VZV seropositive
- Severe GVHD, acyclovir prophylaxis effective long term
- Recent study: 1% rate of infection, high rate after 1 yr

Baumrin et al. Biol Blood and Marrow Trans 2019 (in press)

PEARLS

- **Fundamentals – Risks (temporality)**
  - **Early – mucositis, neutropenia**
  - **Late – GVHD (steroids, asplenia, T cell dysfunction)**
- **Syndromes**
  - **Early pulmonary syndromes**
    - **Bacterial, fungal pneumonia**
    - **Non-infectious: Alveolar hemorrhage, IPS**
  - **Late pulmonary syndromes**
    - **CMV, respiratory viruses, IFI**
    - **Non-infectious: BOOP**
- **Hemorrhagic cystitis**
  - **BK**
  - **Non-infectious: conditioning**
- **Diarrhea – colitis – hepatitis**
  - **Herpes viruses**
  - **Non-infectious: GVHD**
- **Neurologic syndromes**
  - **Herpes viruses (+HHV-6), west nile, angio-invasive, toxoplasmosis**
  - **PML**
  - **Non-infectious: PRES, antibiotics**

Thank you

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45

Solid Organ Transplantation

Dr. Barbara Alexander

45 – Solid Organ Transplantation

Speaker: Barbara Alexander, MD

Solid Organ Transplantation

Barbara D. Alexander, MD, MHS
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6/27/2023

Disclosures of Financial Relationships with Relevant Commercial Interests

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

Infections in Solid Organ Transplant (SOT) Recipients

- SOT is a life-saving intervention
  - 940,143 SOTs performed in U.S. since 1988
  - 42,889 SOTs performed in 2022
- SOT recipients
  - have compromised immunity / increased infection risk
  - are targets for common, emerging & opportunistic pathogens encountered pre- and post-transplant
  - often have atypical infection presentation owing to their compromised immunity / decreased inflammatory response
  - are on complex medical regimens; drug interactions common

Data from Organ Procurement and Transplantation Network database as of June 27, 2023

WHAT YOU SHOULD KNOW FOR THE BOARD EXAM:

- Infection risk varies based on
  - Organ transplanted
  - Time post transplant
  - Degree of immunosuppression
  - Prophylaxis regimen
  - Unique exposures
- Key drug interactions and drug-induced syndromes
  - Calcineurin inhibitors and azoles, macrolides, rifampin (covered in Dr. Gilbert's antibiotic lecture)
  - Sirolimus associated pneumonitis
  - Calcineurin inhibitors and TTP and PRES

WHAT YOU SHOULD KNOW FOR THE BOARD EXAM:

- The following major clinical syndromes:
  - CMV syndrome & disease
  - EBV & Post Transplant Lymphoproliferative Disorder (PTLD)
  - BK virus nephropathy
  - Aspergillosis, Mucormycosis & Cryptococcosis
  - Tuberculosis
  - Toxoplasmosis
  - Donor-derived infections

PLAY THE ODDS

The data in the stem let's you "play the odds" as to the most likely diagnosis

- **Patient completing valganciclovir prophylaxis 6 weeks prior presenting with fatigue, low grade fever and leukopenia**
  - **CMV**
- **Donor died from skiing accident in fresh water lake in Florida and recipient presents 3 weeks post transplant with encephalitis**
  - **Naegleria**
- **Renal transplant recipient on valganciclovir prophylaxis presents with asymptomatic renal dysfunction**
  - **BK Virus**
- **Lung transplant recipient planted vegetable garden 2 weeks prior while on posaconazole prophylaxis and presents with productive cough and cavitary lung lesion**
  - **Nocardia**

FREQUENCY, TYPE & INFECTION SOURCE IN THE 1ST POST TRANSPLANT YEAR

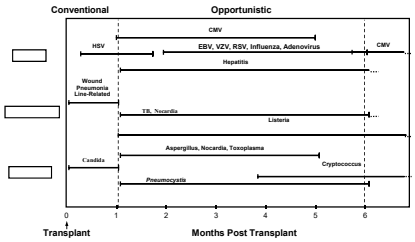
Transplant Type	Infection Episodes per Patient	Bacteremia	CMV Disease * (%)	Fungal Infections (%)	Most Common Source
Lung	3.19	8-25	39	8.6	Pulmonary
Liver	1.86	10-23	29	4.7	Abdomen & Biliary tract
Heart	1.36	8-11	25	3.4	Pulmonary
Kidney	0.98	5-10	8	1.3	Urinary tract

*CMV, Cytomegalovirus; CMV disease rates in the absence of routine antiviral prophylaxis

Table Modified from: Principles and Practices of Infectious Diseases, 9th Edition. Chapter 313. Infections in Solid-Organ Transplant Recipients by Nina Singh and Ajit Lalvani. Editors: Bennett JE, Dolin R, and Blaser MJ. Elsevier Saunders, Philadelphia, PA, 2015.

CLASSIC TIMING OF INFECTIONS FOLLOWING SOLID ORGAN TRANSPLANTATION

Timing altered by:
- Enhanced immunosuppression
- Prophylaxis regimen
- Unique exposures



"EARLY" BACTERIAL INFECTIONS FOLLOWING SOT

Type & site of early bacterial infection varies based on organ transplanted, surgical approach/technique & transplant center

- Risk of peritoneal soilage/infection greater in liver transplantation with Roux-en-Y biliary drainage
- Recipient colonization with resistant organisms (e.g. MRSA, VRE, CRE) pre-transplant, confers risk of post-transplant infection
- Cluster with unusual pathogen - environmental problem? (e.g. *Legionella, M. abscessus* from hospital water distribution systems)

"LATE" BACTERIAL INFECTIONS FOLLOWING SOT

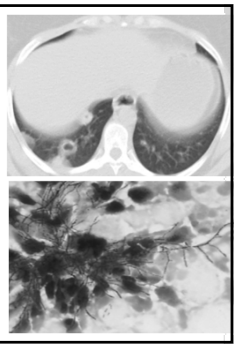
80% OF LATE BACTERIAL INFECTIONS ARE COMMUNITY ACQUIRED

- *Streptococcus pneumoniae*
  - Incidence significantly > in SOT (146/100,000) vs general population (12/100,000)
  - Vaccination recommended
- *Listeria monocytogenes*
  - Bacteremia (Gram + Rods) / Diarrhea / Meningitis
  - Ampicillin treatment of choice
  - High relapse rate, treat for at least 3-6 wks

Kumar D et al., *Am J of Transplant* 2007;7:1209

LATE BACTERIAL INFECTIONS, CONT.

- *Nocardia* species
  - 1%-6% of all SOT recipients
  - Presents most often as pulmonary nodules, CNS (15-20%), skin (15%), or bone (2-5%) lesions
  - Diagnosis: Culture and/or histopathology
    - Branching, filamentous Gram + Rods
    - Partially acid-fast by modified Kinyoun stain
    - *Nocardia* is *Neurotropic*; brain imaging critical
  - Treatment:
    - High dose TMP-SMX drug of choice
    - Otherwise, based on susceptibility data & site of infection
  - TMP-SMX dose used for PCP prophylaxis not protective



CMV DISEASE AFTER SOT
INDIRECT AND DIRECT EFFECTS

INDIRECT Effects:
- Acute and Chronic Rejection
- Opportunistic Super-Infections (Gram negative bacteria & Molds)

DIRECT Effects:
- CMV Syndrome – most common presentation
  - CMV in blood + fever + malaise, leukopenia, atypical lymphocytosis, thrombocytopenia
- Tissue Invasive Disease
  - Evidence of CMV on biopsy + compatible signs/symptoms

RISK OF CMV DISEASE AFTER SOT

CMV Serologic Status	Risk Category	Incidence of Disease (%)
D+/R-	High	50+
D+or D-/R+	Intermediate	10-15
D-/R-*	Low	0
ALA Therapy (R+)		
Induction	Intermediate	25-30
Rejection	High	65

D, Donor; R, Recipient; ALA, Antilymphocyte Antibody

*Should receive leukocyte depleted blood products

CMV DISEASE AFTER SOT
PROPHYLACTIC APPROACHES

UNIVERSAL

All SOT recipients receive therapy during highest risk periods

- Expensive
- May induce resistance
- Some pts exposed unnecessarily

PREEMPTIVE

Treatment based on asymptomatic viral replication in blood

- Optimal viral threshold for initiating therapy not well defined
- Requires serial weekly monitoring with detection assay

NOTE: Typically Valganciclovir or IV Ganciclovir used for prophylaxis
Letermovir now approved for use after Renal Transplant

CMV PROPHYLAXIS AFTER SOT

Bottomline:

•D+/R- or ALA for rejection → Universal
- First 3-6 months post-transplant
- At least 1 month post-ALA for rejection

•R+ → Universal or Preemptive
- First 3-6 months post-transplant

CMV DISEASE AFTER SOT

- Typically occurs 1-3 months post-transplant
  - Or after prophylaxis is stopped ("late onset")
- Disease of GI Tract and Eye may not have concurrent viremia
  - Diagnosis often requires biopsy/aspiration
- Viral load may continue to rise during first 2 weeks of Rx
  - Don't repeat PCR until Day 14 of treatment, then weekly until negative
- Treat for 2-3 weeks…
  - Resolution of symptoms AND clearance of CMV DNAemia
  - DO NOT STOP TIL VIREMIA CLEARs (high risk for relapse)

CMV DISEASE AFTER SOT
GANCICLOVIR RESISTANCE

- **Suspect resistance if prolonged (> 6 weeks) (val)ganciclovir exposure AND:**
  - No reduction in viral load after 14 days of treatment
  - No clinical improvement after 14 days of treatment
- **Management of suspected ganciclovir resistance:**
  - Reduce immunosuppression
  - Switch to maribavir or foscarnet (± CMV hyperimmune globulin)

Lurain et al.JID 2002; Limaye et al Lancet 2000; Limaye et al JID 2002; Kotton et al Transplantation 2013.

CMV DISEASE AFTER SOT
ANTIVIRAL RESISTANCE

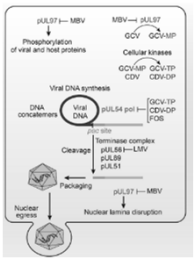
Key mutations have been associated with resistance

•UL97 CMV Phosphotransferase gene mutations (most common)
- Imply ganciclovir resistance

•UL54 CMV DNA Polymerase gene mutations
- May confer resistance to ganciclovir, foscarnet, & cidofovir

Lurain et al JID 2002; Limaye et al Lancet 2000; Limaye et al JID 2002;
Kotton et al. Transplantation 2018;102(6):900-931. Torre-Cisneros et al Transplantation Reviews 2016.

CMV RESISTANCE: NEW DRUG



Maribavir (MBV)

- Multi-modal CMV activity
  - Inhibits CMV DNA replication
  - Interferes with nuclear egress of viral capsid by inhibiting UL97 kinase
- UL97 kinase activates ganciclovir (GCV), thus MBV inhibits GCV activity
  - ⚠ MBV & GCV should not be used together
- MBV is active against many GCV resistant strains
  - Superior to SOC (Valgan/Gan, Foscarnet, or Cidofovir) in HSCT & SOT pts with refractory/resistant CMV infection
    - Cleared CMV viremia & resolved symptoms at 8 weeks
  - FDA approved Nov 2021 for "CMV (with or without genetic mutations that cause resistance) that does not respond to available antiviral treatment…"
  - ⚠ No activity against other herpes viruses (HSV/VZV)

Piret J, Boivin G. Antiviral Research 2019;163:91-105.
Avery RK, et al. Clin Infect Dis. 2021 Dec: Online ahead of print.

CASE 1

IDBR 2023 PREVIEW QUESTION

- 54 yo male 60 days post-cardiac transplant was treated for rejection with steroids when fever and a non-tender anterior cervical mass appeared.
- Biopsy showed nodal replacement by lymphocytes, many of which stained positively for Epstein-Barr virus as well as for the B cell marker, CD20.
- His plasma EBV viral load was 10,000 copies /ml.

QUESTION #1

IDBR 2023 PREVIEW QUESTION

The most appropriate treatment for this condition is:

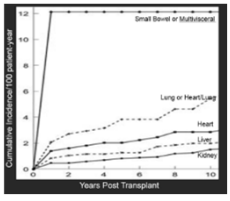
A. Cidofovir
B. Ganciclovir
C. Acyclovir
D. Cyclophosphamide
E. Rituximab

EPSTEIN BARR VIRUS: POST TRANSPLANT LYMPHOPROLIFERATIVE DISORDER (PTLD)

- Virus establishes latency in B-lymphocytes which serve as lifelong reservoirs
- EBV transformed B-lymphocytes give rise to PTLD (a few cases may arise from T-lymphocytes)
- Risk factors:
  - 1° EBV infection
  - Donor seropositive, Recipient seronegative
  - Antilymphocytic antibody therapy (T-cell depletion)
  - Organ transplanted (Intestine > Lung > Heart > Liver > Kidne)y

EPSTEIN BARR VIRUS POST TRANSPLANT LYMPHOPROLIFERATIVE DISORDER (PTLD)

- ~3% Cumulative 10 year incidence in SOT population
- Incidence varies based on organ transplanted
  - Small Bowel / Multivisceral – up to 32%
  - Lung / Heart / Liver - 3-12%
  - Kidney - 1-2%
- Biphasic pattern of disease after SOT:
  - First peak (20% cases) occurs 1st post-tx year
  - Second peak occurs 7-10 years post-tx



Olagne, J, et al. Am J Transplant. 2011 Jun;11(6):1260-9.

EPSTEIN BARR VIRUS *POST TRANSPLANT* LYMPHOPROLIFERATIVE DISORDER (PTLD)

Clinical manifestation - wide range

- Febrile mononucleosis-like illness with lymphadenopathy
- Solid tumors
  - Often involve transplanted graft
  - 50% are extranodal masses
  - 25% involve CNS

Definitive diagnosis requires tissue biopsy

- WHO Pathology Classification based is gold standard for diagnosis
- Molecular (PCR) tests available
  - WHO Standard for Assay Calibration available
  - Whole Blood vs Plasma controversial
  - Misses EBV-negative and some localized cases
  - Used as an aid for Diagnosis and Pre-emptive monitoring with stepwise reduction in immunosuppression to reduce PTLD rates

Petit B et al. Transplantation. 2002;73(2):265.
Peters AC et al. Transplantation. 2018; 102(9):1553.

EPSTEIN BARR VIRUS *POST TRANSPLANT LYMPHOPROLIFERATIVE DISORDER (PTLD)*

Treatment:

- Antivirals not effective on latently infected lymphocytes (antivirals only work in lytic phase)
- Reduce Immunosuppression (Response ~ 45%)
- Rituximab: Anti-CD20 monoclonal antibody (Response ~ 55%)
- Cytotoxic Combination (CHOP, ACVBP) Chemotherapy
  - Reserved for non-responsive disease
  - High treatment associated mortality (13%-50%)
- Adoptive Immunotherapy (EBV cytotoxic T-cells)
  - Under study

Allen et al. Clin Transplant. 2019;33(9):e13652.

CASE 2

2023 PREVIEW QUESTION

- 52 yo female S/P cadaveric renal transplant receiving tacrolimus, prednisone and mycophenylate.
- Week 30 post transplant serum creatinine rose from 1.5 to 2.3 mg/dl.
- Tacrolimus levels were in therapeutic range.
- Urinalysis revealed one plus protein and no cells or casts.

QUESTION #2

2023 PREVIEW QUESTION

Which would be most helpful in understanding if BK virus was causing her renal failure?

A. Presence of decoy cells in urine cytology
B. Urine BK viral load
C. Urine culture for BK virus
D. Plasma BK viral load
E. Demonstration of BK inclusions in renal tubular epithelium on renal biopsy

POLYOMAVIRUS *BK VIRUS NEPHROPATHY*

- Ubiquitous, DNA virus
  - 1° infxn – URI during early childhood
  - 80% worldwide population sero+
  - Renal & uroepithelial cells, site of latency
- Cause of nephropathy post renal transplant
  - Up to 15% of renal recipients effected
  - Time to onset 28-40 weeks (majority within 1st yr post tx)
  - Manifests as unexplained renal dysfunction (as does rejection)

Hayashi RY et al. UNOS Database; Abstract 76, 2006 World Transplant Congress; Ramos et al. *J Am Soc Nephrol* 2002;13:2145; Hirsch et al. Transplantation 2005;79:1277-1286

BK VIRUS NEPHROPATHY *DIAGNOSIS*

- Replication in urine precedes replication in blood precedes nephropathy
- Renal Bx - "Gold Standard" for diagnosis
- Blood PCR
  - Sensitive (100%) but less specific (88%)
  - Cannot rule out rejection
  - Useful as indicator for biopsy
- Urine Cytology, Electronmicroscopy, & PCR
  - Detection in urine: Low PPV but High NPV

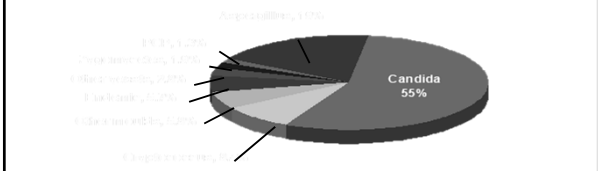
Hirsch et al, Transplantation 2005;79:1277-1286; Nickeleit et al, NEJM 2000;342 (18):1309-1315; Ramos et al. *J Am Soc Nephrol* 2002;13:2145

BK VIRUS NEPHROPATHY *TREATMENT*

- Reduce immunosuppression
- Case series with variable success using:
  - Low-dose cidofovir
  - Leflunomide
- New drugs & randomized controlled trials needed
- Preemptive monitoring key to prevention

Hirsch et al. Transplantation 2005;79:1277-1286; Farasati et al. Transplantation 2004;79:116; Vats et al. Transplantation 2003;75:105; Kabambi et al. Am J Transplant 2003;3:186; Williams et al N Engl J Med 2005;352:1157-58.

INVASIVE FUNGAL INFECTIONS IN SOLID ORGAN TRANSPLANT RECIPIENTS



Type of fungal infection varied depending on organ transplanted

Pappas P et al. CID. 2010;50:1101-1111.

INVASIVE FUNGAL INFECTIONS ACCORDING TO ORGAN TRANSPLANTED N=16,808

	Kidney	Heart	Pancreas	Liver	Lung	Small Bowel
12 Month IFI Incidence (%)	1.3	3.4	4.0	4.7	8.6	11.6
IFI Type (%)					70% Molds	
Candidiasis	49	49	76	68	23	85
Aspergillosis	14	23	5	11	44	0
Other molds	7	10	3	6	26	0
Cryptococcosis	15	10	5	6	2	5
Endemic	10	3	6	5	1	0
Pneumocystosis	1	3	1	0	2	0
Other	4	2	4	4	2	10

Pappas P, Alexander B, Andes D, et al. CID 2010;50:1101-1111

INVASIVE FUNGAL INFECTIONS *RISK FACTORS AFTER SOT*

Each solid organ group will have unique risks for IFIs

Strongly influenced by medical & surgical factors including technical complexity

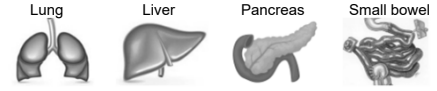
Liver
- Re-transplantation
- Pre-tx fulminant hepatic or renal failure
- Heavy *Candida* colonization peri-tx
- Large volume intra-operative transfusions
- Bleeding complications requiring re-operation
- Choledochojejunostomy

CANDIDA

Lung
- Vulnerable anastomotic site
- Continuous environmental exposure
- *Aspergillus* colonization of airways
- CMV pneumonitis
- Acute rejection
- Obliterative bronchiolitis

ASPERGILLUS

ANTIFUNGAL PROPHYLAXIS FOR SOLID ORGAN TRANSPLANT RECIPIENTS



Husain S, et al. *J Heart Lung Transpl.* 2016;35:261-82. Silveira FR, Kusne, AST ID COP. *Am J Transpl.* 2013;13:220-37. Singh NM, Husain S, AST ID COP. *Am J Transpl.* 2013;13:228-41.

TUBERCULOSIS

- 34-74 fold higher risk of active disease in SOT recipients than general population
- Incidence 1% - 6% (up to 15% in endemic areas)
- Median onset 9 months post-tx (0.5-144 months)
- 33% of infections are disseminated at diagnosis
- Treatment
  - Rifampin-based regimens associated with graft loss/rejection in 25%
- Mortality ~30%
- Treat latent TB prior to transplant when possible

CASE 3

2023 PREVIEW QUESTION

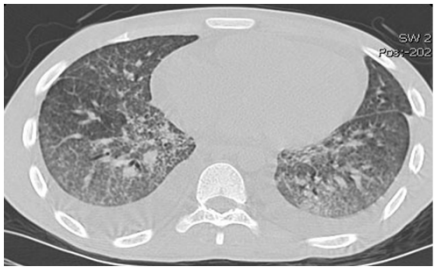
- 35 yo female s/p heart transplant in France 90 days prior presented with fever, dyspnea and a diffuse pneumonia on chest CT.
- She was receiving prednisone, tacrolimus & mycophenolate.
- Both recipient & donor were CMV negative; she was not on CMV prophylaxis.
- She was on inhaled pentamidine for PCP prophylaxis.

45 – Solid Organ Transplantation

Speaker: Barbara Alexander, MD

CHEST CT

2023 PREVIEW QUESTION



CASE 3

2023 PREVIEW QUESTION

Trimethoprim-sulfamethoxazole was started empirically and she began improving.

Bronchoalveolar lavage (BAL) was negative for:

- pneumocystis by direct fluorescent antibody stain & PCR,
- fungi by calcifour white / potassium hydroxide stain,
- mycobacteria by AFB smear,
- bacteria by Gram stain, and
- respiratory viruses by multiplex PCR

Routine bacterial BAL and blood cultures were negative.

QUESTION #3

2023 PREVIEW QUESTION

Assuming trimethoprim-sulfamethoxazole was causing her improvement, which additional test on the BAL might have explained her improvement?

A. PCR for CMV

B. PCR for toxoplasmosis

C. PCR for tuberculosis

D. Galactomannan

E. Cold enrichment culture for Listeria

TOXOPLASMOSIS

- After SOT, acute toxoplasmosis can develop from reactivation, acquisition via blood transfusion or ingestion of contaminated food or water, or from the donated organ
- Donor seropositive/Recipient seronegative at high risk
- HEART > LIVER > KIDNEY TRANSPLANT
- Presents with myocarditis, pneumonitis & meningitis
- DIAGNOSIS:
  - PCR
  - Giemsa smear of BAL
  - Brain aspirate for tachyzoites
  - Immunoperoxidase stain of endocardial biopsy or other tissue
- TREATMENT: sulfadiazine-pyrimethamine-leucovorin

CASE 4

Liver transplant recipient on bactrim & valganciclovir prophylaxis

presented 21 days post transplant with confusion, tremors, lethargy, anorexia

- Rapid progressive neurologic decline → agitation & delirium →intubation
- Brain MRI: non-revealing
- Blood & urine cultures: negative
- CSF: lymphocytic pleocytosis (25 WBCs/mm^3) & elevated protein
  - Gram stain, bacterial, fungal cultures negative for organisms
- Empiric intravenous ganciclovir, vancomycin, ceftriaxone & ampicillin
- Day 6 Repeat MRI: diffuse encephalitis
- Expired 13 days after neurologic symptom onset
- Donor was previously healthy presenting with subarachnoid hemorrhage
  - Toxicology screen: + cocaine & marijuana
  - Brain CT: expanding subarachnoid hemorrhage
  - Recently on camping trip

QUESTION #4

This presentation is most consistent with:

A. CMV encephalitis

B. HHV6 encephalitis

C. VZV encephalitis

D. Rabies encephalitis

E. Cryptococcal meningitis

45 – Solid Organ Transplantation

Speaker: Barbara Alexander, MD

"EXPECTED" DONOR-DERIVED INFECTIONS

- **Expected = known before tx or for which there are recognized standard prevention guidelines**
  - Cytomegalovirus (CMV)
  - Epstein–Barr virus (EBV)
  - Toxoplasmosis

*United Network for Organ Sharing / Organ Procurement and Transplant Network

Ison M et al. Am J Transplant. 2009;9:1929-1935.

"UNEXPECTED" DONOR-DERIVED INFECTIONS
VIRUSES, VIRUSES, & PARASITES, OH MY…

- Lymphocytic choriomeningitis virus (LCMV)
  - Hamsters and rodents
  - 4 outbreaks (3 USA, 1 Australia); 9 deaths

- Rabies virus
  - Unreported bat bite in donor
  - 3 outbreaks (2 USA, 1 Germany); 8 deaths

- Chagas' Disease (Trypanosoma cruzi)
  - Reduviid bug (Latin America)
  - Screening tests lack sensitivity
  - Multiple transmissions reported

- HIV, Hep C, Hep B, West Nile Virus (WNV)
  - Remember the "Window" prior to development of antibodies
  - Nucleic Acid Tests decrease "window" to ~5-10 days (HIV), 6-9 days (HCV)

Fisher SA et al. N Engl J Med. 2006;354:2235-2249. MMWR Morb Mortal Wkly Rep. 2008;57:799-801. Kusne S et al.Transpl. 2005;11:1295-1297. Maier T et al. CID 2010;50:1112-1119.Mattner F et al.Infection. 2007;35(4):219-24. Grossi PA, et al. Am J Transpl. 2009;9:S19-S26.

TYPICAL PRESENTATIONS OF UNEXPECTED DONOR DERIVED INFECTIONS

- Most present in the first 3 months post transplant
- Look for epidemiologic clues for potential donor exposure in the stem (e.g. possible bat bites, new pet hamsters, tap water nasal irrigations, recent travel to a region endemic for certain pathogens)

PATHOGEN	PRESENTATION
LYMPHOCYTIC CHORIOMENINGITIS VIRUS	ENCEPHALITIS
RABIES	ENCEPHALITIS
TOXOPLASMOSIS	DIFFUSE PNEUMONIA MYOCARDITIS RETINITIS ENCEPHALITIS
WEST NILE VIRUS	MENINGITIS ENCEPHALITIS POLIOMYELITIS-LIKE FLACCID PARALYSIS
CHAGAS' DISEASE	FEVER MYOCARDITIS
ACANTHAMOEBA	SKIN LESION ENCEPHALITIS
BALAMUTHIA MANDRILLARIS	ENCEPHALITIS
VISCERAL LEISHMANIASIS	PANCYTOPENIA HEPATOSPLENOMEGALY
MALARIA	FEVER

VACCINATION RECOMMENDATIONS FOR SOT

Update vaccinations pre SOT:

- COVID
- Hepatitis A, Hepatitis B, Flu, TDaP, Pneumococcal
- Live Varicella, MMR vaccines (≥4 wks pre-tx)
- HIB, Meningococcal if planned splenectomy (e.g. Multivisceral Tx)

Recommended post SOT:

(Delay 1 month post-tx; 3–6 months to maximize response)

- COVID
- Pneumococcal
- Tetanus-diphtheria toxoid
- Inactivated Influenza

Live vaccines are NOT recommended after SOT including:

- Measles Mumps Rubella
- Varicella
- Inhaled influenza
- Oral polio
- Yellow fever
- BCG
- Small pox
- Salmonella typhi (oral)

SOLID ORGAN TRANSPLANT
PATIENT TRAVEL

- **REGIONAL EXPOSURES**
  - **COCCIDIOIDOMYCOSIS: Southwest U.S.**
  - **HISTOPLASMOSIS: Central/Mid-Atlantic U.S.**
  - **VISCERAL LEISHMANIASIS: Spain, Mediterranean Basin**
  - **MALARIA: Tropics**
  - **BABESIA MICROTI: Northeast & Upper Midwest U.S.**
- **AND ALL THE "NORMAL" RISKS TO TRAVELERS**
  - **DIARRHEA**
  - **STIs**
  - **MDR-TB**
  - **BLOOD SUPPLY (need for TRANSFUSIONS), etc….**
- **AVOID LIVE VACCINES: Yellow Fever, Oral typhoid, etc.**
- **DRUG INTERACTIONS →Transplant meds + travel related prophylactic agents**

KEY DRUG TOXICITIES / SYNDROMES

- Calcineurin inhibitors and TTP and PRES (RPLS)
- Sirolimus-induced pneumonitis
  - Progressive interstitial pneumonitis (22% in one study)
  - Risk factors: late switch to sirolimus & impaired renal function
  - Symptoms: dyspnea, dry cough, fever, and fatigue
    - Radiographic & bronchoalveolar lavage consistent with bronchiolitis obliterans organizing pneumonia & lymphocytic alveolitis
  - Recovery with sirolimus withdrawal

Euvrard S et al. N Engl J Med. 2012;367(4):329. Champion L et al. Ann Intern Med 2006;144:505. Weiner SM et al. Nephrol Dial Transplant. 2007;22(12):3631.

45 – Solid Organ Transplantation

Speaker: Barbara Alexander, MD

OTHER PEARLS FOR BOARDS…

If you're thinking PCP but its not → think TOXO

Patient presenting atypically during first month post transplant → think donor transmitted infection
- Rabies, WNV, Coccidioides, Chagas, LCMV (look for epidemiologic clues in stem)

Remember drug interactions and syndromes
- Addition of mold active azole leading to acute kidney injury from elevated CNI
- TTP and PRES induced by calcineurin inhibitors
- Sirolimus-induced pneumonitis

Remember *Strongyloides* hyperinfection syndrome

TB- Don't miss a case!

BKV, CMV and EBV/PTLD – know how to diagnose and manage

Thank You!

barbara.alexander@duke.edu

46

Nontuberculous Mycobacteria in Normal and Abnormal Hosts

Dr. Kevin Winthrop

46 – Nontuberculous Mycobacteria in Normal and Abnormal Hosts

Speaker: Kevin Winthrop, MD

Nontuberculous Mycobacteria in Normal and Abnormal Hosts

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

6/30/2023

Disclosures of Financial Relationships with Relevant Commercial Interests

- **Grant: Insmed**
- **Consultant: Insmed, Spero, Red Hills, Paratek, AN2**

Nontuberculous Mycobacterium (NTM)

- "MOTT" or "Atypical"
- Environmental organisms
  - Soil, lakes, rivers, municipal water systems
  - Resistant to chlorine and most disinfectants
- Biofilm
  - Live within amoeba, legionella, others

Laboratory Growth Characteristics

- "Slow" growers (>2 weeks in AFB media, liquid media more quickly)
  - M. avium complex (MAC), *M. kansasii, M. marinum, M. xenopi*
- "Rapid" growers (4-7 days in routine blood agar)
  - *M. abscessus, M. chelonae, M. fortuitum*
- *"Need help" growing*
  - *M. marinum, M. haemophilum, M. ulcerans,*
  - *M. genavense (often molecular ID)*

NTM Disease Clinical Manifestations

- Pulmonary (75%)
  - MAC
  - *M. kansasii*
  - *M. xenopi*
  - *M. abscessus*
  - *M. malmoense*

NTM Disease Clinical Manifestations

Skin and Soft tissue (15%)
- MAC, *M. marinum, M. abscessus, M. chelonae, M. fortuitum, M. kansasii, M. ulcerans*

- Lymph node disease (5%)
  - *MAC, (historically also M. scrofulaceum*)

Disseminated (5%)
- MAC, *M. kansasii, M. abscessus, M. chelonae, M. haemophilum*

- Hypersensitivity pneumonitis (0%)
  - *MAC and hot-tubs*

Important Bug-Setting Associations

- Corneal Disease
  - *M. chelonae*
- Healthcare/hygiene associated outbreaks
  - *M. chelonae, M. fortuitum, M. abscessus*
- Line-associated
  - *M. mucogenicum*
- HIV setting
  - *MAC, M. kansasii, M. genavense, M. haemophilum*
- Tropical setting
  - *M. ulcerans* (buruli ulcer)

Other Pearls Based on Species

- *M. gordonae*
  - *Contaminant*
- NTM are not communicable
  - CF?
- *M. immunogenum, M. simiae*
  - Pseudo-outbreaks
- *M. szulgai*, *M. kansasii*, and *M. marinum*
  - Cross-react with IGRAs
- *M. fortuitum* lung disease
  - Aspiration
- *M. marinum*
  - Fish and fishtanks

Question #1

72 year old female with chronic cough, normal CXR, and 1/3 sputums grow MAC. Which one of the following you do recommend ?

A. CT scan of chest AND Additional sputum AFB cultures
B. Empiric therapy with azithromycin, ethambutol, and rifampin
C. Additional sputum AFB cultures
D. Wait for in vitro susceptibility data and then treat.

Pulmonary NTM

2007 ATS/IDSA diagnostic criteria:

- Patient has both radiographic evidence of disease and pulmonary symptoms

AND

- At least 2 sputum cultures positive, or
- One BAL or tissue specimen with positive culture, or
- Tissue with granulomatous histopathology in conjunction with positive culture (BAL or sputum)

Griffith D et al. *AJRCCM* 2007

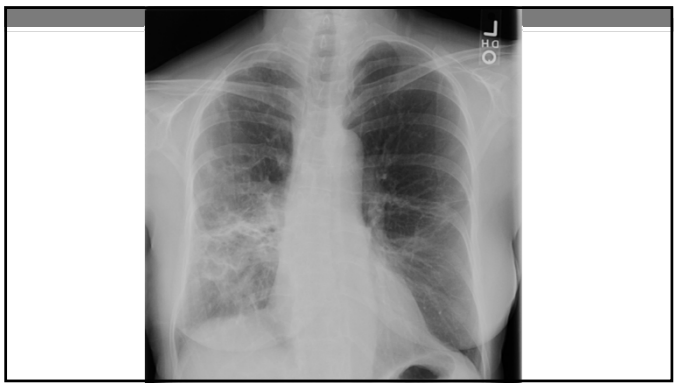
Pulmonary NTM

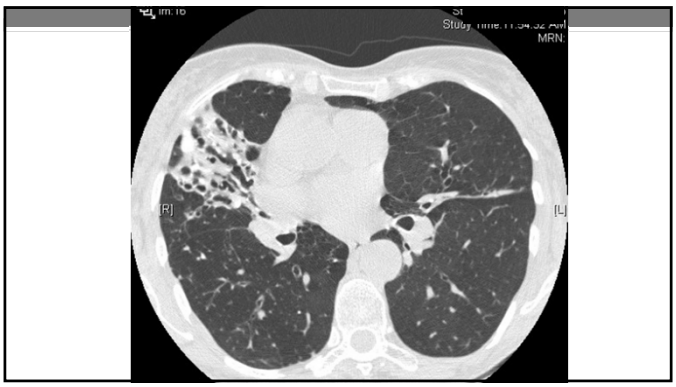
- MAC is most common etiology (60-90%)
- M. kansasii and M. abscessus
  - *M. kansasii* primarily in the South
  - Recent *M. abscessus* increase in CF
- Other organisms of importance
  - *M. xenopi* (northern US/ Canada, Europe)
  - *M. malmoense* (Europe)

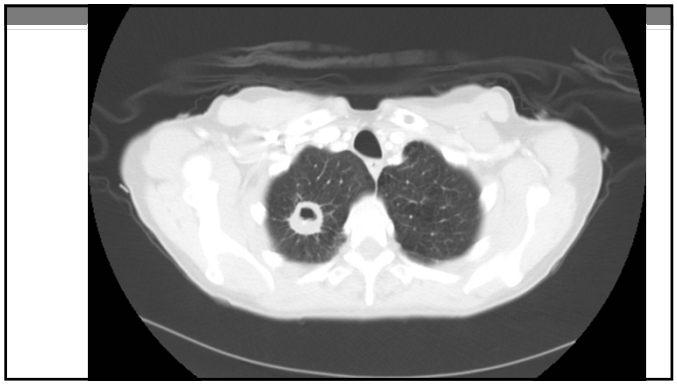
Two Types of MAC Pulmonary Diseases

- Older male, smoker, COPD
  - Apical cavitary or fibronodular disease
  - More rapidly progressive
- Older female ("Lady-Windermere")
  - Scoliosis, thin, pectus deformities*, hypomastia
  - Nodular and interstitial nodular infiltrate
  - Bronchiectasis right middle lobe / lingula
  - Bronchiolitis ("tree and bud") on HRCT
  - Slowly progressive

***Iseman MD et al. *Am Rev Respir Dis.* 1991**







Pulmonary NTM Risk Factors

- Underlying lung architectural abnormalities
  - Bronchiectasis, CF, α-1, emphysema
  - Prior TB, GERD/aspiration
- Exposure/transmission
  - Gardening/soil, Hot tubs
- Immunosuppressives
  - Prednisone, inhaled corticosteroids, biologics

NTM Pulmonary Disease Diagnosis

- Diagnosis ≠ decision to treat
  - Observation vs. suppression vs. cure

MAC Therapeutic Options

- Treatment best defined for MAC
  - Start Macrolide, rifampin, ethambutol
  - Amikacin first 1-2 months for cavitary disease
  - Treatment duration 18-24 months (12 month culture negative)
  - Macrolide monotherapy is contraindicated
  - Recommended to test susceptibility for macrolide
  - TIW okay if non-cavitary or not re-infection

Pulmonary M. kansasii Therapy

- *M. kansasii* clinically more like TB
  - Thin-walled cavities, upper lobes
  - Treatment with INH, RIF, EMB
  - TIW therapy ok
  - Treatment duration: 12 months culture negativity
  - High treatment success rates (90%+)
  - RIF is key drug.

Pulmonary M. abscessus ssp. Therapy

- *M. boletti, M. massiliense, M. abscessus*
  - Inducible macrolide resistance--erm (41) gene
- "Cure" = rare
- Can be more rapidly progressive than MAC
- 3-4 drugs for 18-24 months
  - 4-6 months "induction" phase
  - "suppressive strategy" thereafter

M. abscessus Therapy

- Parenteral agents
  - Omadacycline 100mg QD, Tigecycline 50mg QD, Cefoxitin 2gm TID, Imipenem 1000mg BID, Amikacin 10mg/kg TIW
- Oral agents
  - Clofazimine 50-100mg QD, Linezolid 600mg QD, moxifloxacin 400mg QD (rarely suscep), Azithromycin 250mg QD (if suscep)
  - Surgical resection

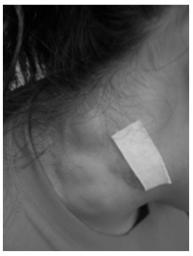
EXTRAPULMONARY NTM

1. Immunocompetent settings
2. Immunocompromised settings

Immunocompetent settings

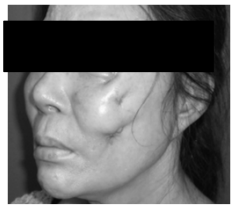
- Nail salon, trauma, surgical or injection procedures, fishtank, hot tubs
- Rapid or slow growing NTM
- Incubation period
  - Infection usually occurs 2-8 weeks after contact with contaminated water source

Children under 5 years NTM > TB



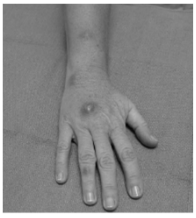
- Usually MAC
  - Males > females, age 1-2 years old
- Surgical resection alone is best therapy
- Adjunctive ABX rarely needed

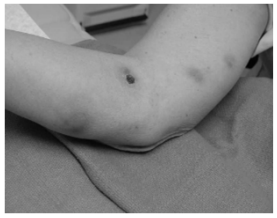
Post- plastic surgery



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

M. marinum---fish tank granuloma



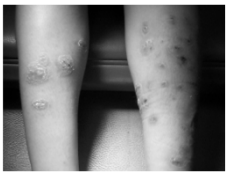


Treatment: multiple drugs

- Macrolides, sulfonamides, doxycycline, rifampin, ethambutol
- Treat with 2 agents X 3-4 months.
- Surgical debridement if necessary

Nail Salon Furunculosis

- Outbreaks and sporadic
- Rapid Growers most common (*M. fortuitum)*
- Oral antibiotics
  - 4 months fluoroquinolone and/or doxycycline
  - Can be self-limited



Tattoo-associated

- *M. chelonae*
- Tattoo-ink outbreaks
- 2-3 months oral therapy
  - Based on *in-vitro* susceptibility
  - 1-2 agents
  - Macrolides almost always

Question # 2

PREVIEW QUESTION

20 y.o. male complains of fever, night sweats and weight loss. Has generalized lymphadenopathy. HIV antibody positive; CD4 20 cells/ul. Node biopsy: non-caseating granuloma, AFB seen.

Question # 2

PREVIEW QUESTION

Based on the most likely diagnosis, which of the following do you recommend :

A. Start MAC therapy
B. Start HAART plus MAC prophylaxis
C. Start MAC therapy and HAART
D. Start HAART only

NTM in HIV

- Disseminated MAC
- GI route of infection
- Less frequent in HAART era
- Related issues
  - Clofazimine = increases mortality?
  - Rifabutin dose adjustment with PI
  - Immune reconstitution inflammatory syndrome (IRIS)

TABLE 7. REGIMENS FOR TREATMENT AND PREVENTION OF DISSEMINATED *MYCOBACTERIUM AVIUM* IN HIV-INFECTED PATIENTS

Preferred (A, I)*	Alternative (B, I)*
Treatment	
Clarithromycin 500 mg orally twice daily + Ethambutol 15 mg/kg orally daily ± Rifabutin† 300 mg orally daily	Azithromycin 500 mg daily + Ethambutol 15 mg/kg daily + Rifabutin† 300–450 mg orally daily
Prevention‡	
Azithromycin 1,200 mg orally weekly	Clarithromycin 500 mg orally twice daily or Rifabutin† 300 mg orally daily

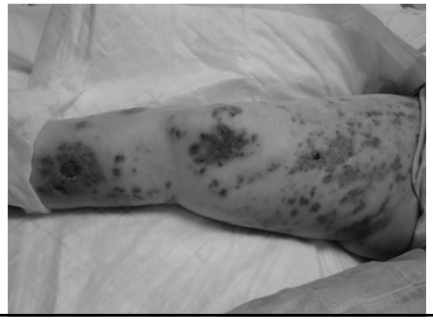
* For evidence quality, *see* Table 1.
† Rifabutin dose may need to be modified based on drug–drug interactions (*see* text).
‡ Preventive therapy indicated for persons with < 50 CD4+ cells/μl; may stop if > 100 cells/μl.

Griffith D et al. AJRCCM 2007

Immunosuppression other than HIV

- Most frequently disseminated
  - Local inoculation versus GI route
- Risk factors and conditions
- ESRD, prednisone, biologic immunosuppressives
- Cancer, transplant, leukemia (hairy cell)
- Auto-antibody and cytokine/receptor deficiency states
  - INF-gamma, IL12-23 pathway, STAT-1
- Disease split between RGM and slow growers
  - RGM more common here than in pulmonary disease

M. chelonae in cancer patient



M. chelonae and *M. fortuitum* treatment

- *M. chelonae*
  - Macrolides,flouroquinolone, linezolid
  - IV drugs include aminoglycosides, imipenem, cefoxitin, tigecycline
  - Note: tobramycin is best for *M. chelonae*
- *M. fortuitum*
  - Macrolides, flourquinolone, bactrim, doxy (50%)
  - IV drugs include aminoglycosides, imipenem, cefoxitin, tigecycline

Length of treatment for disseminated infection
3 drugs (including 1 IV) X 4-6 months
Depends on immunosuppression reversal

M. chimaera

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

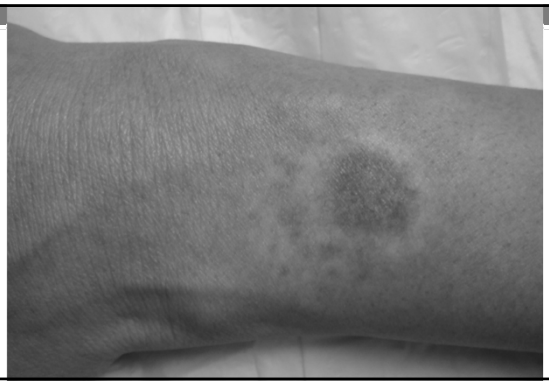
Hansen's Disease (Leprosy)

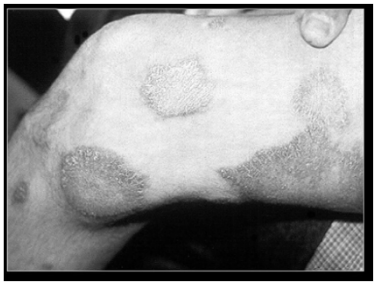
- Rare in US (100-200 cases per year)
  - Armadillos and gulf region
  - Rest imported
- Most humans resistant
  - Household contacts at risk (low risk)
  - Nasopharyngeal transmission?
- *M. leprae* does not grow in culture

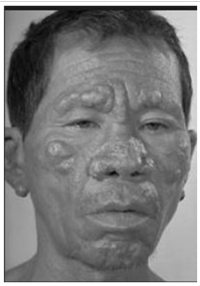
Leprosy Disease Classification

- Paucibacillary (PB)
- Most common form
  - *"Tuberculoid"*
  - Bacillary load < 1 million
  - Skin biopsy: AFB negative
  - ≤5 skin lesions

- Multibacillary (MB)
  - *"Lepromatous"*
  - Massive bacillary load
  - Skin biopsy: Floridly positive for AFB
  - >5 skin lesions.







Leprosy Treatment

- PB (6 months)
  - Dapsone 100mg daily
  - *Rifampin 600mg once monthly
- MB (12+ months)
  - Dapsone 100mg daily
  - Clofazimine 50mg daily
  - Rifampin 600mg daily

Complications: reversal reactions, erythema nodosum
Treat with prednisone, thalidomide, other

*US guidelines is daily

Top 10 or 12 NTM pearls for the Boards

- Footbaths = *M. fortuitum* or other RGM
- *Plastic Surgery* = *M. chelonae* or other RGM
- Equitorial Africa = *M. ulcerans*
- HIV disseminated MAC that doesn't grow = think of *M. genavense*
- *M. abscessus* usually has inducible macrolide resistance (erm gene)
- Macrolide, EMB, RIF for 18-24 months for pulmonary MAC
- *M. gordonae* is 99.9% a contaminant
- ATS/IDSA pulmonary case definition: need one BAL or two sputums or tissue
- Know NTM species that cross-react with TB IGRAs
- No clofazimine in HIV related MAC
- *M. kansasii* behaves like TB---responds to TB drugs (RIF, EMB, INH)
- PZA not useful for any NTM

47

Lots of Protozoa

Dr. Edward Mitre

47 – Lots of Protozoa

Speaker: Edward Mitre, MD

Lots of Protozoa

Edward Mitre, MD
Bethesda, MD

7/25/2023

Disclosures of Financial Relationships with Relevant Commercial Interests

- **None**

Disclaimer: Dr. Mitre is giving this presentation in a personal capacity. The views expressed in this presentation are the sole responsibility of the presenter and do not necessarily reflect the views, opinions, or policies of the Uniformed Services University of the Health Sciences, the Department of Defense, or the United States Government.

Protozoa

Protozoa - Extraintestinal	Protozoa - Intestinal
Apicomplexa Plasmodium Babesia (Toxoplasma)	**Apicomplexa** Cryptosporidium Cyclospora Cystoisospora
Flagellates Leishmania Trypanosomes (Trichomonas)	**Flagellates** Giardia Dientamoeba
Amoebae Naegleria Acanthamoeba Balamuthia	**Amoebae** Entamoeba
	Ciliates Balantidium

National Institutes of Health

National Institute of Allergy and Infectious Diseases **Not Protozoa**

Kingdom Fungi: Microsporidiosis agents
Kingdom Chromista: Blastocystis

Protozoa

Protozoa - Extraintestinal	Protozoa - Intestinal
Apicomplexa Plasmodium Babesia (Toxoplasma)	**Apicomplexa** Cryptosporidium Cyclospora Cystoisospora
Flagellates Leishmania Trypanosomes (Trichomonas)	**Flagellates** Giardia Dientamoeba
Amoebae Naegleria Acanthamoeba Balamuthia	**Amoebae** Entamoeba
	Ciliates Balantidium

National Institutes of Health

National Institute of Allergy and Infectious Diseases **Not Protozoa**

Kingdom Fungi: Microsporidiosis agents
Kingdom Chromista: Blastocystis

PREVIEW QUESTION

Question 1: A 54 yo woman presents with fever, chills, and oliguria one week after travel to Malaysia.

Vitals: **39.0** ° C, HR 96/min, RR 24/min, **BP 86/50**

Labs: Hct 31%, platelets14,000/μl, Cr of 3.2 mg/dL.

Peripheral blood smear has intraerythrocytic forms that are morphologically consistent with *Plasmodium malariae*.

National Institutes of Health

The most likely infectious agent causing the patient's illness is:

A. Plasmodium malariae
B. Plasmodium knowlesi
C. Plasmodium vivax
D. Plasmodium falciparum
E. Babesia microti

National Institute of Allergy and Infectious Diseases

P. knowlesi

morphologically similar to *P. malariae*

usually a parasite of long-tailed macaques

increasingly recognized in Myanmar, Phillipines, Indonesia, and Thailand.

causes high parasitemia

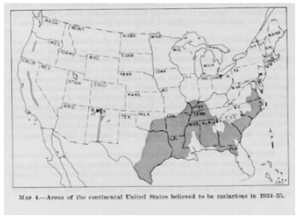
highly morbid and can be lethal

47 – Lots of Protozoa

Speaker: Edward Mitre, MD

MALARIA

one of the most important pathogens in the history of the world

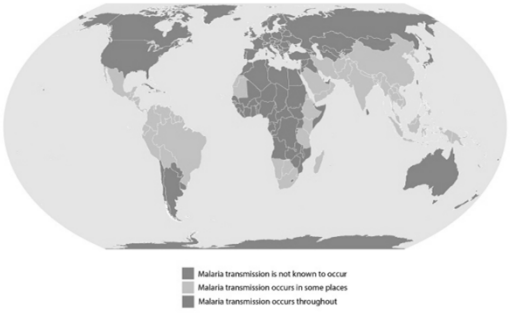


Map 4.—Areas of the continental United States believed to be malarious in 1934-35.

National Malaria Elimination Program: 1947- 1951
→ DDT spraying, drainage of wetlands
→ Atlanta was chosen for the Office of Malaria Control in War Areas (the predecessor agency of the CDC) in part because of its location in a malaria-endemic region

In 1775 the Continental Congress purchased quinine for George Washington's troops

MALARIA EPIDEMIOLOGY



Malaria transmission is not known to occur
Malaria transmission occurs in some places
Malaria transmission occurs throughout

This map shows an approximation of the parts of the world where malaria transmission occurs.

https://www.cdc.gov/malaria/about/distribution.html

MALARIA EPIDEMIOLOGY

P. vivax cases 2023

Malaria transmission is not known to occur
Malaria transmission occurs in some places
Malaria transmission occurs throughout

This map shows an approximation of the parts of the world where malaria transmission occurs.

https://www.cdc.gov/malaria/about/distribution.html

In non-immune patients, falciparum malaria is a medical emergency!!

→one of the most common causes of fever in a returned traveler

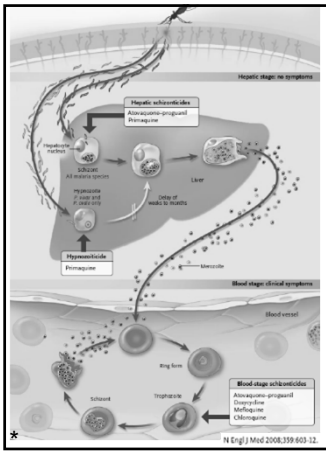
→ infected individuals can rapidly progress from appearing well to being critically ill

---Some helpful heuristics---

If patient has	**make sure patient doesn't have**
Fever and freshwater contact	
Fever and unpasteurized milk	
Fever and undercooked meat	
Fever and raw vegetables	
Fever and untreated water	
Fever and wild dog bite	
Fever and abdominal pain	
Fever and headache	
Fever and diarrhea	
Fever and cough	
Fever and dysuria	

---Some helpful heuristics---

If patient has	**make sure patient doesn't have**
Fever and freshwater contact	**Malaria**
Fever and unpasteurized milk	**Malaria**
Fever and undercooked meat	**Malaria**
Fever and raw vegetables	**Malaria**
Fever and untreated water	**Malaria**
Fever and wild dog bite	**Malaria**
Fever and abdominal pain	**Malaria**
Fever and headache	**Malaria**
Fever and diarrhea	**Malaria**
Fever and cough	**Malaria**
Fever and dysuria	**Malaria**



Sporozoites
- **Infective stage**
- Come from mosquito

Liver schizont
- **Asymptomatic replicative stage**
- Become 10,000 to 30,000 merozoites

Hypnozoite
- Dormant liver stage in **vivax and ovale**
- Release merozoites weeks to months after primary infection

Merozoites
- Infect RBCs and develop into ring-stage trophozoites
- Mature into schizonts, which release merozoites which infect more RBCs

Gametocytes
- Infective stage for mosquitoes

characteristics of human malaria species

	P. falciparum	P. knowlesi	P. vivax	P. ovale	P. malariae
incubation	8 - 25 d	prob 8-25 d	~ 2 wks	~ 2 wks	~ 3-4 wks
hypnozoite	no	no	yes	yes	no
RBC age	any	any	young	young	old
parasitemia	high	high	< 2%	< 2%	< 1%
morbidity	high	high	high	moderate	low
mortality	high	moderate	low	low	low

Possible evolutionary defenses against malaria

Duffy antigen negative (*P. vivax* uses Duffy Ag to enter RBCs)

Sickle cell trait (increases survival during *P. falciparum* infection, perhaps by selective sickling of infected RBCs)

Glucose-6-phosphate dehydrogenase deficiency
(malaria parasites grow poorly in G6PD deficient RBCs, perhaps b/c this results in an overall increase in reactive oxygen species in RBCs)

Uncomplicated (mild) malaria

Symptoms: fevers, chills, headache, fatigue
***NOTE: abdominal pain presenting symptom in 20%**

→ periodicity of fevers not common when patients seen acutely

Labs: Thrombocytopenia in 50%
mild anemia in 30%
typically no leukocytosis
may see evidence of hemolysis with mild increase T bili and LDH

Complicated (severe) malaria

- Cerebral malaria (altered mental status, seizures)
- Respiratory distress/pulmonary edema
- Severe anemia (hct <15% in children, <20% in adults)

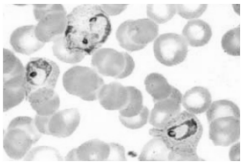
} Often seen in children of endemic countries. Adults more often get multiorgan failure.

- Renal failure
- Hypoglycemia
- Shock (SBP < 80 mm Hg or capillary refill > 3 seconds)
- Acidosis (often lactic acidosis)
- Jaundice (total bilirubin > 3 mg/dL)
- Bleeding disorder (spontaneous bleeding or evidence of DIC)

These complications primarily occur with *Plasmodium falciparum,* usually when parasitemia >2%.

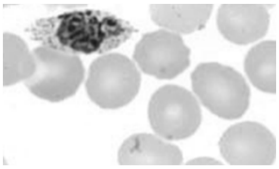
NOTE: in the absence of end organ damage, parasitemia >10% is often used as the cut-off to treat for severe malaria

P. vivax or ovale



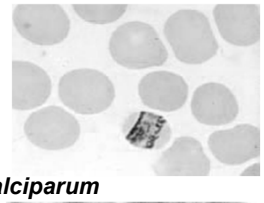
Both have
- intracellular Schüffner's dots
- enlarged infected cells

P. ovale



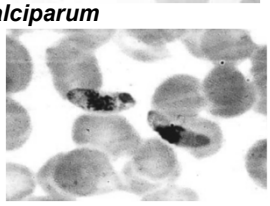
P. ovale
-elongated or oval
-6-12 merozoites (vs 12-24 for vivax)

P. malariae



-band form
(also seen in *P. knowlesi*)

P. falciparum



Banana shaped gametocyte

Malaria: Diagnosis

Rapid diagnostic (antigen capture) tests
→ sensitivity 95% for P. falciparum (about 85% for other species)

Binax Now® ICT assay for the detection of *Plasmodium falciparum* malaria according to the level of parasitemia

Parasitemia (no. of parasites/μL of whole blood)	Microscopy (no. positive)	NOW ICT (no. positive)	Sensitivity (%)
1–100	4	3	75.0
101–1,000	26	25	96.2
1,001–10,000	37	36	97.3
>10,000	34	33	97.1

Am. J. Trop. Med. Hyg., 69(6), 2003, pp. 589–592

for P. falciparum (T1) → tests for histidine-rich protein 2
for all species (T2) → tests for aldolase

Most false-negative antigen tests are due to low parasite burden. So, retest suspected patients that initially test negative.

Note: there are some false negative cases that have occurred due to mutations in HRP2 protein.

Question 2: A 33-year-old woman is traveling to Uganda to do field studies in anthropology. She is two months pregnant. Which of the following do you prescribe for malaria prophylaxis?

National Institutes of Health

A. Doxycycline
B. Chloroquine
C. Mefloquine
D. Atovaquone/proguanil
E. No prophylaxis

National Institute of Allergy and Infectious Diseases

Malaria Chemoprophylaxis **(note: no vax for travelers)**

CENTRAL AMERICA and MIDDLE EAST

	Pre-Exposure	During	Post-Travel
Chloroquine 500mg tabs	1 tab/wk x 2 wks	1 tab/wk	4 weeks
EVERYWHERE			
Atovaquone/proguanil 250/100mg	1 tab daily x 2 d	1 daily	7 days
Doxycycline 100mg tabs	none	1 daily	4 weeks
Tafenoquine* 100mg tabs	2 tab daily x 3 d	2 tab/wk	2 tab after 1 wk
Mefloquine (not SE Asia)** 250mg tabs	1tab/wk x 2-3 wks	1 tab/wk	4 weeks

* *Tafenoquine can precipitate severe hemolytic anemia in individuals that are G6PD deficient*

** *FDA black box warning mefloquine can cause neurologic symptoms, hallucinations, and feelings of anxiety, mistrust, and depression. Can also cause QT prolongation. Thus, many U.S. practitioners now reserve mefloquine for pregnant travelers to areas with chloroquine resistance*

P. falciparum treatment

Excellent review → 2022 JAMA, 328(5):460-47, PMID: 3591684

Uncomplicated P. falciparum malaria (no organ dysfunction, low parasitemia, able take po)

if chloroquine sensitive area → chloroquine or hydroxychloroquine

if not chloroquine sensitive area (most cases) → **artemether/lumefantrine (Coartem)**
ACTs are treatment of choice, WHO 2022 guidelines
alternatives if artemether/lumefrantrine not available
→ atovaquone/proguanil (Malarone), quinine + doxycycline, mefloquine

Severe Malaria

→ **IV artesunate** (CDC malaria hotline: 770-488-7788)

NOTES

1) Treatment failures can occur with artemether/lumefrantrine, especially when > 65 kg
Sonden K. et al, *Clinical Infectious Diseases* 2017 PMID: 27986683

2) Artemisinin resistance has been reported in SE Asia (Cambodia, Laos, Myanmar, Thailand, Vietnam), parts of Africa (Uganda, Rwanda), and in S. America (Guyuna)

3) Delayed-onset anemia in 2.7% of U.S. patients after treatment with artesunate
Abanyie F. et al, *Clinical Infectious Diseases* 2022 PMID: 36052468

P. vivax/P.ovale Treatment

chloroquine x 3 days, or ACT (artemether/lumefrantrine in U.S.)
note: PNG, Indonesia, Oceania have CLQ R P. vivax → use ACT)

then ANTIRELAPSE THERAPY

→ Need to check G6PD status before administering primaquine OR tafenoquine
(as both can cause severe hemolysis in patients with G6PD deficiency)
→ Both primaquine and tafenoquine contraindicated during pregnancy

- **primaquine – weight based dosing and duration as determined by G6PD activity**
  *****ALWAYS LOOK THIS UP BEFORE ADMINISTERING*****
  -> usually 30 mg primaquine base per day x 14 days if normal G6PD activity
  -> do not exceed 30 mg primaquine base per day
  -> if over 70 kg, calculate total dose 6 mg/kg, extend duration of 30 mg daily doses until total goal met
  -> if intermediate G6PD activity, then can treat with 45 mg weekly for 8 weeks)

or

- **tafenoquine (two 150 mg tabs once, given on 1st or 2nd day of chloroquine therapy)**
  (Tafenoquine was approved for radical cure of *P. vivax* in 2018, *P. ovale* treatment is off-label)

2020 : Company (GSK) reported some failures when tafenoquine was used after ACT treatment of P. vivax.
NEW FDA LABELING: **Tafenoquine now only approved and recommended after chloroquine treatment**

https://www.cdc.gov/malaria/resources/pdf/Malaria_Treatment_Table_202208.pdf

* Suggestions for all ID practitioners *

1) Make sure the facility where one works has the means to rapidly test for malaria

2) Ensure that hospital pharmacy has access to appropriate medications for treatment of malaria

Babesia

Transmission

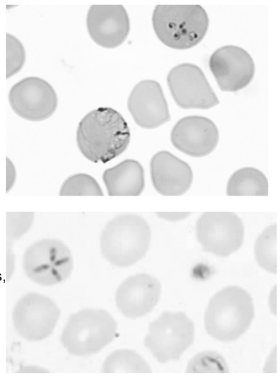
- Ixodes ticks in Northeast and upper midwest
  →co-infection with Lyme and Anaplasma
- Transfusion
  (Ab screening tests approved by FDA in 2018)

Symptoms: fever, headache, chills, myalgias
less common: nausea, dry cough, neck stiffness, vomiting, diarrhea, arthralgias
→ severe disease: in HIV, asplenia

Labs: anemia, thrombocytopenia, mild increase LFTs, normal/low/high WBC

Diagnosis: small ring forms in RBCs, PCR, Ab
merozoites can make tetrad ("Maltese cross")

Treatment: azithromycin + atovaquone
(clindamycin + quinine is alternative)
→ Exchange transfusion for severe disease



CDC DpDx

Protozoa

Protozoa - Extraintestinal

Apicomplexa
Plasmodium
Babesia
(Toxoplasma)

Flagellates
Leishmania
Trypanosomes
(Trichomonas)

National Institutes of Health

Amoebae
Naegleria
Acanthamoeba
Balamuthia

Protozoa - Intestinal

Apicomplexa
Cryptosporidium
Cyclospora
Cystoisospora

Flagellates
Giardia
Dientamoeba

Amoebae
Entamoeba

Ciliates
Balantidium

National Institute of Allergy and Infectious Diseases

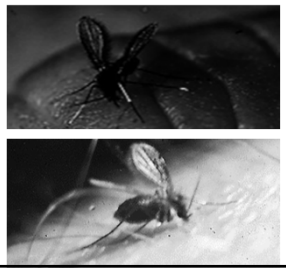
Not Protozoa **Kingdom Fungi**: Microsporidiosis agents
Kingdom Chromista: Blastocystis

Leishmaniasis

→obligate intracellular protozoan infection
→transmitted by sand flies (noiseless, active in evenings)

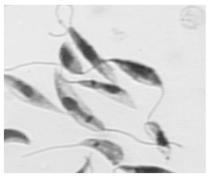
Lutzomyia
New world leishmaniasis

Phlebotomus
Old world leishmaniasis

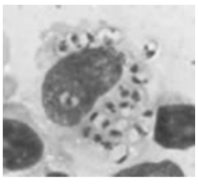


Leishmania life cycle – Two stages

Promastigote
extracellular, in sand fly
2µm wide x 20µm long
+ flagella
large central nucleus
band shaped kinetoplast



Amastigote
Intracellular (macrophages)
Round or oval
Wright-Giemsa:
dark-purple nucleus
small rod shaped kinetoplast



CDC DpDx

Question 3: A 42 yo man from Bolivia presents with nasal stuffiness and is found to have nasal septal perforation. Biopsy demonstrates intracellular amastigotes consistent with Leishmania.

Which is the most likely species?

National Institutes of Health

A. L. mexicana
B. L. braziliensis
C. L. peruviana
D. L. infantum chagasi
E. L. major

National Institute of Allergy and Infectious Diseases

47 – Lots of Protozoa

Speaker: Edward Mitre, MD

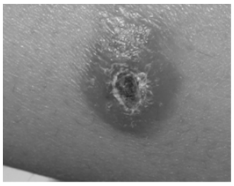
Leishmania taxonomy and disease simplified

	Cutaneous	Mucosal	Visceral
NEW WORLD			
L. mexicana complex	X		
L. braziliensis	X	X	
L. infantum chagasi			X
OLD WORLD			
L. tropica	X		
L. major	X		
L. donovani			X
L. infantum chagasi			X

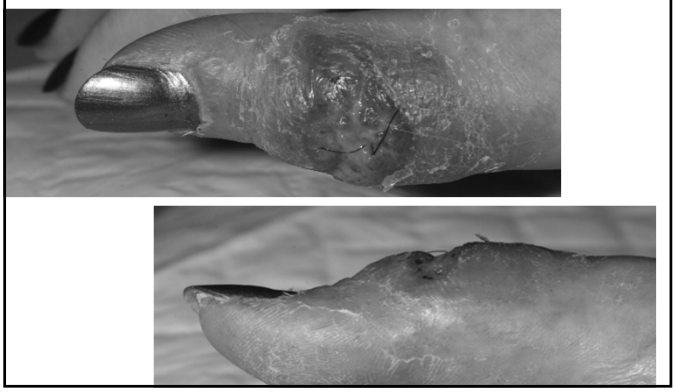
*note: *L. braziliensis* is in the Viannia subgenus. *L. V. guyanensis* and *L. V. panamensis* also cause mucosal disease. *L. peruviana* DOES NOT

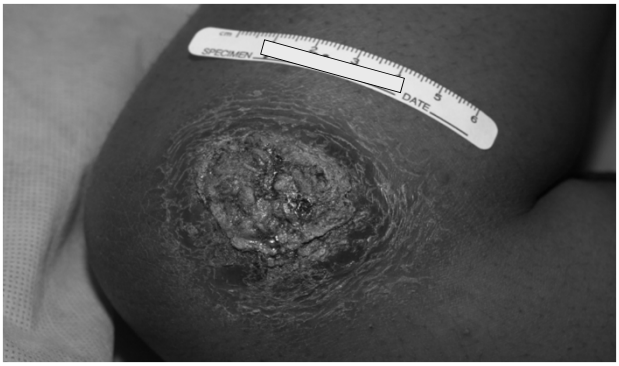
Cutaneous Leishmaniasis – Clinical Presentation

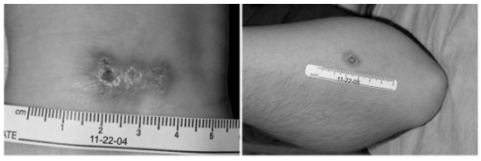
- papule → nodule →ulcerative lesion → atrophic scar
  - ulcerative lesion may have:
    - induration,
    - scaliness
    - central depression
    - raised border

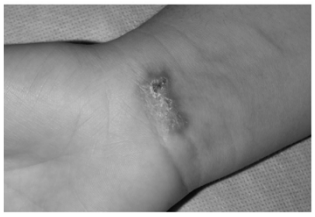


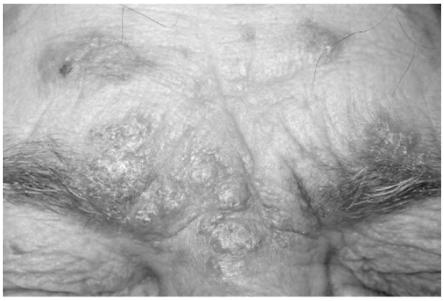
- takes weeks to months to develop
- usually painless, unless superinfected
- most lesions will eventually resolve on their own











Cutaneous Leishmaniasis – Diagnosis

Definitive diagnosis is very helpful because

1. **Allows you to rule out other possibilities**
2. **May help in deciding whether and how to treat**

Diagnostic Tools (edge of ulcer skin: scraping, aspirate, punch)

Touch prep with examination under oil looking for amastigotes

Culture on triple N media (may take weeks to grow)

(Nicolle's modification of Novy and MacNeal's medium – biphasic)

Histology

PCR

Cutaneous Leishmaniasis – Treatment Recommendations

→ Treat systemically if *L. (V.) braziliensis, guyanensis, panamensis*

→ If not, ok to observe if there are:

few lesions, they are < 5 cm, not on face/fingers/toes/genitals, normal host, no subcutaneous nodules

Treatment Options

local: heat with radiotherapy (FDA approved), cryotherapy, intralesional therapy

systemic

oral: miltefosine for certain species, especially New World CL species ketoconazole, fluconazole (off-label)

IV: liposomal amphotericin B (off-label)

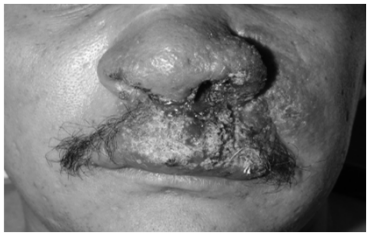
(June 2021:pentavalent antimony aka stibogluconate no longer avaialable from CDC on IND)

*****2016 IDSA GUIDELINES FOR TREATMENT OF LEISHMANIA*****

http://www.idsociety.org/Guidelines/Patient_Care/IDSA_Practice_Guidelines/Infections_by_Organism/Parasites/Leishmaniasis/

Mucosal leishmaniasis

Leishmania (Viannia) braziliensis, Guyanensis, panemensis



- dissemination to nasal mucosa
- slow, progressive, destructive
- can occur months or years after cutaneous ulcer

Treatment:
- oral miltefosine (FDA approved for *L. braziliensis*)
- IV lip. amphotericin (off-label)
- IV antimony (no longer commercially available)

Miltefosine notes
side effects: nausea, vomiting, diarrhea, increased AST/ALT
contraindicated in pregnancy, use contraception for 5 months after treatment ($t_{1/2}$ = 30 d)

Visceral Leishmaniasis

L. donovani *(South Asia, East Africa)*

L. infantum chagasi *(Middle East, Central Asia, Mediterranean, Central and S. America)*

amastigotes in macrophages go to local LNs then hematogenously to liver, spleen, bone marrow

A peristent disease that can reactivate
TNF blockade, HIV CD4 < 200

Weeks/months: fevers, chills, fatigue, hepatosplenomegaly

pancytopenia & hypergammaglobulinemia

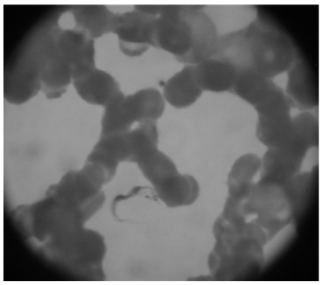
Diagnosis: intracellular amastigotes in bone marrow or splenic aspirate
antibody to rK39 recombinant Ag (dipstick test)

Treatment: liposomal ampho B (FDA approved)
miltefosine (oral) FDA approved for *L. donovani*

Question 4:

INFECTIOUS DISEASE BOARD REVIEW AUGUST 18-23 2023 **PREVIEW QUESTION**

A 41 yo woman presented to a local emergency department with a one day history of fever associated with swelling and redness in her groin four days after returning from safari in Tanzania. Peripheral blood smear is obtained.



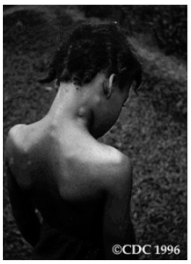
What is the most likely diagnosis?

National Institutes of Health

A. Leishmania donovani
B. Plasmodium vivax
C. Trypanosoma brucei
D. Wuchereria bancrofti
E. Leptospira interrogans

National Institute of Allergy and Infectious Diseases

African Trypanosomiasis (sleeping sickness)



Vector = tse tse fly (Glossina sp)

Trypanosoma brucei gambiense (W. Africa)
- humans as reservoirs
- progression over many months

Trypanosoma brucei rhodesiense (E. Africa)
- cattle and game park animals as reservoirs
- progression over weeks

DISEASE
within 5 days: chancre at Tse Tse fly bite
regional lymphadenopathy

for weeks: fever, hepatosplenomegaly, lymphadenopathy, faint rash, headache

late: mental status changes, terminal somnolent state

W.H.O.

African Trypanosomiasis – Lab findings

Non-specific lab findings

- anemia
- thrombocytopenia
- elevated IgM
- hypergammaglobulinemia

Diagnostic lab findings

- detection of parasite in lymph node, circulating blood, or CSF

-->do FNA of lymph node while massaging node, then push out the aspirate onto a slide and immediately inspect under 400x power. Trypanosomes can be seen moving for 15-20minutes, usually at edge of the coverslip

- a card agglutination test that detects T.b.gambiense sp. antibodies.
  -->V. sensitive (94-98%), but poor specificity
  --> can get false +s in pts with Schisto, filaria, toxo, malaria

African Trypanosomiasis - Life Cycle

Q. Why are Trypanosoma brucei infections associated with persistently elevated IgM levels?

African Trypanosomiasis - Life Cycle

Q. Why are Trypanosoma brucei infections associated with persistently elevated IgM levels?

A. because they keep changing their outer surface protein

- T. brucei contains as many as 1000 genes encoding different VSGs (VSG = variant surface glycoprotein)
- each trypanosome expresses one, and only one, VSG at a time
- individual parasites can spontaneously switch the VSG they express

African Trypanosomes – The Lady Gaga of the Microbial World

African Trypanosomiasis –Treatment

West African (T. gambiense)

If < 6 yo or < 20 kg: lumbar puncture
CSF < 5 WBC/ul → iv pentamidine
CSF > 5 WBC/ul → iv eflornithine + nifurtimox

If adult: confusion, ataxia, anxiety, abnl speech, motor weakness, abnl gait?
no suspicion of late disease → oral fexinidazole
if suspicion of CNS disease → obtain lumbar puncture
CSF < 100 cells/ul (non-severe 2nd stage) → oral fexinidazole
CSF > 100 cells/ul → iv eflornithine+ nifurtimox

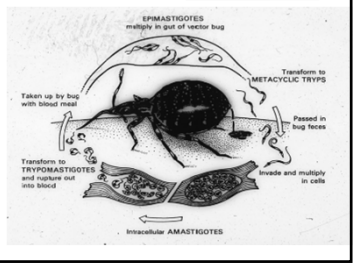
East African (T. rhodesiense): Rx always guided by lumbar puncture
CSF < 5 WBC/ul → suramin
CSF > 5 WBC/ul → melarsoprol

Juy 16, 2021: Oral fexinidazole FDA approved for T. gambiense

Notes: 1) Melarsoprol associated with ~5% death rate due to reactive encephalopathy.
2) This is reduced by co-administration of corticosteroids.

Chagas disease

- transmitted by *Trypanosoma cruzi*
  (also blood transfusion and congenitally)
- vector: reduviid (triatomine) bugs
- reservoirs: opossums, rats, armadillos, raccoons, dogs, cats
- autochthonus cases in the U.S.
  Texas
  Louisiana
  Mississippi
  Missouri
  California
- oral ingestion of food and drinks (acai and sugar cane juice) a major route of infection



47 – Lots of Protozoa

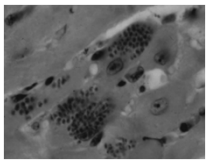
Speaker: Edward Mitre, MD

Chagas – Clinical Disease

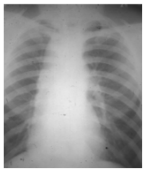
Acute (starts 1 week after infection, can persist for 8 weeks)
- fever
- local lymphadenopathy
- unilateral, painless periorbital edema

Indeterminate stage
- serology positive, no evidence of disease

Chronic

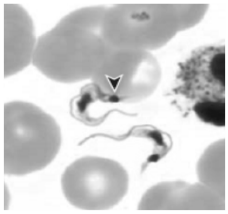


dilated cardiomyopathy, R>L
(CHF, syncope, arrythmia)



megaesophagus

Chagas Diagnosis & Rx



Acute disease
- identification of parasites in blood

Chronic disease
- *T. cruzi* specific IgG antibodies in serum

→ **two antibody tests using different antigens and different techniques recommended for dx**
(research: xenodiagnosis, hemoculture, PCR)

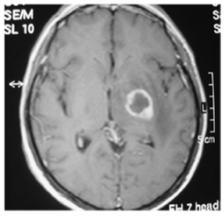
NOTE: U.S. blood supply screened for 1st time donors

Treatment

Benznidazole for 30 – 60 d, alternative: Nifurtimox (both FDA approved)
Benznidazole AEs: peripheral neuropathy, granulocytopenia, rash
Nifurtimox AEs: abdominal pain/vomiting, tremors, peripheral neuropathy

Always offer: acute infection, congenital, < 18 yo, reactivation disease
Usually offer: 19-50 years old and no advanced cardiac disease
Individual decision: > 50 years old and no advanced cardiac disease

Chagas in immunosuppressed patients



2008 Int J Infectious Diseases

***T. cruzi* and AIDS**

Primarily reactivation neurologic disease
- → acute,diffuse, necrotic meningoencephalitis
- → focal CNS lesions (similar to Toxo)**

***T. cruzi* and solid organ transplant**
- → recipient of infected organ: fevers, hepatosplenomegaly, myocarditis
- → disease often does not occur until months after transplant

ALSO…. reactivation myocarditis occurs in ~40% of patients that receive heart transplant because of Chagas cardiomyopathy

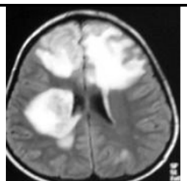
Protozoa

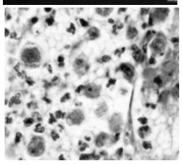
Protozoa - Extraintestinal	Protozoa - Intestinal
Apicomplexa Plasmodium Babesia (Toxoplasma)	**Apicomplexa** Cryptosporidium Cyclospora Cystoisospora
Flagellates Leishmania Trypanosomes (Trichomonas)	**Flagellates** Giardia Dientamoeba
National Institutes of Health **Amoebae** Naegleria Acanthamoeba Balamuthia	**Amoebae** Entamoeba
	Ciliates Balantidium

National Institute of Allergy and Infectious Diseases **Not Protozoa**

Kingdom Fungi: Microsporidiosis agents
Kingdom Chromista: Blastocystis

Free-living amoebae





Naegleria fowleri
- warm freshwater exposure
- enters through olfactory neuroepithelium
- fulminant meningoencephalitis
- immunocompetent children/young adults

Acanthamoeba
- found in soil and water
- enter through lower respiratory tract or broken skin
- subacute granulomatous encephalitis
- Immunocompromised hosts

National Institutes of Health
- chronic granulomatous keratitis (contact lens, LASIK)

Balamuthia mandrillaris
- likely enters through lower respiratory tract or broken skin
- transmission by solid organ transplantion has been reported
- subacute granulomatous encephalitis
- and immunocompromised hosts

National Institute of Allergy and Infectious Diseases

Outcome → often fatal (amphotericin B, azoles, pentamidine, others tried)

Protozoa

Protozoa - Extraintestinal	Protozoa - Intestinal
Apicomplexa Plasmodium Babesia (Toxoplasma)	**Apicomplexa** Cryptosporidium Cyclospora Cystoisospora
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	Ciliates Balantidium

National Institute of Allergy and Infectious Diseases **Not Protozoa**

Kingdom Fungi: Microsporidiosis agents
Kingdom Chromista: Blastocystis

When to suspect an intestinal protozoan infection:

Patient has: Protracted watery diarrhea (weeks to months)

AND/OR:
- **history of travel [domestic (esp. camping) or foreign]**
- **recreational water activities**
- **altered immunity (HIV infection)**
- **exposure to group care (daycare)**

Note: discussion will focus on intestinal protozoa as they occur in patients seen in the U.S. These are leading causes of diarrhea, morbidity, and mortality worldwide, especially in young children.

Intestinal Apicomplexa parasites

Cryptosporidium
- *C. parvum:* cows
- *C. hominis:* humans

Cyclospora cayetanensis

Cystoisospora belli

Cryptosporidium in enterocyte. CDC DpDx

- all have worldwide distribution
- all transmitted by water or food contaminated with oocysts
- organisms invade enterocytes
- all cause watery diarrhea that can be prolonged & severe in immunocompromised

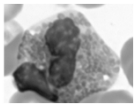
Intestinal Apicomplexa: clinical clues

Cryptosporidium
- watery diarrhea of several weeks
- cattle workers and daycare outbreaks
- cysts are resistant to chlorine (water supply outbreaks)
  --> #1 cause of water park/swimming pool outbreaks

Cyclospora cayetanensis - self-limited immunocompetent BUT can last up to 10 weeks!

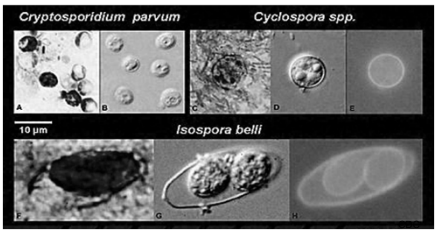
- abrupt onset with nausea, vomiting, and fever early
- anorexia, weight loss, fatigue late in course
- food associated outbreaks: raspberries, lettuce, herbs
- esp. Nepal, Peru, Guatemala

Cystoisospora belli
- no animal reservoirs known
- watery diarrhea
- may be associated with a peripheral eosinophilia!
  (the ONLY intestinal protozoa that does this)



Intestinal Coccidia characteristics

Pathogen	Size	Stain	Treatment
Cryptosporidium	4 μm	m acid-fast	(none) nitazoxanide or paromomycin
Cyclospora	10 μm	m acid-fast	TMP/SMX
Cystoisospora	20 μm	m acid-fast	TMP/SMX



Molecular tests
most stool multiplex PCR assays detect cryptosporidium AND Cyclospora but NOT Cystoisospora
stool Ag tests commercially available for cryptosporidium

Morbidity and Mortality Weekly Report

Cryptosporidiosis Outbreaks — United States, 2009–2017

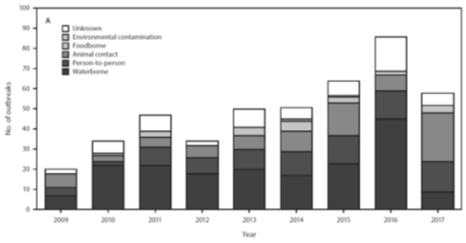
MMWR / June 28, 2019 / Vol. 68 / No. 25

47 – Lots of Protozoa
Speaker: Edward Mitre, MD

Morbidity and Mortality Weekly Report

Cryptosporidiosis Outbreaks — United States, 2009–2017

MMWR / June 28, 2019 / Vol. 68 / No. 25



"The number of reported outbreaks has increased an average of approximately 13% per year."

Question 5: A 28 year old woman returns after studying mosquito breeding habits in Honduras for one year. She reports intermittent abdominal pain and diarrhea for several months. Stool ova and parasite exam is positive for the presence of a ciliated single cell organism.

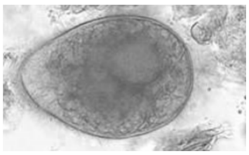
What is the most likely diagnosis?

National Institutes of Health

A. Balantidium coli
B. Entamoeba histolytica
C. Giardia lamblia
D. Dientamoeba fragilis
E. Endolimax nana

National Institute of Allergy and Infectious Diseases

Balantidium coli

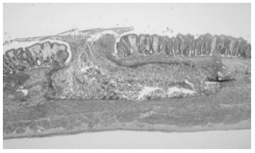


CDC DpDx

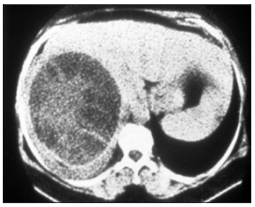
- the only ciliated pathogen of humans!
- largest protozoan pathogen of humans!
  (about 70 μm wide and up to 200 μm long)
- found worldwide, especially Central and S. America, S.E. Asia, and Papua New Guinea
- associated with eating food/water contaminated with pig feces
- Symptoms: most people asymptomatic
  can cause colitis with abdominal pain, weight loss, +/- diarrhea
  (especially in malnourished and immunocompromised)
- Treatment: tetracycline (!) or metronidazole

Entamoeba histolytica

- strictly human pathogen
- fecal/oral (contaminated food/water)
- cysts = infective stage
- trophozoites = active form, tissue-destructive

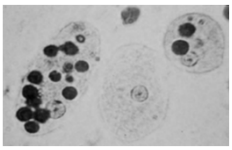


clinical presentations
- asymptomatic
- traveler's diarrhea
- colitis
  sharp abdominal pain
  bloody diarrhea
  fever
  flask-shaped ulcerations
  →onset can occurs weeks to months after travel
- ameboma
- liver and brain abscesses, esp in young men, usually 2-5 months after travel



Entamoeba histolytica

Diagnosis



E. histolytica trophozoites with ingested RBCs.

Stool PCR (multiplex or single)
- **close to 100% sensitivity and specificity**

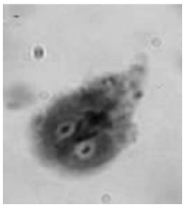
Stool O/P
- only 50% sensitive for colitis and abscess
- poor specificity b/c unable to differentiate *E.histolytica* from non-pathogenic *E. dispar* and the diarrhea-only causing *E. moshkovskii*
  (note: ingested RBCs suggestive of Eh, but not 100%)

Stool antigen testing > 85% sensitive for intestinal disease

Serology 95% sensitive for liver abscess, 85% sensitive for intestinal infection

Treatment
- asymptomatic: luminal agents such as paromomycin
- symptomatic: tissue agents such as metronidazole or tinidazole THEN luminal agent
- liver abscess: medical therapy (tissue agent then luminal agent) usually sufficient!
  drainage if no response to medical therapy or dx unclear or v large abscess

Giardia duodenalis → *described by Antony van Leeuwenhoek in 1681!*



Flagellated protozoan
- fecal/oral via ingestion of cyst form in food/water
- cyst is chlorine resistant
- cysts from humans (beavers, muskrats)

Disease in U.S.
- most common parasitic infection in the U.S
  (20k cases reported/year, likely 2M)
  → U.S-acquired cases peak in the late summer/early fall
  → a leading cause of traveler's diarrhea

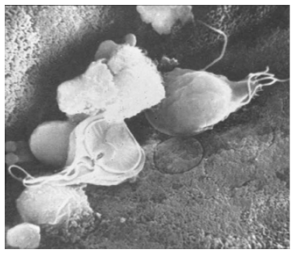
Symptoms
- intermittent watery diarrhea weeks to months
- foul smelling stools, flatulence, "sulfur burps"

47 – Lots of Protozoa
Speaker: Edward Mitre, MD

Giardia

At risk populations

- international travelers
- swimming in lakes/streams, outdoor survival/camping
- infants in daycare
- child care workers
- immunoglobulin deficiencies (esp CVID)
- HIV when CD4 < 100



Diagnosis

- stool antigen test
- stool multiplex PCR

Treatment

tinidazole (FDA approved)

metronidazole (off-label), nitazoxanide (FDA-approved), and albendazole (off label)

Other intestinal protozoa

Non-pathogens

amoebae
- *Entamoeba dispar*
- *Entamoeba hartmanni*
- *Entamoeba coli*
- *Endolimax nana*
- *Iodamoeba bütschlii*

flagellates
- *Chilomastix mesnili*
- *Trichomonas hominis*

Treat if symptomatic: *Dientamoeba fragilis* (implicated in IBS)

Protozoa

Protozoa - Extraintestinal

Apicomplexa
- Plasmodium
- Babesia
- (Toxoplasma)

Flagellates
- Leishmania
- Trypanosomes
- (Trichomonas)

National Institutes of Health

Amoebae
- Naegleria
- Acanthamoeba
- Balamuthia

Protozoa - Intestinal

Apicomplexa
- Cryptosporidium
- Cyclospora
- Cystoisospora

Flagellates
- Giardia
- Dientamoeba

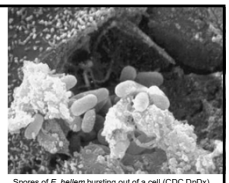
Amoebae
- Entamoeba

Ciliates
- Balantidium

National Institute of Allergy and Infectious Diseases **Not Protozoa**

Kingdom Fungi: Microsporidiosis agents
Kingdom Chromista: Blastocystis

Microsporidia – obligate intracellular fungi!

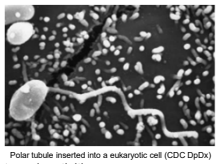


Spores of *E. hellem* bursting out of a cell (CDC DpDx)

→Produce extracellular, 1-2 micron, infective spores
→Spores have a coiled organelle called a polar tubule
→After ingestion, the spore germinates and the polar tubule is used to inject sporoplasm into a host cell

Enterocytozoon bieneusi
- watery diarrhea
- biliary disease (cholangitis, acalculous cholecystitis)

Encephalitozoon intestinalis
- watery diarrhea
- biliary disease
- disseminated disease (liver, kidney, lung, sinuses)



Polar tubule inserted into a eukaryotic cell (CDC DpDx)

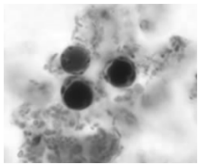
Encephalitozoon cuniculi, hellem
- can cause disseminated disease of multiple organs, plus eye

Many species (including *Vittaforma corneae*): punctate keratoconjunctivitis (contact lens use, after eye surgery, bathing in hot springs)

DIAGNOSIS: modified trichrome stain, Calcofluor white, IFA
TREATMENT: albendazole (not effective for *E. bieneusi*)

Blastocystis

What is it?



Blastocystis cyst-like forms , trichrome (CDC DpDx)

Nobody really knows!! Might be a protozoa.

Might also be a part of a new kingdom (Chromista!), with kelp and diatoms!

Forms are 5-40 microns wide. Anaerobic. Eukaryotic.
→ cystic, ameboid, granular, and vacuolar forms

Does it cause disease?
Maybe.
Associated with watery diarrhea, abdominal discomfort, nausea, and flatulence.

Diagnosis: light microscopy of stool samples

Treatment?
metronidazole, tinidazole, TMP/SMX, or nitazoxanide (none FDA-approved)

Protozoan infections that can reactivate in the severely immunocompromised

- Toxoplasmosis
  - encephalitis with mass lesions
  - pneumonitis
  - retinitis
- Leishmania
  - reactivation of visceral and cutaneous reported
  - visceral with fever, hepatosplenomegaly, pancytopenia
- Chagas
  - encephalitis with mass lesions
  - hepatosplenomegaly and fevers
  - myocarditis in 40% that receive heart transplant b/c Chagas disease
- Malaria

Some other protozoa that can cause severe disease in immunocompromised

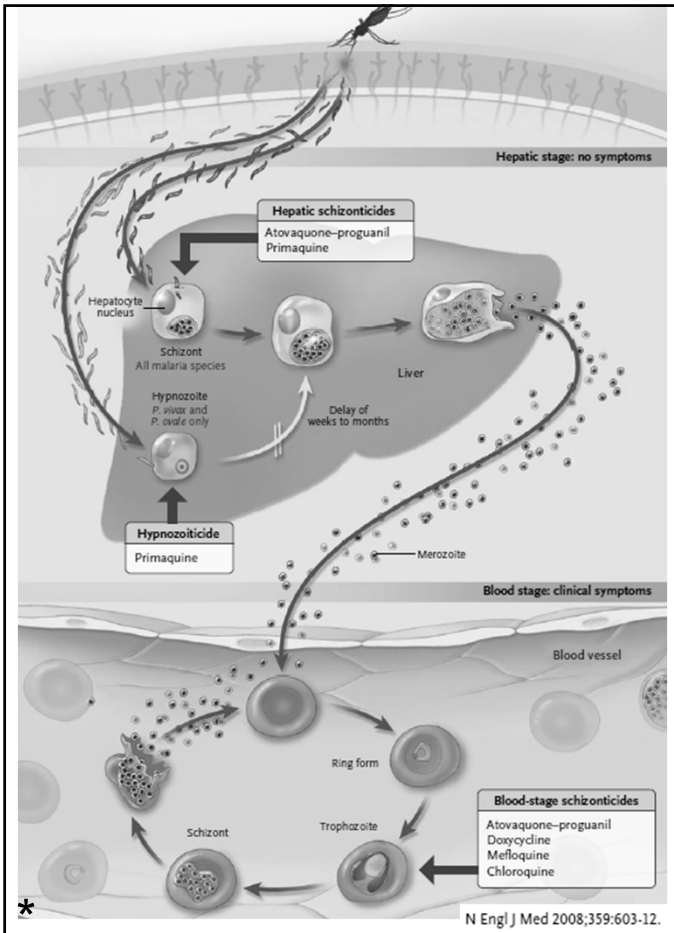
- Cryptosporidium
- Giardia
- Microsporidia
- Babesia
- Acanthamoeba

47 – Lots of Protozoa

Speaker: Edward Mitre, MD

NOAA photo library

Edward Mitre, M.D.
edwardmitre@gmail.com



Sporozoites
- **Infective stage**
- Come from mosquito

Liver schizont
- **Asymptomatic replicative stage**
- Become 10,000 to 30,000 merozoites

Hypnozoite
- Dormant liver stage in **vivax and ovale**
- Release merozoites weeks to months after primary infection

Merozoites
- Infect RBCs and develop into ring-stage trophozoites
- Mature into schizonts, which release merozoites which infect more RBCs

Gametocytes
- Infective stage for mosquitoes

BR5

Board Review Session 5

Drs. Alexander (Moderator), Marr, Mitre, Nelson, Rose, Winthrop, and Whitley

BR5 –Board Review: Day 5

Moderator: Barbara Alexander, MD

Board Review: Day 5

Moderator: Barbara Alexander, MD, MHS
Faculty: Drs. Marr, Mitre, Nelson, Rose, Winthrop, and Whitley

8/2/2023

BOARD REVIEW DAY 5 IDBR INFECTIOUS DISEASE BOARD REVIEW 2023

#61 **A 43-year-old man with short gut syndrome and TPN dependence presents with fever, chills, and rigors.**

Blood cultures are drawn and are positive for MRSA.

The vancomycin MIC is 4 mcg/mL.

1 of 3

BOARD REVIEW DAY 5 IDBR INFECTIOUS DISEASE BOARD REVIEW 2023

#61 **Which mechanism is likely responsible for his vanco MIC:**

A) Vancomycin efflux pump expression
B) Van A gene induction
C) Increased D-ala-D-ala expression
D) Hydrolytic enzyme induction

2 of 3

BOARD REVIEW DAY 5 IDBR INFECTIOUS DISEASE BOARD REVIEW 2023

#62 **A 25-year-old female with acute myelogenous leukemia is currently in complete remission and is being scheduled for an allogeneic stem cell transplantation in the near future.**

The patient's CMV IgG is positive, and her identified donor's CMV IgG is negative.

1 of 3

BOARD REVIEW DAY 5 IDBR INFECTIOUS DISEASE BOARD REVIEW 2023

#62 **Which of the following would you recommend regarding prevention of CMV infection post-transplantation?**

A) Letermovir
B) Brincidofovir
C) Acyclovir
D) Monthly IVIG
E) Valganciclovir

2 of 3

BOARD REVIEW DAY 5 IDBR INFECTIOUS DISEASE BOARD REVIEW 2023

#63 **A 28-year-old man from Baltimore, Maryland with long-standing sickle cell disease is admitted in December for suspected sickle cell vaso-occlusive crisis and fever developing over the past week.**

He has a mild cough but no dyspnea, though he also complains of headache, myalgia, arthralgia, fatigue, and vague abdominal discomfort without diarrhea.

He has not traveled outside of Baltimore City in more than one year.

1 of 6

BOARD REVIEW DAY 5 INFECTIOUS DISEASE BOARD REVIEW 2023

#63 **He is now maintained on regular red blood cell exchange transfusions.**

His exam is notable for a fever of 39°C, mild tachycardia 108 bpm, BP 100/72, normal respirations.

He does not look toxic, but he is icteric and a systolic flow murmur; there is no abdominal tenderness or other physical exam findings.

Laboratories include WBC 2300 cells per cubic mL, platelet count of 66,000 per cubic mL.

2 of 6

BOARD REVIEW DAY 5 INFECTIOUS DISEASE BOARD REVIEW 2023

#63 **Other notable labs include hemoglobin of 6.2 g/dL (below his usual baseline of 8.0-8.5 g/dL), elevated LDH of 536 U/L, total bilirubin 3.5 mg/dL, and undetectable haptoglobin.**

An abdominal CT scan without IV contrast had no new findings compared to earlier studies. His chest radiograph had a suggestion of atelectasis vs.

infiltrate in the left lower lung. A multiplex respiratory viral panel was negative.

3 of 6

BOARD REVIEW DAY 5 INFECTIOUS DISEASE BOARD REVIEW 2023

#63 **Upon admission, he was started on vancomycin and ceftriaxone.**

However, fevers continued, and blood cultures yielded no growth at 72h. His total bilirubin has escalated to 6.5 mg/dL, with some rise in transaminases; his platelet count has fallen to 47,000.

His renal function has worsened, and he is requiring oxygen supplementation.

4 of 6

BOARD REVIEW DAY 5 INFECTIOUS DISEASE BOARD REVIEW 2023

#63 **What diagnostic test would be most useful to diagnose a treatable cause of this febrile syndrome?**

A) HIDA scan (cholescintigraphy)

B) Peripheral blood smear

C) Indium 111 – tagged white blood cell scan

D) ADAMTS13 antibody

E) Bartonella serology

5 of 6

BOARD REVIEW DAY 5 INFECTIOUS DISEASE BOARD REVIEW 2023

#64 **A 29-year-old woman presents complaining of right-sided hip and thigh pain. She denies any trauma before her pain began.**

She is not exactly sure when the pain started but it has been present for at least two months. She denies fevers and night sweats. She's noticed recently that her gait has changed.

She is otherwise healthy and takes no medications. She is a nonsmoker and drinks alcohol occasionally. She denies any recent travel.

1 of 5

BOARD REVIEW DAY 5 INFECTIOUS DISEASE BOARD REVIEW 2023

#64 **She is a semi-professional soccer player, but the pain has prevented her from participating in any soccer games over the past two weeks.**

On examination, her vital signs are normal. She has a wide-based gait and pubic symphysis tenderness on deep palpation.

The patient experienced pain with resisted strength testing of the adductor and lower abdominal muscle groups.

2 of 5

BOARD REVIEW DAY 5 | INFECTIOUS DISEASE BOARD REVIEW 2023

#64 **Her complete blood count is normal. An anterior posterior pelvic film is obtained demonstrating evidence of bone remodeling at the pubic symphysis.**

An MRI is obtained which revealed subchondral sclerosis of the pubic symphysis and a small amount of fluid in the pubic symphysis joint.

3 of 5

BOARD REVIEW DAY 5 | INFECTIOUS DISEASE BOARD REVIEW 2023

#64 **Which of the following interventions is most appropriate at this time?**

A) Blood cultures

B) Bone biopsy of the pubic symphysis

C) Bone Scan

D) Empiric systemic antibiotics

E) Nonsteroidal anti-inflammatory agents

4 of 5

BOARD REVIEW DAY 5 | INFECTIOUS DISEASE BOARD REVIEW 2023

#65 **A 25-year-old pregnant woman (G1P0) is referred to Infectious Diseases from her OBGYN due to a positive PPD test.**

The patient is originally from El Salvador and has lived in the United States for 10 years.

She has no known medical problems. She has been healthy all her life, and wants to do everything she can to promote a healthy pregnancy.

1 of 4

BOARD REVIEW DAY 5 | INFECTIOUS DISEASE BOARD REVIEW 2023

#65 **The records from the referring provider show that the patient had a positive PPD (12 mm of induration) as part of routine prenatal screening; chest x ray showed no abnormalities.**

The patient believes she had a positive TB skin test when she immigrated to the United States, but does not recall receiving treatment.

2 of 4

BOARD REVIEW DAY 5 | INFECTIOUS DISEASE BOARD REVIEW 2023

#65 **Which of the following describes the most appropriate management of this patient?**

A) Initiate treatment for latent tuberculosis with rifampin
B) Initiate treatment for latent tuberculosis with isoniazid
C) Defer treatment of latent tuberculosis until 2-3 months post-partum
D) Perform interferon gamma release assay in order to determine therapy
E) Defer treatment indefinitely but reassess patient every 3 months for 2 years

3 of 4

BOARD REVIEW DAY 5 | INFECTIOUS DISEASE BOARD REVIEW 2023

#66 **A 62-year-old male was seen for low grade fever and weight loss over the past month.**

He had undergone aortic valve replacement in 2015 with a bioprosthesis.

Transesophageal echocardiography found no evidence of endocarditis and routine blood cultures were negative.

1 of 4

BOARD REVIEW DAY 5 INFECTIOUS DISEASE BOARD REVIEW 2023

#66 **Mycobacterial blood cultures grew Mycobacterium chimaera.**

The patient lived in a rural area, drank well water and had a pond in this back yard with Koi fish.

2 of 4

BOARD REVIEW DAY 5 INFECTIOUS DISEASE BOARD REVIEW 2023

#66 **The most likely source of this Mycobacterial infection is which of the following:**

A) Operating room air

B) Bioprosthetic valve

C) Well water

D) Fish pond

E) Intestinal lesion

3 of 4

BOARD REVIEW DAY 5 INFECTIOUS DISEASE BOARD REVIEW 2023

#67 **An 18-year-old man is seen in May in the pediatric out-patient clinic. The clinic heat has been turned off and it is not warm enough to use the clinic's window air conditioners.**

The man has a febrile illness and sore throat for which he is examined over the course of 45 minutes by the attending pediatrician, a resident, and two medical students.

1 of 5

BOARD REVIEW DAY 5 INFECTIOUS DISEASE BOARD REVIEW 2023

#67 **The healthcare workers all wear masks; the patient does not.**

Because of a borderline rapid strep test from a throat swab, the patient is given a prescription for amoxicillin and sent home.

2 of 5

BOARD REVIEW DAY 5 INFECTIOUS DISEASE BOARD REVIEW 2023

#67 **After the patient leaves, the exam room door is left open to "air out the room" for 20 minutes and then the exam room continues in use.**

A follow-up by phone 2 days later reveals that the patient continues to be febrile and now has a diffuse, macular, nonvesicular rash.

3 of 5

BOARD REVIEW DAY 5 INFECTIOUS DISEASE BOARD REVIEW 2023

#67 **Which of the following infection possibilities in this patient, given his clinical course described above, would be most likely to infect the next exam room occupant, if that individual is not immune?**

A) Chickenpox

B) CMV

C) Measles

D) Rubella

E) Mononucleosis

4 of 5

BOARD REVIEW DAY 5 INFECTIOUS DISEASE BOARD REVIEW 2023

#68 **A 59-year-old Caucasian male from Maryland presents in October with ischemic cardiomyopathy and is under consideration for listing status 1A for heart transplantation.**

You are consulted to screen for infectious issues in the pre-transplant window.

1 of 5

BOARD REVIEW DAY 5 INFECTIOUS DISEASE BOARD REVIEW 2023

#68 **The patient works as an accountant and has no significant travel history outside of the Maryland/Washington DC area. He enjoys golfing as a hobby.**

He has been afebrile during his 10-day hospitalization and routine infection control screens for MRSA, VRE and CRE colonization are negative.

2 of 5

BOARD REVIEW DAY 5 INFECTIOUS DISEASE BOARD REVIEW 2023

#68 **Pre-transplant serologies are as follows:**

- **Varicella zoster virus antibody positive**
- **Hepatitis B surface antibody negative**
- **Hepatitis B core antibody negative**
- **Hepatitis B surface antigen negative**
- **Hepatitis C antibody negative**
- **Herpes Simplex 1 and 2 (combined) antibody positive**
- **EBV**
  - **Viral capsid antigen (VCA) IgG positive**
  - **VCA IgM negative**
  - **EBV nuclear antigen (EBNA)-1 IgG positive**

3 of 5

BOARD REVIEW DAY 5 INFECTIOUS DISEASE BOARD REVIEW 2023

#68 **You recommend which one of the following pre-transplant immunizations:**

A) PPSV23 (Pneumovax 23) now and 8-weeks later single dose PCV13 (Prevnar 13)

B) Hepatitis B vaccine series, now

C) Nasal spray flu vaccine now

D) MMR now if rubeola IgG ≤ 29.9 AU/mL or mumps IgG ≤ 10.9 AU/mL

4 of 5

BOARD REVIEW DAY 5 INFECTIOUS DISEASE BOARD REVIEW 2023

#69 **A 55-year-old CMV seronegative woman with type 1 diabetes mellitus and end stage renal disease received a cadaveric renal allograft from a CMV positive donor five months prior.**

She is on valganciclovir prophylaxis.

She now presents with decreasing renal function despite increased immunosuppression with tacrolimus and prednisone given for suspected graft rejection.

1 of 4

BOARD REVIEW DAY 5 INFECTIOUS DISEASE BOARD REVIEW 2023

#69 **Tacrolimus levels are in the therapeutic range.**

Ultrasound did not show obstruction of the implanted kidney.

You are consulted about possible infectious causes of renal failure.

She is afebrile and routine urinalysis with bacterial culture is unremarkable.

2 of 4

BOARD REVIEW DAY 5 INFECTIOUS DISEASE BOARD REVIEW 2023

#69 **Your preferred approach to establish the cause of the renal failure is which of the following:**

A) Quantitative urine PCR for BK virus

B) Quantitative urine PCR for adenovirus

C) Renal biopsy

D) Blood for quantitative CMV viral load

E) Blood for quantitative JC viral load

3 of 4

BOARD REVIEW DAY 5 INFECTIOUS DISEASE BOARD REVIEW 2023

#70 **A 47-year-old female grew up in an impoverished farming community in Argentina. She moved to the United States when she was 16 years of age.**

Three years ago, she developed progressive dyspnea on exertion.

A cardiac workup revealed a markedly enlarged heart, ejection fraction of 25%, and no obstruction of the coronary arteries by angiography.

1 of 3

BOARD REVIEW DAY 5 INFECTIOUS DISEASE BOARD REVIEW 2023

#70 **The most likely pathogen causing her cardiac disease, assuming it is due to an infection acquired in Argentina, is:**

A) Leishmania donovani

B) Taenia solium

C) Trypanosoma cruzi

D) Toxoplasma gondii

E) Trichinella spiralis

2 of 3

BOARD REVIEW DAY 5 INFECTIOUS DISEASE BOARD REVIEW 2023

#71 **A 62-year-old nurse presents to your clinic with a six-month history of pain and swelling involving her third finger.**

She has been treated sequentially with cephalexin, amoxicillin-clavulanate, and clindamycin without effect.

1 of 4

BOARD REVIEW DAY 5 INFECTIOUS DISEASE BOARD REVIEW 2023

#71 **She is an avid gardener and enjoys digging for clams in a marshy area near to her home. She admits to frequent abrasions and scratches.**

MRI has demonstrated diffuse soft tissue inflammation with tenosynovitis, septic arthritis of the interphalangeal joints, and early phalangeal osteomyelitis.

2 of 4

BOARD REVIEW DAY 5 INFECTIOUS DISEASE BOARD REVIEW 2023

#71 **What is the most likely microbiologic agent?**

A) Methicillin-resistant Staphylococcus aureus

B) Aeromonas hydrophila

C) Nocardia nova complex

D) Nontuberculous mycobacteria

E) Sporothrix schenckii

3 of 4

BR5 –Board Review: Day 5

Moderator: Barbara Alexander, MD

BOARD REVIEW DAY 5 | INFECTIOUS DISEASE BOARD REVIEW 2023

#72 **A 33-year-old man with advanced HIV infection (most recent CD4 =50 cells/uL, VL =500,000 copies/uL) comes to the emergency room complaining of "the worst sore throat of my life."**

He is hoarse but has no coughing.

He is seen intermittently in the HIV clinic but refuses to take antiretroviral therapy or Pneumocystis prophylaxis claiming that "those medicines" killed a friend of his.

1 of 5

BOARD REVIEW DAY 5 | INFECTIOUS DISEASE BOARD REVIEW 2023

#72 **His temperature is 102.6F. He looks flushed; his heart rate is 120.**

His oral exam shows thrush on his tongue and buccal mucosa, but his throat appears normal.

There is no cervical adenopathy.

His wbc is 14.7 cells/uL and his monospot test and a rapid test for Group A Strep are negative.

2 of 5

BOARD REVIEW DAY 5 | INFECTIOUS DISEASE BOARD REVIEW 2023

#72 **He is given oral fluconazole and discharged with clinic follow-up.**

He returns to the emergency room three days later saying in an extremely hoarse voice that his sore throat is worse and he is having pain on swallowing.

His temperature is 102.2. His thrush appears slightly improved; again the pharynx appears normal. He is observed spitting out his saliva into a tissue because swallowing is so painful.

3 of 5

BOARD REVIEW DAY 5 | INFECTIOUS DISEASE BOARD REVIEW 2023

#72 **Which one of the following is the most likely cause of his sore throat?**

A) Peritonsillar abscess

B) Retropharyngeal abscess

C) Esophagitis

D) Epiglottitis

E) Ludwig's angina

4 of 5

BOARD REVIEW DAY 5 | INFECTIOUS DISEASE BOARD REVIEW 2023

#73 **A 52-year-old woman with no prior medical conditions presents with a 6-month history of shortness of breath and cough.**

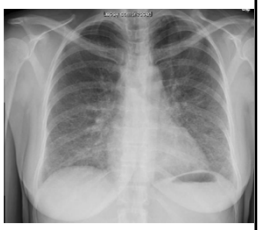
She has no fever, and her CBC and Chemistry panel is normal.

Oxygen saturation on room air = 80%.

1 of 4

BOARD REVIEW DAY 5 | INFECTIOUS DISEASE BOARD REVIEW 2023

#73 **Her chest x-ray is shown.**



She reports that she installed a hot tub at home which she uses daily; she has no other unusual exposures.

2 of 4

BOARD REVIEW DAY 5 INFECTIOUS DISEASE BOARD REVIEW 2023

#73 **If this syndrome is related to her hot tub, which of the following organisms is most likely related to the pulmonary process?**

A) Acanthamoeba
B) Legionella pneumophila
C) Aeromonas hydrophila
D) Mycobacterium avium complex
E) Nocardia asteroides

3 of 4

BOARD REVIEW DAY 5 INFECTIOUS DISEASE BOARD REVIEW 2023

#74 **A 2-year-old child is admitted to a pediatric hospital with pertussis.**

What preventive therapy should be given to the mother?

A) Treat only if the mother becomes symptomatic
B) Culture the oropharynx and treat only if positive
C) Administer pertussis immune globulin only
D) Administer Tdap only if the mother was never immunized
E) Treat with a 5-day course of azithromycin

1 of 2

BOARD REVIEW DAY 5 INFECTIOUS DISEASE BOARD REVIEW 2023

#75 **A 31-year-old woman has a 2-week history of swelling, low grade fevers, and serous discharge from a wound over her lumbar spine.**

She had posterior spinal fusion rods placed 6 months ago for idiopathic scoliosis.

Lumbar spine CT shows a fluid collection posterior to the hardware.

1 of 4

BOARD REVIEW DAY 5 INFECTIOUS DISEASE BOARD REVIEW 2023

#75 **Treatment with oral doxycycline and metronidazole a couple of weeks ago resulted in minimal improvement.**

Debridement and washout is undertaken and a deep wound culture grows *Cutibacterium acnes*. Intravenous antibiotic therapy with penicillin is initiated.

2 of 4

BOARD REVIEW DAY 5 INFECTIOUS DISEASE BOARD REVIEW 2023

#75 **Which of the following additional procedures provides the best likelihood for resolution of the infection?**

A) Removal of hardware
B) Wound vacuum
C) Implanted antibiotic beads
D) Antibiotic wound irrigation
E) Addition of rifampin

3 of 4

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Bone and Joint Infections

Dr. Sandra Nelson

Bone, Joint and Musculoskeletal Infections

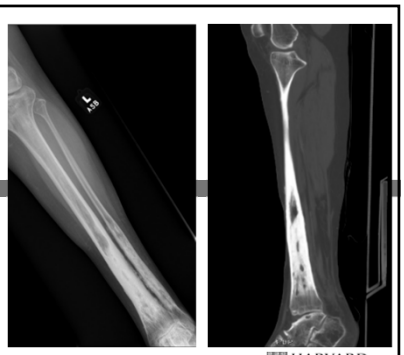
Sandra B. Nelson, MD
Director, Musculoskeletal Infectious Diseases
Division of Infectious Diseases
Massachusetts General Hospital

6/30/2023

Disclosures of Financial Relationships with Relevant Commercial Interests

- **None**

Osteomyelitis



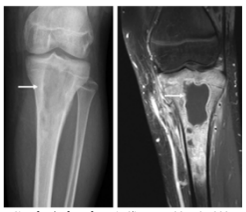
Osteomyelitis: Unifying Principles

- Radiographic studies:
  - MRI is the most sensitive imaging study for diagnosis
  - Serial plain films and CT are the most useful in subacute and chronic infection
  - Bone scan is an excellent "rule-out" test when negative, but lacks specificity
  - No imaging test can confirm the diagnosis of osteomyelitis, nor confirm cure
- Diagnosis can only be confirmed through bone histopathology and culture
  - Swab cultures of drainage have poor concordance with bone cultures
- Optimal route and duration of therapy are an evolving target
  - 6 weeks of antimicrobial therapy commonly used
  - Oral therapy increasing supported
  - Longer oral suppression in setting of retained hardware

4

Brodie's Abscess (Subacute hematogenous osteomyelitis)

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

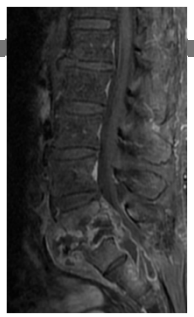


Simpfendorfer Infect Dis Clin N Am 2017;31:299

5

Case #1

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



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Case #1: Vote

What is the best next step in management?

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

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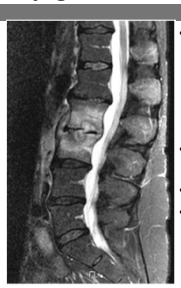
Pyogenic Vertebral Osteomyelitis: diagnosis



- Imaging pearls
  - Plain films and CT for subacute to chronic infection; MRI for early infection
  - Findings: disc hyperintensity, loss of disc height, bone marrow edema, endplate erosions, paraspinal and/or epidural collections
  - Infection almost always involves two contiguous vertebral bodies
- Blood cultures are often positive in early infection
  - No further diagnostics if *Staph aureus* or *Staph lugdunensis*
- Brucella serologies, PPD/IGRA when appropriate epidemiology
- Percutaneous biopsy when blood cultures negative
  - Hold antibiotics 1-2 weeks prior if sepsis or neurologic compromise
  - If negative, repeat percutaneous biopsy or consider open procedure

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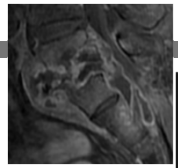
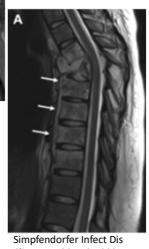
Reference: 2015 IDSA Guidelines
HARVARD MEDICAL SCHOOL 9

Pott's Disease





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

Simpfendorfer Infect Dis Clin N Am 2017;31:299

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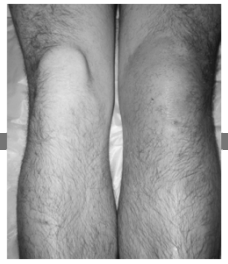
Septic Arthritis



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Septic Arthritis: Clinical Pearls

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

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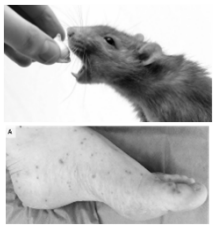
Polyarthritis

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



Giorgiutti NEJM 2019: 381:1762

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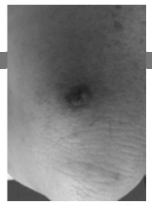
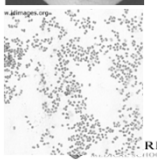
Gonococcal Arthritis





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

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Viral arthritides

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

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

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HARVARD MEDICAL SCHOOL

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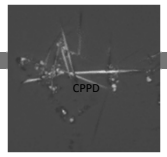
Crystalline arthritis: clinical pearls



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

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Images: Taljanovic RadioGraphics 2015;35:2026

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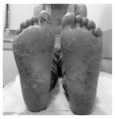
Masquerading as Infection…

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



Coelho BMJ Case Reports 2017-222475

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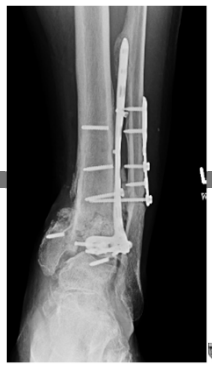
Osteofixation Infections



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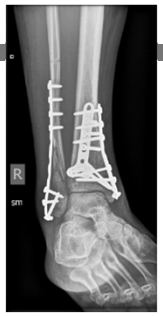
Case #2

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



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HARVARD MEDICAL SCHOOL

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Case #2: Vote

What are your next steps?

A. 4 weeks of nafcillin, then long-term trimethoprim- sulfamethoxazole
B. Hardware removal; 6 weeks of oxacillin
C. Hardware removal; 6 weeks of oxacillin and rifampin
D. Debridement without hardware removal; 6 weeks of oxacillin and rifampin
E. Debridement and hardware replacement; 6 weeks of oxacillin and rifampin

MASSACHUSETTS GENERAL HOSPITAL HARVARD MEDICAL SCHOOL 21

Osteofixation Infections

Goals: fracture consolidation and infection eradication
Removal of hardware depends upon fracture healing
Antibiotic duration not well studied

	Early or delayed infections prior to fracture union	Late nonunion	Late, healed fracture
Microbiology	Virulent organisms *Staph aureus* most common	Indolent organisms (coagulase-negative Staphylococcus, *Cutibacterium acnes*)	Often indolent organisms, or recurrence of early infection
Surgical Strategy	Debride and retain (assuming implants well fixed)	Hardware removal Revision or external fixation	Hardware removal
Antimicrobial Management	Pathogen-directed therapy Addition of rifampin if Staph Duration often 12 weeks or until fracture heals	Pathogen-directed therapy Duration often six weeks	Pathogen-directed therapy Duration often two weeks following hardware removal

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Oral antibiotics for bone and joint infections

- Now supported by a large body of literature for any type of bone and joint infection
  - Caution with life- or limb-threatening infections
- Usually after an IV lead-in and after clinical response
- Relative contraindications/exclusions:
  - Lack of suitable oral option
  - Other indication for IV treatment (e.g. endocarditis and bacteremia)
  - Not well studied for drug-resistant bacteria (e.g. MRSA)
  - Concern for malabsorption
- Little data to support "bone-penetrating antibiotics"
  - Some advantage to quinolone + rifampin in Staphylococcal PJI

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Rifampin in orthopedic infections

- Considered a "biofilm active" agent
- Best studied for Staphylococcal PJI in setting of hardware retention
  - Data extrapolated for other hardware infections (osteofixation, spinal implant)
  - Lower treatment failure in PJI with implant retention
- Specifics
  - Never to be used in monotherapy of established infection
  - Should not be used prior to surgical debridement and until partner drug therapeutic
  - Multiple drug interactions (primarily via Cyp 3A4 pathway)

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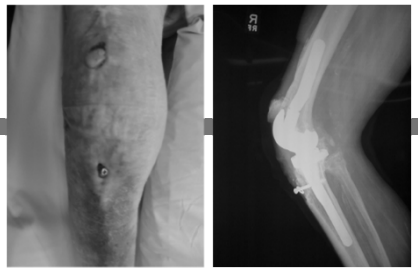
Prosthetic Joint Infection



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Prosthetic Joint Infection (PJI): Clinical presentations

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

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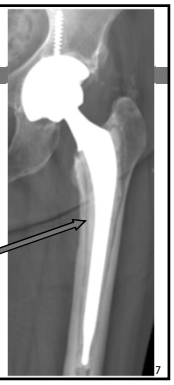
Prosthetic Joint Infection: Diagnostic pearls

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

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



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PJI Management

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

* 2012 IDSA Guidelines; duration of therapy based on limited literature

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Case #3

PREVIEW QUESTION

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

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Case #3: Vote

PREVIEW QUESTION

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

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

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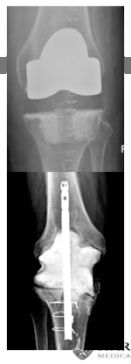
Antimicrobial Cement (PMMA)

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



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Case #4

- A 63-year-old woman with rheumatoid arthritis is scheduled for knee arthroplasty in 2 weeks. She takes methotrexate, hydroxychloroquine and low dose prednisone (2.5 mg daily). She has a history of recurrent urinary tract infections, last one month ago. She asks how she might prevent infection after knee replacement.

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Case #4: Vote

What do you advise?

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

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Prevention of PJI

- Immunosuppressives:
  - Stop biologics, no need to stop DMARDs or low dose prednisone
- Surgical antibiotic prophylaxis: one dose prior to surgery
- Urinary tract infections:
  - Diagnose and treat symptomatic UTI
  - Do not screen for asymptomatic bacteriuria
- Dental prophylaxis: no more!
- *Staph aureus* decolonization reduces surgical site infection

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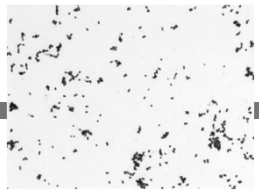
Microbiology of Musculoskeletal Infections



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Case #5

A 56-year-old man with poorly controlled diabetes presents to ED with a one-week history of low-grade fevers and gradually progressive right knee pain and swelling. He traveled to the Dominican Republic one month ago and had no illnesses while traveling. He last saw a dentist six months ago and denies tooth pain. There is no history of injection drug use.

On exam he has a moderate effusion and pain with passive range of motion of the knee. His ESR (68) and CRP (17 mg/dL) are elevated, and synovial fluid is inflammatory (45,000 WBCs, with 82% neutrophils) with a negative gram stain.

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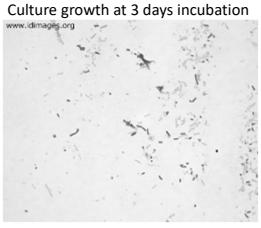
Case #5: Vote

Culture growth at 3 days incubation



What is the most likely organism?

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

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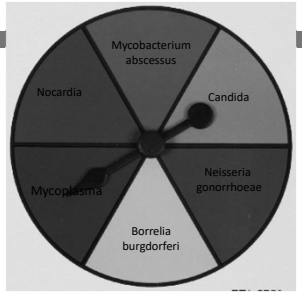
Guess the Bug

Musculoskeletal Edition



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Salmonella Species

- Clinical
  - Seen in sickle cell disease, immunocompromised, diabetes
  - Hematogenous infection (septic arthritis, spondylodiscitis, long bone infection)
- Epidemiology
  - Reptile exposure
  - Travel to developing world
  - Unsafe food hygiene

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Serratia and Pseudomonas

- Risk Factors
  - Injection Drug Use (tap water)
  - Immunocompromised host
  - Indwelling lines
- Clinical factors
  - Usually hematogenous
  - Predilection for sacroiliac and sternoclavicular joints in injection drug use

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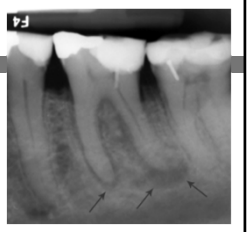
HACEK Organisms



- Clinical
  - Usually hematogenous
- Epidemiology
  - Antecedent mouth trauma, gum or dental infection, or dental procedure
  - Odontogenic infection may be silent
- Microbiology
  - Late growth in culture, may be culture negative
- *Kingella kingae*
  - Most common cause of osteoarticular infection in young children; diagnosed by pcr

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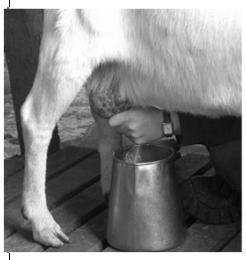
Brucella species



- Clinical
  - Fevers often precede musculoskeletal symptoms
  - Septic arthritis with predilection for sacro-iliac joint
  - Also causes spondylodiscitis
- Epidemiology
  - Endemic in Latin America, Mediterranean, Middle East, parts of Asia
  - Consumption of unpasteurized dairy most common
- Microbiology
  - Small gram-negative coccobacillus; grows late in culture
  - Laboratory biohazard
  - Serologies helpful in non-residents of endemic areas

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Pasteurella species

- Clinical
  - Direct inoculation (bite)
  - Hematogenous spread
  - Rapid clinical onset
- Epidemiology
  - Exposure to cats/dogs
  - Bite history not always elicited in hematogenous infection

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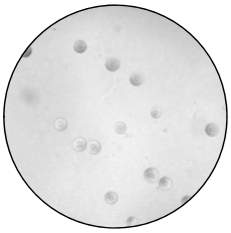
Mycoplasma hominis

- Host factors
  - Immunodeficiency, especially humoral (CVID, XLA)
  - Postpartum women
- Clinical factors: hematogenous infection
- Microbiology
  - Difficult to grow in routine culture
  - Fried egg morphology in culture



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Borrelia burgdorferi (Lyme)

- Clinical
  - Large effusions; some resolve over weeks but may recur
  - Warmth and swelling out of proportion to pain
  - Mono-arthritis of the knee most common
- Epidemiology
  - Northeast U.S. and upper mid-west with tick exposure
- Micro: culture-negative
  - Diagnosed serologically or with synovial fluid Borrelia pcr

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Non-tuberculous mycobacteria

- Clinical
  - Slowly progressive tenosynovitis; can spread to bones and joints
  - May be accompanied by nodular lymphangitis
  - May cause polyarthritis in immunocompromised hosts
- Epidemiology
  - Environmental sources of water
  - Marine injury/trauma
  - Fish-tank exposure
- Microbiology
  - Some organisms (marinum) grow better in cooler temperatures

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Yeasts and molds

- Clinical
  - May be contiguous inoculation or hematogenous spread
  - Often more indolent than bacterial organisms
  - In the spine may mimic tuberculosis
- Epidemiology
  - Candida: injection drug use, indwelling lines, immunocompromise, antibiotic exposure
  - Molds: soil contamination (trauma), barefoot walking (Madura foot), immunocompromise (neutropenia), medical tourism

Karrakchou BMC Dermatology 2020

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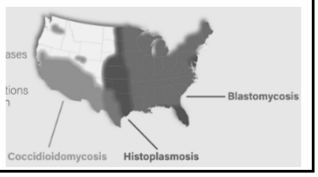
Endemic mycoses

- Coccidiodes and Blastomyces > Histoplasma
- Clinical
  - Subacute septic arthritis and long bone osteomyelitis
  - May see draining sinuses adjacent to osteomyelitis
  - In spine, may also mimic tuberculosis
  - Host immunocompromise more common in coccidoides
  - May see concomitant pulmonary infection



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Thank you!

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HSV and VZV in Immuno-competent and Immunocompromised Hosts

Dr. Richard Whitley

49 – HSV and VZV in Immuno-Competent and Immunocompromised Hosts

Speaker: Richard Whitley, MD

IDBR INFECTIOUS DISEASE BOARD REVIEW AUGUST 19-23 2023

HSV and VZV in Immunocompetent and Immunosuppressed Patients

Richard J. Whitley, MD
Co-Director, Pediatric Infectious Diseases
Children's Hospital of Alabama
Loeb Eminent Scholar Chair in Pediatrics
Distinguished Professor of Pediatrics
Professor of Microbiology, Medicine, and Neurosurgery
The University of Alabama at Birmingham

7/6/2023

IDBR INFECTIOUS DISEASE BOARD REVIEW AUGUST 19-23 2023

Disclosures of Financial Relationships with Relevant Commercial Interests

- **Steering Committee: NIAID COVID-19 Recover Study**
- **Scientific Advisory Board: Treovir, LLC**
- **Scientific Advisory Board: Altesa Biosciences**
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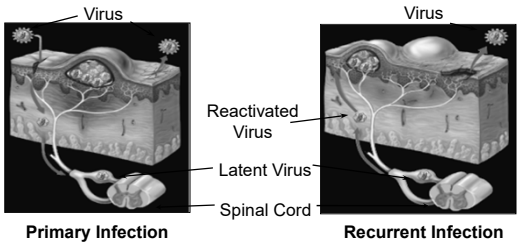
- **Member, Board of Directors: Virios Therapeutics**
- **Chairperson: Merck Letermovir DMC and GSK IDMC for Zoster**
- **Past Chairperson: NIAID COVID-19 Vaccine DSMB**

Herpes Viruses: The Family

- Herpes simplex virus, type 1 (HSV-1)
- Herpes simplex virus, type 2 (HSV-2)
- Varicella zoster virus (VZV)
- Cytomegalovirus (CMV)
- Epstein Barr virus (EBV)
- Human herpesvirus 6 (HHV 6 A and B)
- Human herpesvirus 7 (HHV 7)
- Human herpesvirus 8 (HHV 8)

Viral Latency and Reactivation



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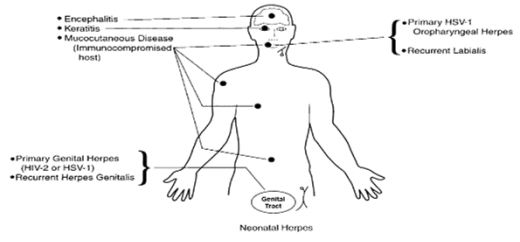
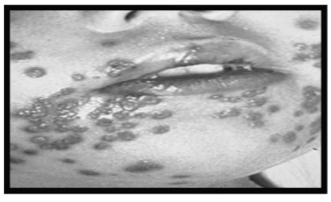
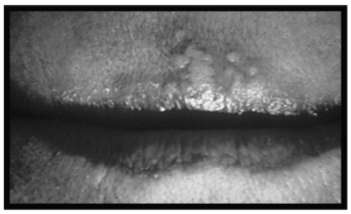
Clinical Manifestations of Herpes Simplex Virus Infections



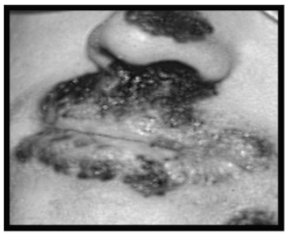
Primary Herpes Simplex Virus Infection: Cutaneous Lesions



Herpes Simplex Labialis

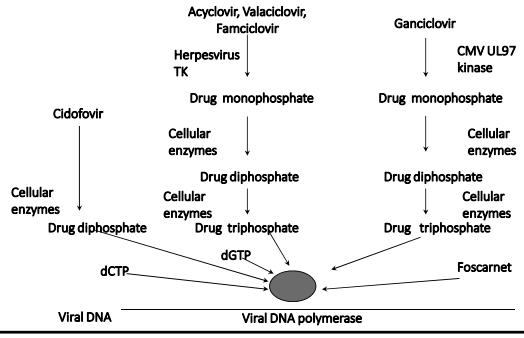


Immunocompromised Host



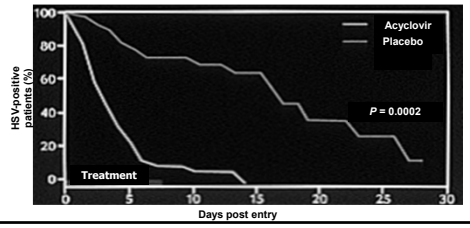
Most Widely Used Systemic Anti-HSV and VZV Drugs

- Acyclovir (ACV, Zovirax)
- Famciclovir (FCV, Famvir)
- Valacyclovir (VACV, Valtrex)
- Foscarnet (PFA, Foscavir)
- Ganciclovir (GCV, Cytovene)
- Val-Ganciclovir (Valcyte)
- Others:
  - Cidofovir



Intravenous Acyclovir for Herpes Simplex Virus Infections in Immunocompromised Hosts

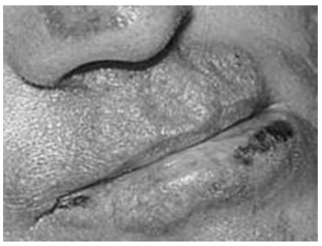
Time to cessation of viral shedding with acyclovir



Acyclovir Prophylaxis for HSV Infection in BMT Patients

Acyclovir (250 mg iv/m2 /tid) or placebo for 18 days beginning 3 days before transplant

Group	Number of Patients	Number of HSV Infections	P
Acyclovir	10	0	~0.003
Placebo	10	7	



Question #1

A 30 year old heart transplant has received acyclovir for the past 60 days for cutaneous HSV infection. The lesions are now progressive in spite of high-dose intravenous therapy. The most likely cause for disease progression is a deficiency or alteration of:

A. Ribonucleotide reductase
B. Reverse transcriptase
C. Protease
D. Thymidine kinase
E. DNA polymerase

Answer #1a and b

- Three types of acyclovir resistant viruses:
  - thymidine kinase negative
  - thymidine kinase altered substrate
  - DNA polymerase mutations
- All populations of HSV contain viruses with resistant genotypes
- Progressive disease has been limited to the immunocompromised host, especially HSCT recipients and those with poorly controlled HIV
- Three normal hosts with documented ACV resistant virus had disease progression

Global Prevalence of HSV-2 Infection

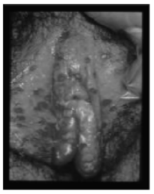
Total estimated number of people (in millions) infected with HSV-2 in 2012 by WHO region, gender and age range.
Source: WHO, as published in PLOS ONE (21 Jan 2015)

Acyclovir Therapy of Genital Herpes

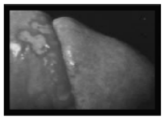
Summary of clinical benefit for treatment of:

- Primary
- Recurrent
- Suppressive

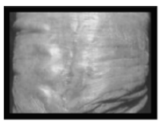
Spectrum of HSV Clinical Presentation



First infection

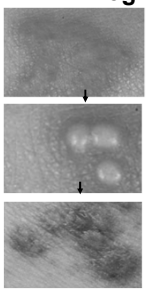


Classical recurrence



Atypical recurrence

Progression of Lesions



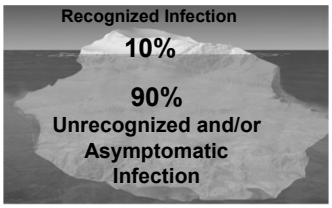
Early Redness/Swelling

Thin-Walled Fluid-Filled Vesicles and Pustules

Early Healing of Vesicles, Erosions, or Ulcers

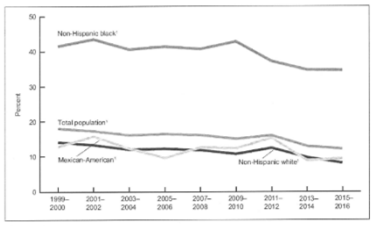
Clinical Spectrum of HSV-2

HSV-2 Seroprevalence



Mertz GJ. *Infect Dis Clin North Am*. 1993;7:825-839.

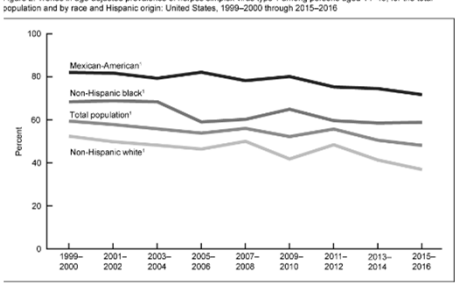
HSV-2 seroprevalence has decreased over time, overall and in all racial/ethnic groups



† Significant decreasing linear trend over time, p<0.05
NOTES: Age adjusted by the direct method to the 2000 US Census population, using age groups 14-19, 20-29, 30-39, and 40-49 years. Total population includes all race and Hispanic origin groups including those not shown separately. Data for the Asian subpopulation are only available since 2011, so this subpopulation is not shown separately, but included in the total population.

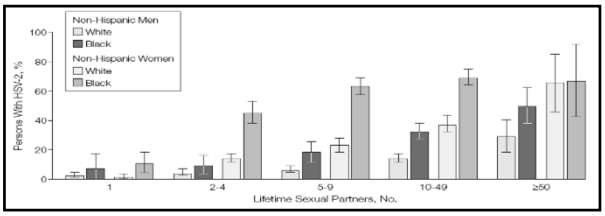
McQuillan, et al. NCHS Data Brief 2018.

Figure 2. Trends in age-adjusted prevalence of herpes simplex virus type 1 among persons aged 14–49, for the total population and by race and Hispanic origin: United States, 1999–2000 through 2015–2016



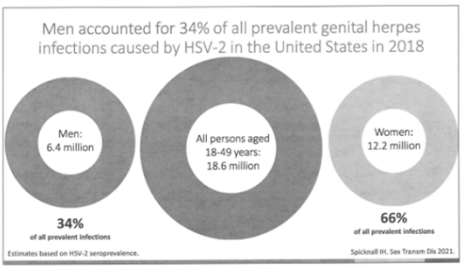
†Significant decreasing linear trend over time. p < 0.05.
NOTES: Age-adjusted by the direct method to the 2000 U.S. Census population, using age groups 14–19, 20–29, 30–39, and 40–49 years. Total population includes all race and Hispanic-origin groups including those not shown separately. Data for the Asian subpopulation are only available since 2011, so this subpopulation is not shown separately, but included in the total population. Access data table for Figure 2 at: https://www.cdc.gov/nchs/data/databriefs/db304_table.pdf#2.
SOURCE: NCHS, National Health and Nutrition Examination Survey, 1999–2016.

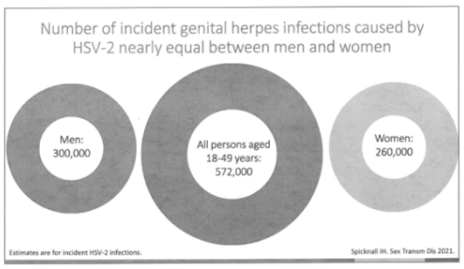
Age-Adjusted Herpes Simplex Virus Type 2 Seroprevalence According to the Lifetime Number of Sex Partners by Race/Ethnicity and Sex on NHANES in 1999-2004



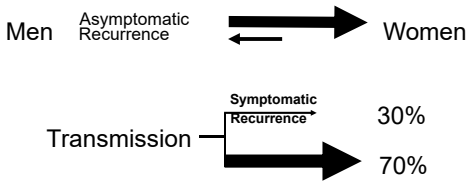
JAMA. August 23/30, 2006-Vol 296, No 8, pp 967

Men accounted for 34% of all prevalent genital herpes infections caused by HSV-2 in the United States in 2018

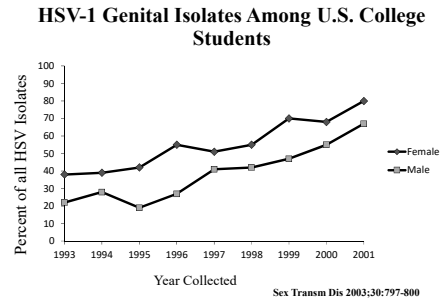


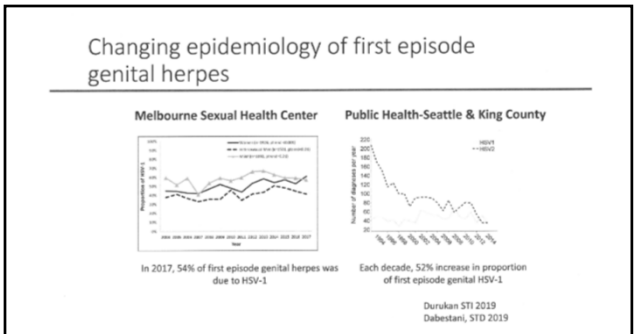


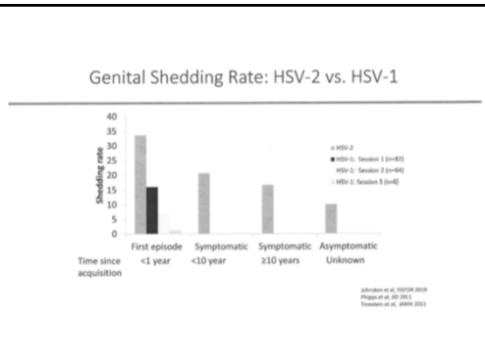
Genital Herpes: Transmission



Corey L. *Sex Transm Dis.* 1994;21(S38-S44.
Mertz GJ, et al. *Ann Intern Med.* 1992;116:197-202.





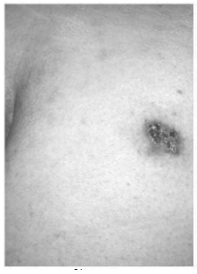


Genital Herpes: Viral Shedding

- Duration is longer in primary than in recurrent episodes
- Higher rates in
  - People with frequent outbreaks
  - First year after acquisition
  - Primary: 12 days
  - Recurrent: 2-3 days
- Oral antiviral suppressive therapy shortens the duration of, but does not eliminate, viral shedding

Genital Herpes – A Clinician's Guide to Diagnosis and Treatment. American Medical Association. 2001:1-20.
Whitley RJ, et al. *Clin Infect Dis.* 1998;26:541-555.

Herpes Presenting as Ulceration



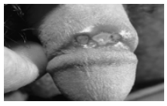
- The patient had been to her doctor 3 times over the past 8 months with this pruritic and mildly painful rash on her right buttock. She had been told that it was an irritation from riding a bicycle.
- What is the key to the diagnosis?
  - A. the fact that lesions recurred
  - B. site of involvement is not unusual
  - C. trauma can induce reactivation

Photo courtesy of Jeffrey Gilbert, MD.

Question #2

PREVIEW QUESTION

An 18 year old man presents with a history of malaise, low-grade fevers, and new-onset painful genital lesions seen in the picture below. He had unprotected sexual intercourse with a female partner 2 weeks earlier. Neither he nor his partner has traveled outside the United States.



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

A. Serum RPR
B. Serum FTA-Abs
C. Darkfield microscopy
D. Glycoprotein-G 1 serum antibodies
E. PCR on lesion swab

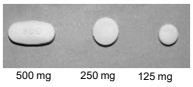
Answer #2

PREVIEW QUESTION

- Historically, culture of HSV was the gold standard. Using daily cultures to detect viral shedding resulted in 4-7% of all days being positive.
- Use of PCR has supplemented culture and detects shedding in up to ~25% of days. More recent data show intermittent shedding on the same day.
- A culture isolate of virus is required to test for resistance
- Serology can be used to assess prior exposure to HSV. The distinction between HSV glycoprotein 1 and 2 is diagnostic.

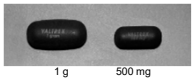
Oral Antiviral Therapies

- Famciclovir [Famvir®]



500 mg 250 mg 125 mg

- Valaciclovir [Valtrex®]



1 g 500 mg

- Acyclovir [Zovirax®]

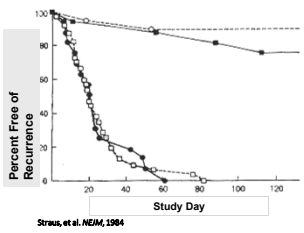
800 mg 600 mg 200 mg

Valtrex® and Zovirax® are registered trademarks of GlaxoSmithKline.

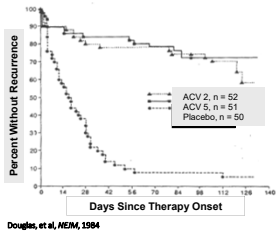
Impact of Acyclovir Therapy on Primary Genital HSV Infection

	Treatment Group (Days)			
	Acyclovir	Placebo	RR	P
Virus Shedding	2.8	16.8	6.82	0.0002
Pain	8.9	13.1	2.00	0.01
Scabbing	9.3	13.5	2.21	0.004
Healing	13.7	20.1	1.83	0.04

Effect of Acyclovir Prophylaxis on Recurrent Genital Herpes



Straus, et al. *NEJM*, 1984



Douglas, et al, *MEJM*, 1984

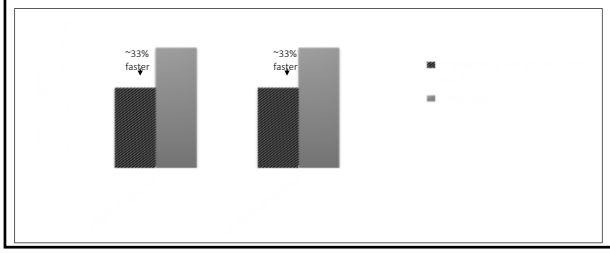
Second Generation Anti-Herpetic Medications

- Valacyclovir (prodrug of acyclovir)
- Famciclovir (prodrug of penciclovir)

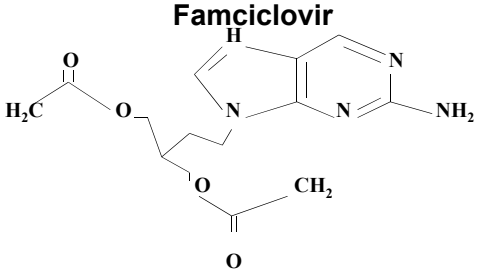
Acyclovir/Valacyclovir Kinetics

DRUG	DOSE	PHARMACOKINETICS	
		C_{max} (μg/mL)	Daily AUC (μg/mL•h)
VALTREX	1 g 3x/d	5.0	47
Oral ZOVIRAX	800 mg 5x/d	1.6	24
IV ZOVIRAX	5 mg/kg 3x/d	9.8	54
	10 mg/kg 3x/d	20.7	107

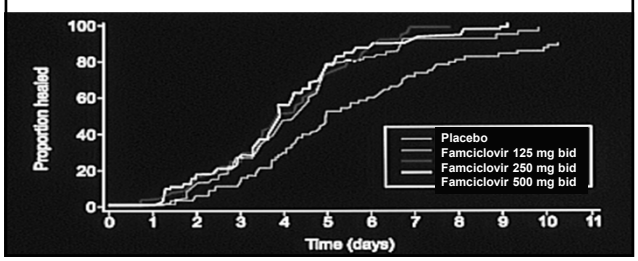
Therapy of Recurrent Genital Herpes: Duration of Disease



Famciclovir



Famciclovir Therapy of Recurrent Genital Herpes



Shorter and Shorter Therapy

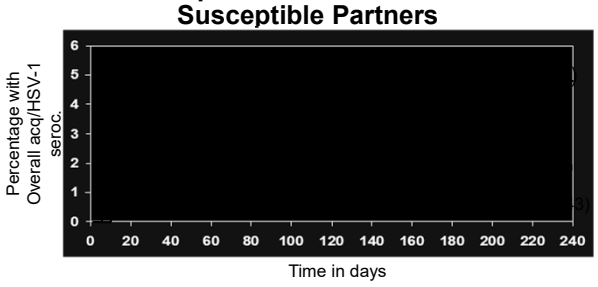
- Genital Herpes
  - Valacyclovir: three days
  - Famciclovir: one day
- Labial Herpes
  - Valacyclovir: two days
  - Famciclovir: one day

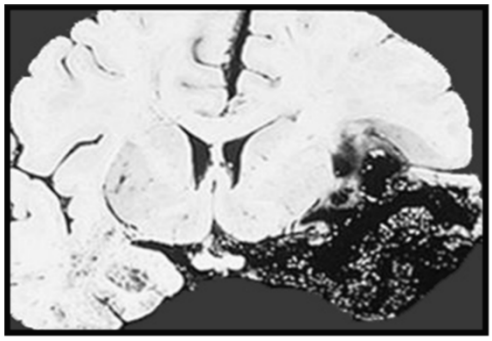
Prevention of Person to Person Transmission

Valacyclovir Prevention of HSV Transmission to Susceptible Partners

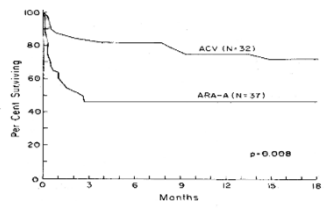
Susceptible Partner	Val-ACV N = 743	Placebo N = 741	Total
No. acquired HSV-2	14	28	42
No. acquired HSV-1	0	4	4
No. developed clinical HSV-2	4	17	21

Time to Acquisition of HSV-1 or HSV-2 in Susceptible Partners





Herpes Simplex Encephalitis Survival



Vidarabine (ARA-A) vs Acyclovir (ACV); P=0.008

HSE Morbidity

Percent Patients
Patient Normal / Mild Impairment

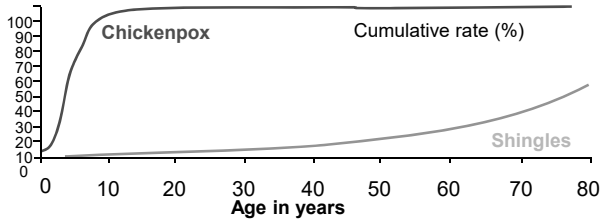
Age	Glasgow Coma Scale	
	≤6	>6
<30	0	60
>30	0	36

Sensitivity and Specificity of PCR

	Biopsy Positive	Biopsy Negative
PCR Positive	53	3
PCR Negative	1	44

Sensitivity 98%
Specificity 94%
Positive Predictive Value 95%
Negative Predictive Value 98%

Varicella Zoster Virus Infection



Adapted from Weller TH. *N Engl J Med.* 1983;309:1362-1368

CHICKEN POX: Is Therapy of Value?

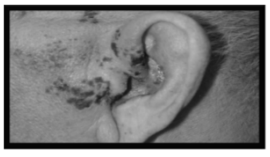
Treatment of Chicken Pox: Adults (>18 Years) < 24 Hour Duration

	Acyclovir (n=38)	Placebo (n= 38)	*P*
Time to maximum number of skin lesions (days)	1.5	2.1	0.002
Days of new lesion information	2.7	3.3	0.03
Time to onset of cutaneous healing (days)	2.6	3.3	<0.001
Time to 100% crusting (days)	5.6	7.4	0.001
Maximum number of lesions	268	500	0.04

Thoracic Herpes Zoster

Questions

1. What is the most likely diagnosis?
2. How would you prove the etiology?



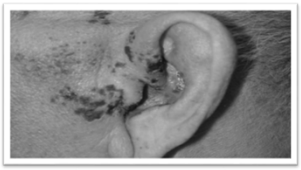
Answer

- Clinically this is herpes zoster
- The lesion shown is Tzank prep positive on skin scraping. The sensitivity of this test is only ~60% and, therefore, is not recommended
- Immunofluorescence is positive for VZV, having a sensitivity of ~80%.
- Preferably, PCR can be performed even when lesions are scabbed and has the highest sensitivity.

Question #3

What complication would you be most concerned about?

A. Facial paralysis
B. Keratitis
C. Encephalitis
D. Optic neuritis
E. Oculomotor palsies



http://www.itfnoroloji.org/kranyalnoropatiler/Kranyalnoropatiler.html

Answer: #3

- This patient has Ramsay Hunt syndrome (Herpes zoster oticus), caused by VZV reactivation in the geniculate ganglion, i.e. zoster of CN VII, presenting with severe ear pain and reduced hearing or deafness. When vesicle are seen in the auditory canal, abnormalities in cranial nerves VII, and sometimes VIII, IX or X, can occur. Thus A, facial paralysis is the best answer. Acyclovir is usually recommended although its not clear if it's effective. The facial paralysis is more severe and less likely to resolve than the usual HSV related Bells Palsy.
- Keratitis would be more typical of a lesion on the tip of the nose, or zoster ophthalmicus involving the CN V ophthalmic branch.
- Encephalitis can be caused rarely by VZV and would not be the best answer. Stroke syndromes due to carotid intimal involvement are associated with zoster, and often with cranial nerve V (trigeminal involvement), but are not offered as an answer
- Optic neuritis and oculomotor paralysis would be uncommon.

Question #4 Stem

The patient has only the observed finding on his nose.

- **What is your most likely diagnosis?**
- **What is the name of this sign?**

www.medscape.com

Question #4

What complication is it most likely to be associated with this illness?

A. Deafness
B. Vertigo
C. Optic neuritis
D. Keratitis
E. Stroke

www.medscape.com

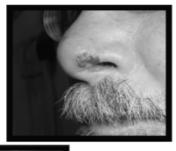
Answer: #4

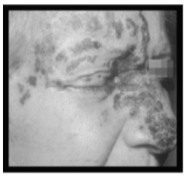
This patient has Hutchison's sign, which indicates involvement of the cranial nerve V, i.e. ophthalmic branch of the trigeminal nerve, which inervates the tip of the nose and the globe. After a prodrome of fever and headache for 1-4 days, patients develop a cutaneous rash. Days or up to 3 weeks later, the sclera and cornea can be involved. Thus, keratitis is the correct answer.

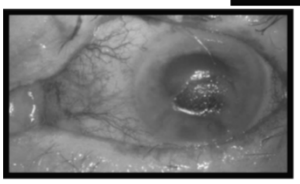
Deafness or vertigo would be more characteristic of geniculate ganglion (CN VII) involvement, i.e. Ramsay Hunt, which is a polyneuropathy involving the cranial nerve VII, and then often involves VIII, IX, X. Thus A and B are not the best answers.

Hutchison's Sign

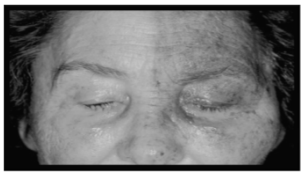
Zoster Involving nasociliary branch, Cranial Nerve VII which inervates the tip of the nose and the cornea







Zoster Ophthalmicus



NATURAL HISTORY OF ZOSTER IN THE NORMAL HOST

- **Acute neuritis may precede rash by 48 - 72 hours**
- **Maculopapular eruption, followed by clusters of vesicles**
- **Unilateral dermatomal distribution**

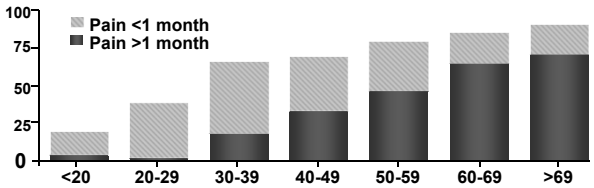
NATURAL HISTORY OF ZOSTER IN THE NORMAL HOST

- **Events of healing:**
  - **Cessation of new vesicle formation: 3 - 5 days**
  - **Total pustulation: 4 - 6 days**
  - **Total scabbing: 7 - 10 days**
  - **Complete healing 2 - 4 weeks**
- **Cutaneous dissemination can occur dissemination is extremely rare**
- **Postherpetic neuralgia in 10% - 40% of cases**

Complications of Zoster

Common	Uncommon
• Postherpetic neuralgia	• Cutaneous dissemination
• Ocular complications	• Herpes gangrenosum
• Ophthalmic zoster	• Hepatitis
• (uveitis, keratitis, scleritis, optic neuritis)	• Encephalitis
• Pneumonitis	• Motor neuropathies
• Scarring	• Myelitis
• Bacterial superinfection	• Hemiparesis (granulomatous CNS vasculitis)

Prevalence and Duration of Pain

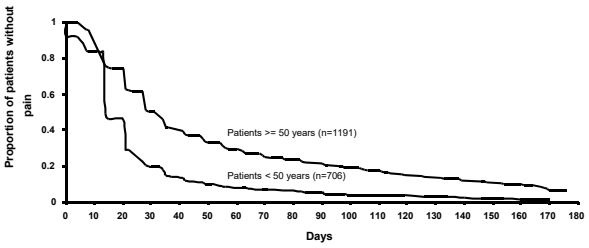


de Moragas et al. *Arch Derm.* 1957;75:193-196.

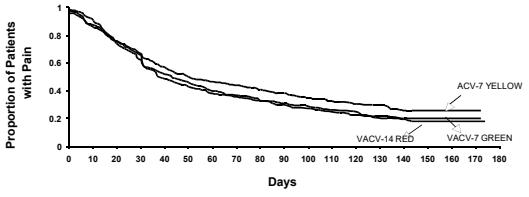
Goals of Therapy

- Accelerate cutaneous healing
- Accelerate loss of pain acute / chronic
- Prevent complications

Time to Cessation of Zoster-Associated Pain

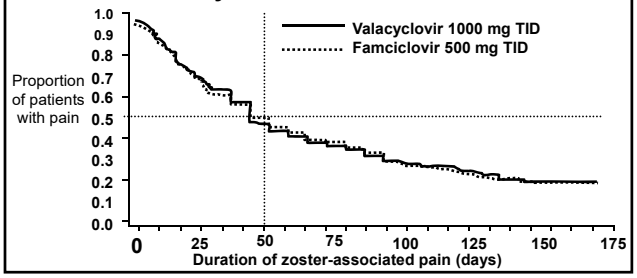


Time to Cessation of Zoster Associated Pain n = 1141



* Beutner, et al. Acyclovir versus Valacyclovir in the treatment of herpes zoster in patients > 50 years old.

Resolution of Pain in Herpes Zoster With Valacyclovir and Famciclovir



Summary of Efficacy of Concomitant Steroid Therapy with Acyclovir

- Accelerates resolution of acute neuritis
- Accelerates:
  - Return to usual activity P<0.001
  - Unaroused sleep P<0.0001
  - Cessation of analgesic use P<0.001
- Effect on chronic pain P=0.06

Question #5

What is the most likely etiologic agent?

A. HSV
B. VZV
C. CMV
D. EBV
E. HHV6

www.cdc.gov

Answer #5

- This patient has facial palsy, also known as Bells palsy. The most likely cause of this lesion is HSV. HIV and Lyme disease are less common causes. Answers d and e are not the best answer. Of note, Lyme is rarely the cause of Bells palsy unless there are other manifestations of Lyme disease.
- For typical facial palsy, prednisone is the preferred therapy, optimally given within 3 days of onset, for one week (prednisone 60-80mg qd). Acyclovir alone is not better than placebo, although there might be some rational (unproven) to add acyclovir to prednisone.
- Ganciclovir would be a therapy for CMV, a rare cause of facial paralysis and thus not the best answer.

METHODS OF PREVENTING / MODIFYING VARICELLA

Pre-exposure:	Oka varicella vaccine
Post-exposure:	VZIG (now available in US)
	Oka varicella vaccine (<3 days after exposure)
	Acyclovir (7-14 days after exposure)

Shingles Prevention Trial: Zostavax

Attenuated, live virus (approved 2006)

- **Efficacy but waning of immunity with time**
  - **Burden Of Illness 61.1% (51.1 – 69.1%)**
  - **Post-Herpetic Neuralgia 66.5% (47.5 – 79%)**
  - **Incidence of Herpes Zoster 51.3% (44.2 – 57.6%)**

Second Generation Vaccine: Shingrix

- **Recombinant adjuvanted vaccine**
  - **Two shots**
  - **> 50 years of age**
- **Efficacy**
  - **Both PHN and incidence of shingles**
  - **>90% for >4 years**
- **Adverse events**
  - **Local reactogenicity: redness and pain ~ 50-70%**
  - **Systemic malaise/fever: ~30%**

Thank You
rwhitley@uab.edu

50

Worms and More Worms

Dr. Edward Mitre

50 – Worms and More Worms

Speaker: Edward Mitre, MD

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

Worms and More Worms

Edward Mitre, MD
Bethesda, MD

7/25/2023

IDBR INFECTIOUS DISEASE BOARD REVIEW AUGUST 19-23 2023

Disclosures of Financial Relationships with Relevant Commercial Interests

- **None**

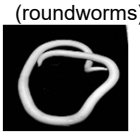
Disclaimer: Dr. Mitre is giving this presentation in a personal capacity. The views expressed in this presentation are the sole responsibility of the presenter and do not necessarily reflect the views, opinions, or policies of the Uniformed Services University of the Health Sciences, the Department of Defense, or the United States Government.

Pathogenic Helminths

Eukaryotic, multicellular animals

----- phylum Platyhelminths -----

--Its own phylum!!--

TREMATODES (flukes)	CESTODES (tapeworms)	NEMATODES (roundworms)
		
Fasciolopsis	*Taenia*	*Ascaris*

Images CDC DPDx

How helminths differ from other pathogens

- **eukaryotic, multicellular organisms**
- **often have complex lifecycles**
- **long lifespans (often for years)**
- **induce Th2 responses with eosinophilia and IgE**
- **with few exceptions*, DO NOT MULTIPLY WITHIN HOST**

(* Strongyloides, Paracapillaria, Hymenolepis)

World Prevalence

Ascaris	> 400 million
Trichuris	> 200 million
Hookworm	> 200 million
Schistosoma	> 150 million

http://ghdx.healthdata.org/gbd-data-tool

But very low ID Boards prevalence

5% of questions are on helminths, protozoa, travel medicine, and ectoparasites

Question #1

28 yo F presents with recurrent crampy abdominal pain for several months. She recently returned to the U.S. after living in Tanzania for two years. Colonoscopy reveals small white papules. Biopsy of a papule reveals an egg with surrounding granulomatous inflammation.

Most likely diagnosis?

A. *Entamoeba histolytica*
B. *Strongyloides stercoralis*
C. *Wuchereria bancrofti*
D. *Schistosoma mansoni*
E. *Paragonimus westermani*

Major Helminth Pathogens

TREMATODES

Blood flukes
- *Schistosoma mansoni*
- *Schistosoma japonicum*
- *Schistosoma haematobium*

Liver flukes
- *Fasciola hepatica*
- *Clonorchis sinensis*
- *Opisthorchis viverrini*

Lung flukes
- *Paragonimus westermani*

Intestinal flukes
- *Fasciolopsis buski*
- *Metagonimus yokagawai*

CESTODES

Intestinal tapeworms
- *Taenia solium*
- *Taenia saginata*
- *Diphyllobothrium latum*
- *Hymenolepis nana*

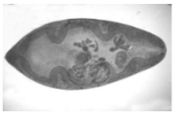
Larval cysts
- *Taenia solium*
- *Echinococcus granulosus*
- *Echinococcus multilocularis*

NEMATODES

Intestinal
- *Ascaris lumbricoides*
- *Ancylostoma duodenale*
- *Necator americanus*
- *Trichuris trichiura*
- *Strongyloides stercoralis*
- *Paracapillaria philippinensis*
- *Enterobius vermicularis*

Tissue Invasive
- *Wuchereria bancrofti*
- *Brugia malayi*
- *Onchocerca volvulus*
- *Loa loa*
- *Trichinella spiralis*
- *Angiostrongylus cantonensis*
- *Anisakis simplex*
- *Toxocara canis/cati*
- *Baylisascaris procyonis*
- *Gnathostoma spinigerum*

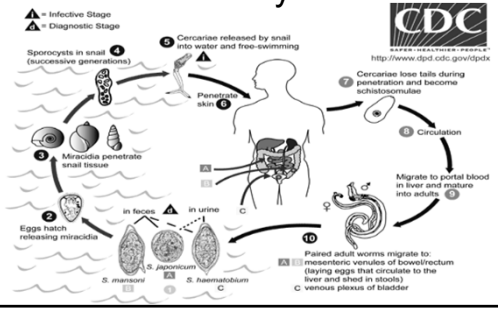
Trematodes (flukes)



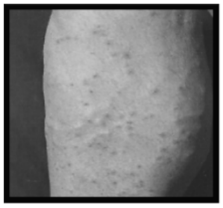
Paragonimus (CDC DpDx)

- flat, fleshy, leaf-shaped worms
- usually have two muscular suckers
- usually hermaphroditic (except Schistosomes)
- require intermediate hosts (usually snails or clams)
- praziquantel treats all (except *Fasciola hepatica*)

Schistosomiasis life cycle



Acute Schistosomiasis (Cercarial dermatitis or Swimmer's Itch)



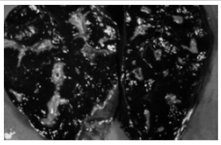
Urticarial plaques and pruritic papules upon reexposure to cercariae penetrating skin in a sensitized individual.

Can occur in response to human or avian schistosomes.

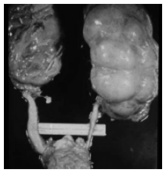
Acute Schistosomiasis: Katayama Fever

- Occurs in previously unexposed hosts.
- Occurs at onset of egg-laying (3-8weeks)
- Symptoms: fever, myalgias, abdominal pain, headache, diarrhea, urticaria
- Eosinophilia, ↑ AST, ↑ alkaline phosphatase
- **No reliable way to confirm the diagnosis acutely as serology and stool O/P frequently negative.**

Schistosomiasis



Chronic disease
- → granulomatous colitis (*S. mansoni*)
- → portal hypertension (*S. mansoni*)

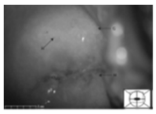


- → granulomatous cystitis *(S. haematobium)*
- → bladder fibrosis and cancer *(S. haematobium)*
- → obstructive uropathy (S. haematobium)

- → CNS disease (eggs to brain/spinal cord, esp *S. japonicum*)

Schistosomiasis

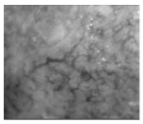

sand grains

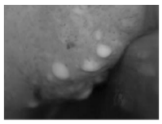

sandy yellow patches

Chronic genital disease
- increasingly recognized
- primarily due to *S. haematobium*

men
- epididymitis
- prostatitis

women (see vaginal and cervical lesions)
- pelvic pain
- dysmenorrhea
- dyspareunia
- post-coital bleeding
- endometritis/salpingitis

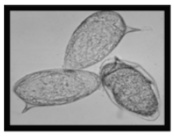

abnormal vessels


rubbery papules

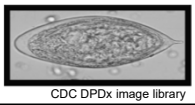
WHO Female Genital Schistosomiasis Pocket Atlas

Schistosome eggs

S. mansoni
(lateral spine)


CDC DPDx image library

S. haematobium
(terminal spine)


CDC DPDx image library

Major Helminth Pathogens

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Liver flukes
- *Fasciola hepatica*
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- *Opisthorchis viverrini*

Lung flukes
- *Paragonimus westermani*

Intestinal flukes
- *Fasciolopsis buski*
- *Metagonimus yokagawai*

CESTODES

Intestinal tapeworms
- *Taenia solium*
- *Taenia saginata*
- *Diphyllobothrium latum*
- *Hymenolepis nana*

Larval cysts
- *Taenia solium*
- *Echinococcus granulosus*
- *Echinococcus multilocularis*

NEMATODES

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- *Angiostrongylus cantonensis*
- *Anisakis simplex*
- *Toxocara canis/cati*
- *Baylisascaris procyonis*
- *Gnathostoma spinigerum*

Fasciola hepatica (a liver fluke)

→acquired by eating encysted larvae on aquatic vegetation (e.g. water chestnuts)

→fluke migration through the liver: RUQ pain and hepatitis

→arrive at biliary ducts in liver and mature over 3-4 months

→can induce biliary obstruction

Dx: eggs in stool exam (low sensitivity), serology

Rx: triclabendazole (FDA approved in 2019!)
(***note: the only trematode that don't respond well to praziquantel)


F. hepatica
(CDC DpDx)

Clonorchis sinensis

"Chinese Liver Fluke"

- eggs→snails→freshwater fish
- Acquisition by ingestion of undercooked fish
- Flukes develop in duodenum then migrate to liver bile ducts
- Can live for > 15 years, making 2000 eggs/day

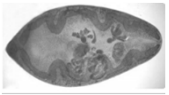
Opisthorchis viverrini

"Southeast Asian Liver Fluke"

- similar lifecycle
- also acquired by eating fish

Both can cause
biliary obstruction
cholelithiasis
cholangiocarcinoma

Paragonimus westermani
"lung fluke"


CDC

eggs→snails→freshwater crabs and crayfish
Ingestion of undercooked seafood
Adults migrate to LUNGS, frequent EOSINOPHILIA
Symptoms:
- *fever, cough, diarrhea during acute migration*
- *later, may have chest pain as worms migrate through lungs*
- *can develop chronic pulmonary symptoms*

Dx: Sputum and/or stool exam for eggs.

NOTE: Cases of Paragonimus kellicotti acquired in U.S. by ingestion of raw crayfish in rivers in Missouri

CID 2009 Sep 15;49(6):e55-61.
Clin Microbiol Rev 2013 Jul;26(3):493-504

Question #2

A 25 yo Peace Corps worker in Madagascar reports passing thin, white, flat tissue fragments in her stool. The microbiology lab reports the tissue fragments are proglottid segments of *Taenia solium*.
A long-term complication that can occur as a result of infection with the larval form of this parasite is:

A. HTLV-1 infection
B. bladder cancer
C. appendicitis
D. liver abscess
E. seizures

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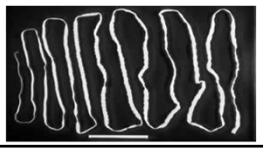
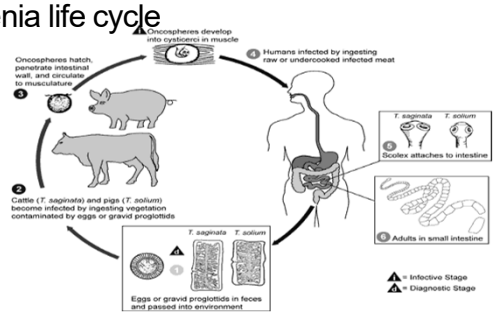
- *Anisakis simplex*
- *Toxocara canis/cati*
- *Baylisascaris procyonis*
- *Gnathostoma spinigerum*

Cestodes (tapeworms)

- all except *D. latum* have suckers with surrounding hooklets on the scolex (head) to attach to intestinal lining
- have flat, ribbon-like bodies composed of proglottid segments which contain reproductive organs
- have no digestive systems (food absorbed through soft body wall of worm)



Taenia life cycle



INTESTINAL TAPEWORMS

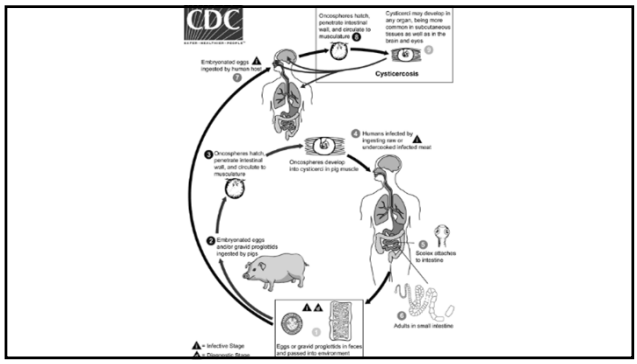
Taenia solium
tapeworm is acquired by eating larvae in pork
adult tapeworm causes few symptoms

Taenia saginatum
acquired by eating larvae in undercooked beef
causes few symptoms
can grow to 10 m

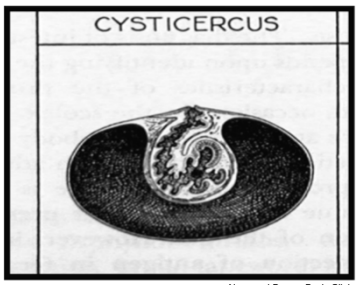
Diphyllobothrium latum *(can grow > 10 m)*
acquired by ingesting fish with larvae
***B12 deficiency in up to 40% of patients**

Dx: eggs/proglottids in stool **Rx**: praziquantel (not FDA-approved)

For some cestodes, humans can be infected by the larval stages and this can cause severe pathology.

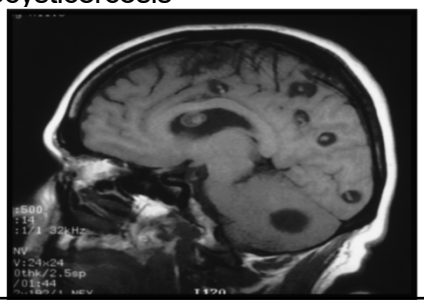


Cysticercus: a fluid filled bladder containing the invaginated head (scolex) of the larval form of a tapeworm.



Neva and Brown_Basic Clinical Parasitology 6th Edition

Neurocysticercosis



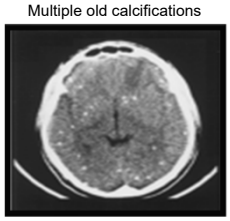
Neurocysticercosis

<u>Can cause:</u>

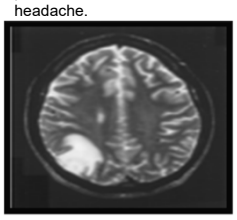
- seizures
- hydrocephalus
- headaches
- focal neurologic deficits

Neurocysticerosis

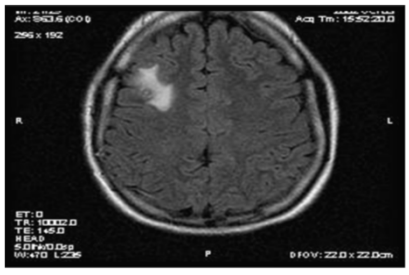
Multiple old calcifications



Perilesional edema – typically occurs around dying cysts and is a frequent finding on initial presentation of seizure or terrible headache.



Cysticercosis – single lesion disease is diagnostic challenge



Neurocysticercosis

Diagnosis:

Definitive = tissue biopsy
multiple cystic lesions each with scolex on imaging
retinal cysticercus seen on fundoscopic exam

Presumptive = suggestive lesions on imaging

Cysticercosis serology → supportive (sensitive if high burden of disease)

Treatment: *Medical therapy decreases risk of future seizures, but has immediate risk of increasing seizures/brain inflammation*

If hydrocephalus or diffuse cerebral edema, treat with steroids and/or surgery, not anti-parasitic therapy

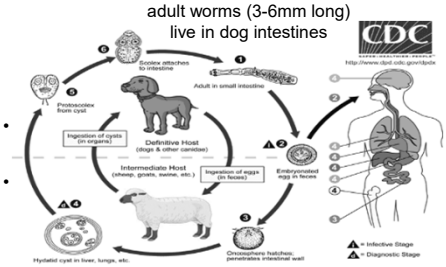
If no increased ICP: 1-2 viable cysts → albendazole for 1-2 viable cysts
> 2 viable cysts → albendazole + praziquantel

AND corticosteroids started before anti-parasitic therapy

****2017 IDSA Guidelines for Diagnosis and Treatment of Cysticercosis****

Echinococcus granulosus

adult worms (3-6mm long)
live in dog intestines



humans = accidental hosts

infected by ingestion of eggs in dog feces

Echinococcus granulosus

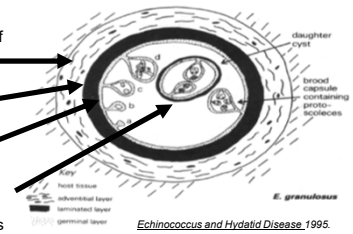
hydatic cyst = "watery vessel"

surrounding inflammatory response of fibrosis and chronic inflammation

outer acellular laminated layer

inner, nucleated germinal layer (PLURIPOTENTIAL TISSUE!)

internal cystic fluid and daughter cysts



Echinococcus and Hydatid Disease 1995.

Echinococcus granulosus - presentation

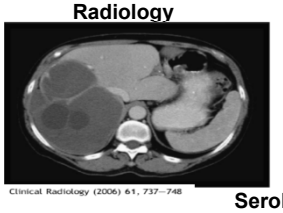
Most cysts (65%) in the liver
25% in the lung, usually in the right lower lobe
Rest occur practically everywhere else in the body

Common presentations
- allergic symptoms/anaphylaxis due to cyst rupture after trauma
- cholangitis and biliary obstruction due to rupture into biliary tree
- peritonitis b/c intraperitoneal rupture
- pneumonia symptoms due to rupture into the bronchial tree

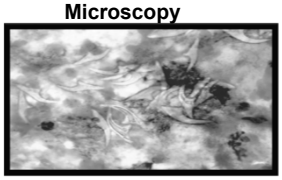
Uncommon presentations
- bone fracture due to bone cysts
- mechanical rupture of heart with pericardial tampanode
- hematuria or flank pain due to renal cysts

Echinococcus granulosus - diagnosis

Radiology



Microscopy



Serology

IgG ELISA about 85% sensitive for liver cysts of E. granulosus

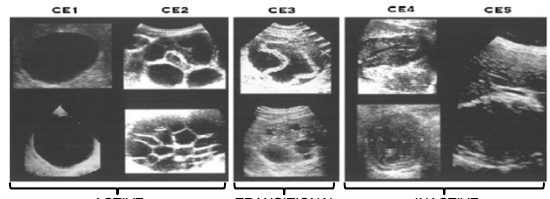
only 50% sensitive in cases of single pulmonary cyst

Echinococcus granulosus – treatment

Reasons for not spilling cyst contents
1. Anaphylaxis may occur
2. Spilled protoscoleces can reestablish infection

Typically treat with albendazole for several days before surgery or PAIR (usually 2d-1wk before, and 1-3 months after)

Cystic Echinococcus Treatment – depends on cyst stage



ACTIVE | TRANSITIONAL | INACTIVE

CE1	CE2	CE3	CE4	CE5
Unilocular Simply cyst Cyst wall visible	Multivesicular Multiseptated cysts	Anechoic content Detached membrane Solid matrix	Heterogenous, hypoechoic or hyperechoic No daughter cysts CE5 with thick calfied wall	
---PAIR or SURGERY---	---SURGERY---	---SURGERY--- ---PAIR if no solid matrix---	---NO TREATMENT---	

Question #3

A 25 yo F from rural Peru presents with shortness of breath, bilateral interstitial infiltrates, fever, loose stools, hypotension, and *E. coli* bacteremia. She has received > 4weeks of high dose corticosteroids and cyclophosphamide for a recent diagnosis of lupus nephritis. Which of the following anthelmintic agents should be included in her treatment regimen:

A. *Albendazole*
B. *Ivermectin*
C. *Praziquantel*
D. *Pyrantel pamoate*
E. *Diethylcarbamazine*

Major Helminth Pathogens

TREMATODES

Blood flukes
- *Schistosoma mansoni*
- *Schistosoma japonicum*
- *Schistosoma haematobium*

Liver flukes
- *Fasciola hepatica*
- *Clonorchis sinensis*
- *Opisthorchis viverrini*

Lung flukes
- *Paragonimus westermani*

Intestinal flukes
- *Fasciolopsis buski*
- *Metagonimus yokagawai*

CESTODES

Intestinal tapeworms
- *Taenia solium*
- *Taenia saginata*
- *Diphyllobothrium latum*
- *Hymenolepis nana*

Larval cysts
- *Taenia solium*
- *Echinococcus granulosus*
- *Echinococcus multilocularis*

NEMATODES

Intestinal
- *Ascaris lumbricoides*
- *Ancylostoma duodenale*
- *Necator americanus*
- *Trichuris trichiura*
- *Strongyloides stercoralis*
- *Paracapillaria philippinensis*
- *Enterobius vermicularis*

Tissue Invasive
- *Wuchereria bancrofti*
- *Brugia malayi*
- *Onchocerca volvulus*
- *Loa loa*
- *Trichinella spiralis*
- *Angiostrongylus cantonensis*
- *Anisakis simplex*
- *Toxocara canis/cati*
- *Baylisascaris procyonis*
- *Gnathostoma spinigerum*

Nematodes (roundworms)

→ Nonsegmented round worms

→ Flexible outer coating (cuticle)

→ Muscular layer under the cuticle

→ Nervous, digestive, secretory, and reproductive systems

How do people get infected with nematodes?

1. Eating eggs in fecally contaminated food or soil
   Ascaris, Trichuris, Enterobius, and Toxocara
2. Direct penetration of larvae through skin
   Hookworms, Strongyloides
3. Eating food containing infectious larvae
   Trichinella, Angiostrongylus, Anisakis
4. Vector transmission
   Wuchereria, Brugia, Oncho, Loa

Intestinal Helminths - Lifecycles

Strongyloides and Hookworms

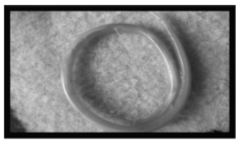
SKIN → LUNGS → GUT

Ascaris

GUT → LIVER → LUNGS → GUT

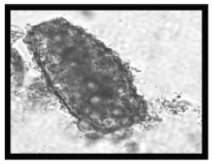
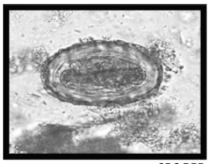
Ascaris lumbricoides

- Large numbers of worms can cause abdominal distention and pain or intestinal obstruction
- can cause "Loeffler's syndrome" - an eosinophilic pneumonitis with transient pulmonary infiltrates
- cholangitis and/or pancreatitis b/c aberrant migration

Ascaris lumbricoides - Diagnosis

Will not find eggs until 2-3 months after pulmonary symptoms occur
After 2-3 months, easy to find eggs since females make 200,000/day


Unfertilized

Fertilized CDC DPDx

Rx: albendazole or mebendazole

HOOKWORMS
Ancylostoma duodenale and Necator americanus
also Ancylostoma ceylanicum (zoonotic from dogs/cats in Asia)

- MAJOR cause of ANEMIA and protein loss (b/c plasma loss)
- pneumonitis associated with wheezing, dsypnea, dry cough (usually a few days to weeks after infection)
- urticarial rash
- mild abdominal pain

If sensitized → papulovesicular dermatitis at entry site "ground itch"

If worms migrate laterally → **cutaneous larvae migrans**
(especially dog and cat hookworms, as late as 2-8 wks after exposure to A. braziliense)

Still endemic in the U.S. → 35% of individuals from a rural community in Alabama had *N. americanus* in their stool samples *Am. J. Trop. Med. Hyg.*, 97(5), 2017, pp. 1623–1628

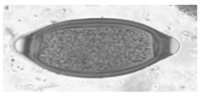
Trichuris trichiura (whipworm)

4cm long nematode

Life cycle: Fecal-oral

In heavy infections:
- loose and frequent stools
- tenesmus
- occ blood to frank blood
- in heavily infected children: rectal prolapse

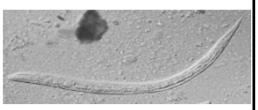
Dx: eggs are football shaped with two polar plugs



CDC DPDx

Strongyloides stercoralis

(can complete lifecycle in host!)

Usual manifestations
GI: mild abdominal/epigrastric pain
Pulm: wheezing, transient infiltrates
Skin: urticarial rashes, larva currens



Hyperinfection syndrome
→immunocompromised state
steroids, TNF-inhibitors, HTLV-1, malignancy, malnutrition….NOT HIV
→large burden of parasites

GI: Nausea, vomiting, abdominal pain, diarrhea, erosions b/c millions of larvae in intestinal mucosa

Pulmonary: diffuse infiltrates, wheezing, dyspnea, cough

Systemic: fever and hypotension due to gram negative sepsis

-- Often do not see eosinophilia in hyperinfection --

Strongyloides stercoralis

Diagnosis
- stool o/p (sensitivity is low - 30-60%)
- serology

Treatment of choice: ivermectin

Prevention in pts from endemic countries who are about to be immunosuppressed
- Empirically treat, or check serology and treat if positive.

Ivermectin

activates nematode glutamate-gated chloride channels causing muscle paralysis

Drug of choice
- Strongyloides
- Onchocerca volvulus (microfilaricidal only)
- Also has activity against Ascaris, whipworm, cutaneous larva migrans, gnathostomiasis AND ectoparasites such as scabies and lice

ADVERSE EFFECTS
→ reports of seizures, ataxia, and confusion after ingestion of large veterinary doses
N Engl J Med 2021; 385:2197-2198

→ altered mental status in 13 yo boy given standard dose for scabies due to a mutation in ABCB1 (aka P glycoprotein 1 and MDR1)
N Engl J Med 2020; 383:787-789

Question #4

A 32 yo M from Cameroon reports intermittently experiencing a worm crawling across his eye. Which of the following tests can be used to confirm the most likely diagnosis?

A. *Brain MRI scan*
B. *Midnight blood draw*
C. *Noon blood draw*
D. *Skin snip*
E. *Scrotal ultrasound*

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- *Schistosoma japonicum*
- *Schistosoma haematobium*

Liver flukes
- *Fasciola hepatica*
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- *Opisthorchis viverrini*

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Intestinal flukes
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Intestinal tapeworms
- *Taenia solium*
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Larval cysts
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- *Echinococcus granulosus*
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- *Angiostrongylus cantonensis*
- *Anisakis simplex*
- *Toxocara canis/cati*
- *Baylisascaris procyonis*
- *Gnathostoma spinigerum*

Filariae: tissue-invasive, thread-like nematodes, transmitted by arthropod vectors

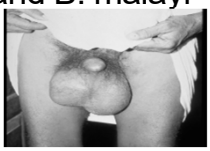
	Adults	Microfilariae
Wuchereria bancrofti *Brugia malayi* (lymphatic filariasis) --mosquitoes--	lymphatics	blood (night)
Loa loa (eyeworm) --Chrysops flies--	SQ tissues (moving)	blood (day)
Onchocerciasis (river blindness) --blackflies--	SQ tissues (nodules)	skin

Treatment of Filariasis

	Treatment	Avoid
Lymphatic filariasis	**DEC**	**-----**
Loa Loa	**DEC**	**DEC and Ivermectin if high microfilaria level**
Onchocerciasis	**ivermectin**	**DEC**

ADVERSE EFFECTS
Loa with high microfilaremia → encephalopathy and death
Onchocerciasis → severe skin inflammation and blindness

W. bancrofti and B. malayi

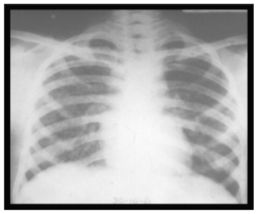




- Asymptomatic microfilaremia
- Lymphangitis
  - retrograde (filarial lymphangitis)
  - bacterial skin/soft tissue infections (dermatolymphangioadenitis)
- Lymphatic dysfunction
  - Lymphedema, elephantiasis, hydrocele, chyluria

Tropical pulmonary eosinophilia

- Paroxysmal nocturnal asthma
- Pulmonary infiltrates
- Peripheral blood eosinophilia (>3,000/mm^3)
- Elevated serum IgE
- Rapid response to anti-filarial therapy

Likely due to excessive immune response to microfilariae in lung vasculature



Lymphatic filariasis: diagnosis

Definitive diagnosis

- Identification of microfilariae in nighttime blood
- Detection of circulating antigen in blood (only Wb)
- Identification of adult worm (by tissue biopsy or ultrasound "filaria dance sign")

Presumptive diagnosis

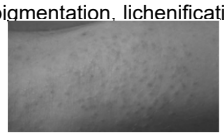
- Compatible clinical picture + positive antifilarial antibodies

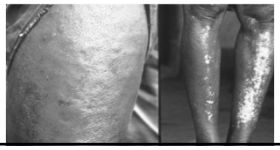
Treatment

- DEC, doxycycline
- NOTE: Triple drug single dose therapy (DEC/albendazole/ivermectin) is now recommended by W.H.O. for mass drug administration eradication campaigns in areas that are NOT co-endemic for Loa loa or Onchocerca

Manifestations of Onchocerciasis

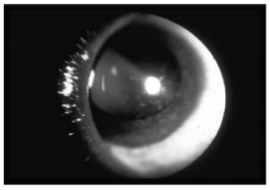
Skin: nodules, pruritus, rash, depigmentation, lichenification

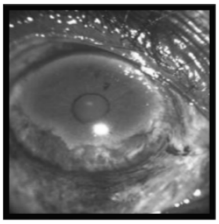




Manifestations of Onchocerciasis

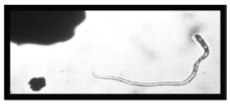
- Eye: punctate keratitis, sclerosing keratitis, chorioretinitis





Onchocerciasis

Diagnosis
- Serology
  - anti-filarial
  - onchocerca-specific
- Parasitologic: skin snips, nodulectomy



Treatment

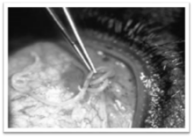
Ivermectin

Moxidectin (FDA approved in 2018…has much longer half-life)
→ both are primarily microfilaricidal
→ therefore need repeated treatments for many years

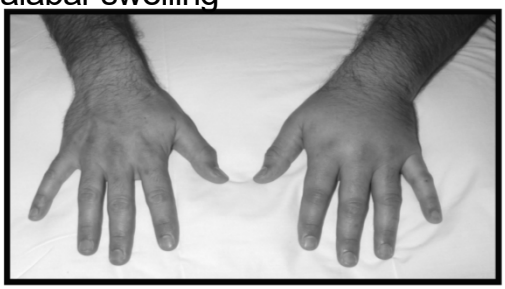
(alternative: **doxycycline** for 6 weeks, which kills endosymbiotic *Wolbachia* bacteria, kills adult worms)

Loiasis: clinical manifestations

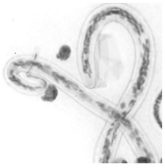
- Asymptomatic microfilaremia
- Non-specific symptoms
  - fatigue, urticaria, arthralgias, myalgias
- Calabar swellings
- Eyeworm
- End organ complications (rare)
  - endomyocardial fibrosis, encephalopathy, renal failure



Calabar swelling



Loiasis: Diagnosis



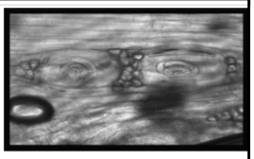
CDC DpDx

Definitive diagnosis
- Identification of adult worm in subconjunctiva
- Detection of Loa microfilaria in **noon blood**

Presumptive diagnosis

Compatible clinical picture + positive antifilarial antibodies

Trichinellosis



CDC DPDx

1. Eat meat containing cysts (pork, boar, horse, wild game)
2. Larvae released from cysts by gastric acid.
3. Adults invade small bowel,
   - mature into adults over 1-2wks.
   --> ABDOMINAL CRAMPS and DIARRHEA IF HEAVY INFXN
4. Adults (who only live for about a month) make larvae.
5. Larvae migrate to striated muscle, encyst, and live in "nurse cells"
   → **SEVERE MUSCLE PAIN**
   → **PERIORBITAL EDEMA**
   → **EOSINOPHILIA**
   +/- fever and urticaria

Diagnosis: serologies are supportive, + biopsy is definitive
Treatment: albendazole + steroids

Angiostrongylus cantonensis

CDC DPDx

Ingestion of larvae in raw or undercooked seafood (found worldwide)

In humans, parasite buries its head into gastric mucosa. Eosinophilia common.

Symptoms
1) due to invasion of worm (pain, vomiting)
2) due to allergic rxn to worm
(mild urticaria, itchy sensation back of throat, naphylactic shock)

Treatment
→ usually simple endoscopic removal
→ for allergic symptoms, avoid contaminated fish

Anisakis

The most common parasitic cause of eosinophilic meningitis worldwide

Appears to be spreading in range

2022, Am. J. Trop. Med. Hyg, 107 (6):1166-72
Creative Commons License

Acquisition by eating raw or undercooked
- snails or slugs
- freshwater prawns, shrimps, crabs, frogs
- contaminated produce (leafy greens)

Diagnosis
- usually presumptive (eosinophilic meningitis + exposure history)
- serology (not commercially available)
- CSF PCR (Hawaii DOH State Laboratory)

Treatment: corticosteroids + albendazole
(see 2021 Guidelines paper in Parasitology, 148,227-233. PMID:32729438).

Possible question hints

Freshwater exposure + eosinophilia → Schistosomiasis
Crab/crayfish + pulmonary sxs + eosinophilia → Paragonimus
Cysticercosis → ANY food contaminated with tapeworm eggs
Allergic symptoms after trauma → Echinococcus
itchy feet return to tropics → ground itch due to hookworms
Gram- sepsis after corticosteroids or TNF inhibitor → Strongyloides hyperinfection
Subcutaneous nodules → Onchocerca volvulus
Blood microfilaria night → lymphatic filariasis (day = Loa loa, skin = Ov)
Muscle pain + eosinophilia → Trichinella
Eosinophilic meningitis → Angiostrongylus
Abdominal pain after sushi → Anisakis
Eosinophilia + F + ↑ AST/ALT in child → visceral larva migrans

Caveat to today's talk – a bit simplistic
Multiple parasites can cause similar diseases

Eosinophilic meningitis

Nematodes:
- Angiostrongylus cantonensis
- Baylisascaris procyonis
- Gnathostoma species
- Toxocara canis & T. cati
- Trichinella spiralis
- Strongyloides stercoralis
- Loa loa
- Meningonema peruzzi

Trematodes:
- Schistosoma species (larvae or eggs)
- Paragonimus westermani
- Fascioliasis

Cestodes:
- Neurocysticercosis
- Echinococcus

Good Luck!

Ed Mitre
edwardmitre@gmail.com

51

Fungal Diseases in Normal and Abnormal Hosts

Dr. John Bennett

51 – Fungal Diseases in Normal and Abnormal Hosts

Speaker: John Bennett, MD

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

Fungal Disease in Normal and Abnormal Hosts

John E. Bennett, MD
Bethesda, Maryland

7/23/2023

IDBR INFECTIOUS DISEASE BOARD REVIEW AUGUST 19-23 2023

Disclosures of Financial Relationships with Relevant Commercial Interests

- **None**

Case 1

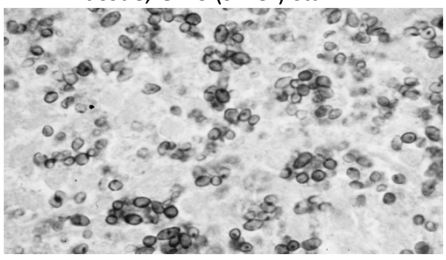
- 42 yr WF with Crohn's disease taking adalimumab is admitted to a Chicago hospital because of 6 weeks of low grade fever, pancytopenia and a 10 pound weight loss. Hydrocortisone 200 mg daily was begun for low serum cortisol not responding to Cortrosyn stimulation. Admission studies found her long standing anemia has worsened, with a hematocrit of 25%, platelet count 30,000, WBC 2,500 with a normal differential, alkaline phosphatase 250, ALT 120, AST 89 and creatinine 2.0 Micafungin was given for yeasts seen in peripheral blood smear that were not growing on routine culture. This infection came from:

a. Her intestinal tract
b. Human (coughing)
c. Pigeon droppings
d. Soil
e. Contaminated food

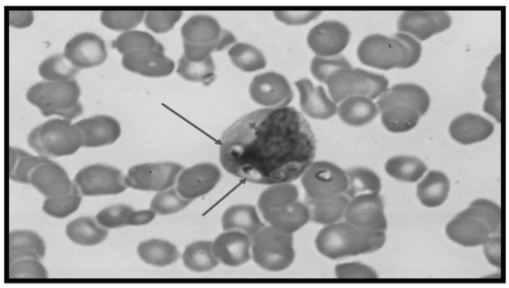
Histoplasma capsulatum

- Central USA highest exposure. Rich moist earth. Subclinical common.
- Disseminated infection mostly immunosuppressed, variable clinical presentation. Fatal in untreated
- Subacute or chronic. Fever. Cytopenias. Addison's. Endocarditis. Mucosal lesions in mouth, larynx, bowel. Miliary lung lesions.
- Diagnosis: antigen in serum, urine or CSF, pathology, culture is slow.
- Rx: ampho if severe. Itraconazole.

HISTOPLASMA CAPSULATUM
in tissue, GMS (silver) stain

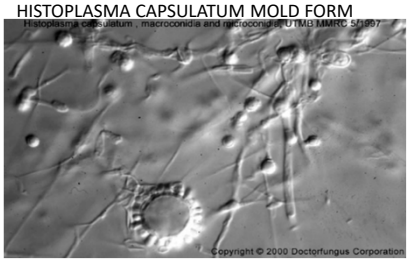


HISTOPLASMA CAPSULATUM YEASTS IN MONOCYTE

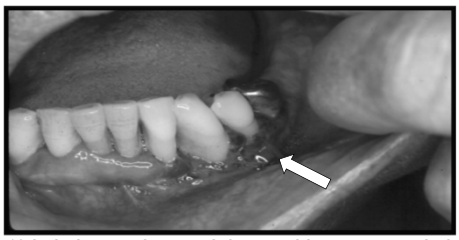


Histoplasma capsulatum growing at room temperature

- HISTOPLASMA CAPSULATUM MOLD FORM

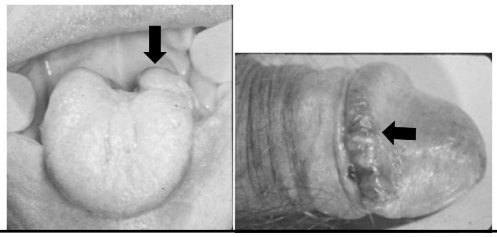


Gingival Ulcer

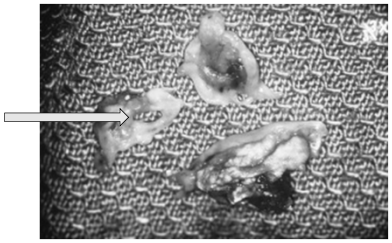


¼ CASES HAVE ORAL LESION IN DISSEMINATED HISTO

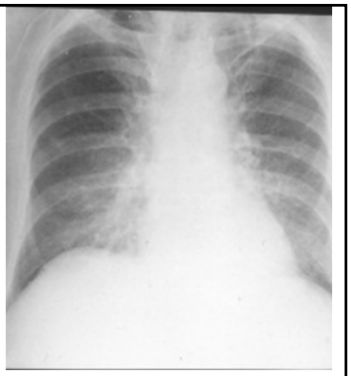
TONGUE AND PENILE LESIONS
MUCOSAL LESIONS CAN RESEMBLE SQUAMOUS CARCINOMA



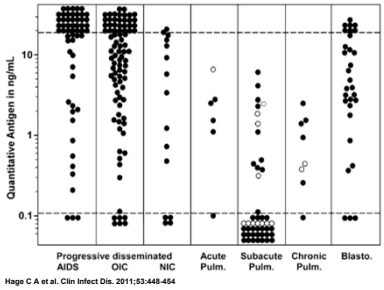
HISTOPLASMA IS A CAUSE OF "CULTURE NEGATIVE" ENDOCARDITIS
(PERFORATED AORTIC VALVE)



MILIARY LUNG LESION IN
DISSSEMINATED HISTOPLASMOSIS
(LOOKS LIKE PCP ON IMAGING)



Results for cases of proven and probable histoplasmosis and proven blastomycosis.



Hage C A et al. Clin Infect Dis. 2011;53:448-454

Clinical Infectious Diseases

REVIEW:
DISSEMINATED HISTOPLASMOSIS
- TNF ALFA INHIBITORS, AIDS, CORTICOSTEROIDS, IMMUNOSUPPRESSION
- NEUTROPENIA DOESN'T PREDISPOSE

SOURCE: INHALATION OF ORGANIC SOIL ENRICHED WITH BIRD DROPPINGS
CLINICAL FEATURES: ONSET SUBACUTRE OR INDOLENT
- PANCYTOPENIA, ORAL LESIONS , MILIARY LUNG LESIONS, ADDISON'S,
- BLOOD CULTURE-NEGATIVE ENDOCARDITIS. HLH-LIKE SYNDROME

DIAGNOSIS
- YEAST IN BLOOD SMEAR OR BIOPSY. GROWS AS MOLD. (DIMORPHIC)
- ROUTINE CULTURES NEGATIVE. FUNGAL CULTURES OFTEN NEGATIVE.
- URINE OR SERUM ANTIGEN BEST (CROSS REACTS WITH BLASTOMYCOSIS)

TREATMENT: FATAL IF UNTREATED
- AMPHOTERICIN FOLLOWED BY ITRACONAZOLE

HISTOPLASMA DUBOISII: AFRICA. SKIN AND BONE LESIONS.

Case 2

44 yr previously healthy male accountant in Washington DC presented with the acute onset of confusion that was preceded by three months of headache. Cranial MRI was normal. Lumbar CSF had an opening pressure of 350mm CSF, WBC 250/cu mm, glucose 22 mg /dl, protein 125 mg/dl and cryptococcal antigen titer 1:512. Liposomal amphotericin B was begun at 5.0 mg/kg IV daily. On the third day of treatment he complained that the room was too dark and was found to have visual acuity of hand motion only in both eyes.

Case 2

The most important next step in this patient is which of the following:

A. start flucytosine
B. start fluconazole
C. Start acetazolamide (Diamox)
D. Begin daily lumbar punctures
E. Start dexamethasone

Cryptococcosis

- Encapsulated yeast inhaled from sources in nature. C. neoformans, worldwide, pigeon droppings., C. gattii: S. California, Vancouver Island, overseas , certain trees
- C. neoformans: corticosteroids, AIDS, normal. C. gattii more often normal patient. Similar diseases.
- Symptoms: indolent onset. Usually present in CNS as headache, altered mentation
- Diagnosis: antigen in serum, CSF. Yeasts on biopsy or smear. Fungal culture good.
- Rx: ampho +/- flucytosine then fluconazole. Maintenance in HIV
- Start ARV after 2-10 wks of antifungal Rx in HIV naïve patients.
- Daily lumbar punctures for pts with opening pressure of ≥25cm and symptoms
- Pregnancy: use ampho until delivery (5FC is category C, azoles all teratogenic)

Q: AmBisome: 10 mg/kg once for crypto? (no, not board exam material)

- Recent study of HIV in Africa: one dose Ambisome (10 mg/kg) followed by 2 weeks of flucytosine + high dose fluconazole (1200 mg) had same 10 week mortality and less toxicity as one week of daily conventional ampho 1 mg/kg + flucytosine then one week of high dose fluconazole. Both groups given fluconazole 800 mg/d for 8 weeks
- Current recommendation in USA for HIV and nonHIV is AmBisome 3-5 mg/kg or conventional ampho 0.7 -1.0 mg/kg daily + flucytosine for at least two weeks followed by fluconazole 400 mg for 8 weeks
- Answer: Africa regimen has no obvious advantage for HIV or non HIV crypto in USA

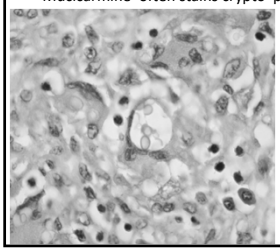
More on Cryptococcosis and IRIS

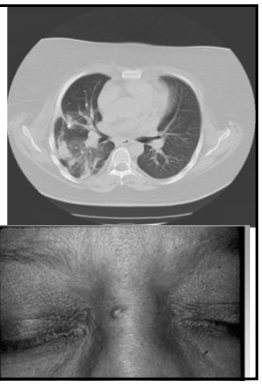
- Weeks or months after ARV and antifungal Rx for meningitis:
- Fever, headache, high opening pressure, seizures, cranial nerve palsies, new MRI lesions
- Key: all cultures negative.
- Dry cough, substernal pain
- Swollen nodes in mediastinum, hilum
- Rx: NSAIDS or prednisone

Cryptococcal lung lesions usually asymptomatic

Skin lesions can resemble molluscum contagiosum

Mucicarmine often stains crypto pink.





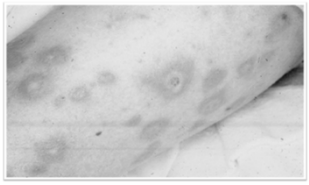
Cryptococcosis review

- Serum antigen good screen in susceptible hosts but can miss early case. LP needed if serum antigen positive. Brain MRI insensitive. CSF antigen sensitive, specific. Titers fall very, very slowly.
- Relieve high intracranial pressure to prevent blindness, death
- Start with ampho with fluconazole later. Start with fluconazole if lung only and otherwise healthy
- Wait to start ARV to delay possible IRIS
- Echinocandins not effective

Case 3

Case 3

35 yr male 68 days post allogeneic bone marrow transplantation for myelodysplastic syndrome, receiving methylprednisolone 500 mg for Grade III GVHD of the gastrointestinal tract developed fever, several painful, red skin nodules and a blood culture growing a mold.



Case 3

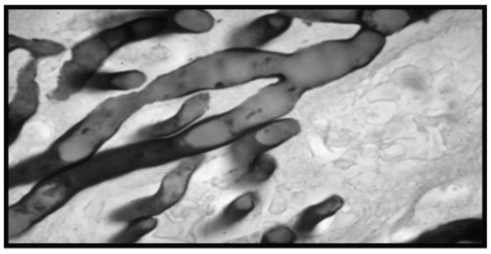
The most likely fungus is which of the following:

A. Scedosporium apiospermum (Pseudallescheria boydii)
B. Lomentospora (Scedosporium) prolificans
C. Apophysomyces elegans
D. Fusarium multiforme
E. Alternaria alternata

Fusariosis

Severely immunocompromised patients
Mold, looks like Aspergillus in tissue
Red, tender skin nodules
Blood culture grows mold in a third to half the patients
RX: response to ampho and vori poor in severe neutropenia. Experimental: PMN transfusion?, fosmanogepix??
Note: fungal meningitis from F. solani, Mexico, epidural anesthesia

Fusarium hyphae. GMS stain



Case 4

- 47 WM executive referred from Baltimore because of severe headaches, diplopia, high fever of 1 wk's duration
- 4 wks PTA: Maui resort one week
- 3 wks PTA: ranch outside Tucson, Arizona 1 wk
- 2 wks PTA: back at work in Baltimore
- 1 wk: PTA: Headache began

- Exam: Temp 38.5 C. Looks ill. Photophobia, nuchal rigidity, right CN6 palsy

- CBC, Routine blood chemistries normal. CSF : Glucose 55, Protein 58, WBC 330 (20% eos). Negative cryptococcal antigen on CSF, serum Lyme serology and serum RPR. MRI with contrast normal. Worsens during 2 wks of ceftriaxone. CSF cultures for bacteria, fungi, tbc neg to date.

CASE 4

The most helpful diagnostic test would be:

A. CSF cytology
B. Stool O&P
C. Dietary history
D. Fungal serology
E. Leptospirosis serology

Coccidioidomycosis=Valley Fever

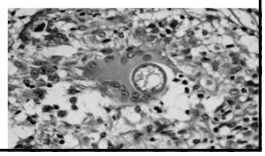
- Two species, one disease:
  - C. immitis and C. posadasii. Both serious lab hazards
  Southwest USA. Washington state
- Acute pneumonia 2 wks after inhalation: arthralgias or erythema nodosum may accompany. Resolves.
- Residual nodule or thin walled cavity may persist
- Dissemination: African americans, HIV, SOT, TNF inhibitors
- Bone, skin, chronic meningitis
- Rx: fluconazole. Nonmeningeal: itraconazole

COCCIDIOIDOMYCOSIS DIAGNOSIS

SEROLOGY
CSF CF serology useful. Serum CF >16 suggests dissemination, falls with Rx
Serum IgG by EIA converts to positive late, stays positive .
Serum antigen may be useful?

CULTURE
Routine cultures negative, fungal cultures positive. Lab hazard

BIOPSY
Distinctive non-budding spherules



Coccidioidomycosis review

Southwest USA, Washington state

Acute pneumonia 2 weeks after desert dust exposure

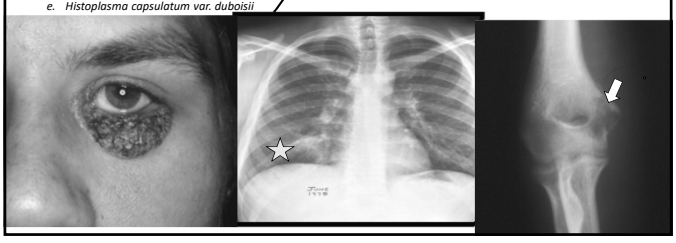
Eosinophilia in blood, CSF (low grade)

Dissemination in African Americans, SOT, HIV, pregnancy

CF antibody in CSF, serum

Ampho, itra, fluconazole

CASE 5
A previously healthy 22 yr old Wisconsin man presented with a face lesion, elbow swelling and pain, had asymptomatic lung lesion on chest xray and lytic lesion on condyle of his humerus.
This is most likely which of the following:
a. Candida auris
b. Trichosporon cutaneum
c. Leishmania donovani
d. Blastomyces gilchristii
e. Histoplasma capsulatum var. duboisii



Blastomyces dermatitidis , B. gilchristii

CENTRAL USA AND CANADA, MOLD IN NATURE LARGE BROAD-BASED BUDDING IN TISSUE

MOIST EARTH NEAR RIVER, BEAVER DAMS.

NORMAL HOST

YEAST WITH BROAD BASED BUD, THICK WALL

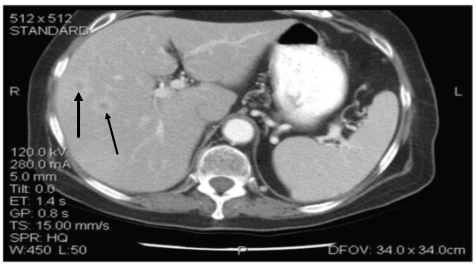
ACUTE PNEUMONIA MAY SELF HEAL

INDOLENT, PROGRESSIVE PNEUMONIA DISSEMINATES TO SKIN, BONE, MALE GU TRACT

OFTEN PRESENTS AS SKIN LESIONS

RX: ITRACONAZOLE, AMPHO B

Case 6: What are these lesions in a febrile, recently neutropenic patient?

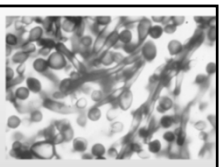


CASE 6

Which is the most likely

A. Babesia microti
B. Candida tropicalis
C. Fusarium oxysporum
D. Aspergillus flavus
E. Streptococcus anginosus

CANDIDA SPECIES



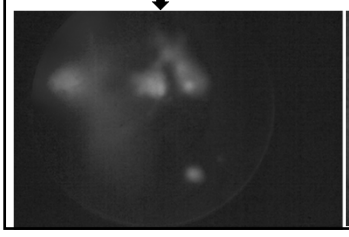
Pseudohyphae (not glabrata)and budding yeast
Infected devices usually require removal: catheters, prostheses, grafts
Candidemia may lead to
- hepatosplenic lesions (neutropenics)
- endophthalmitis
- multiple skin lesions (neutropenics)
- endocarditis

Candida auris often misidentified as unusual species (e g. C. haemulonii,)
- Colonizes skin and hospital equipment, causes hospital outbreaks. Contact isolation.
- Antifungal drug resistant. (Azoles, ampho?)
- CDC: in 2022, there were 2,377 clinical cases and 5,754 colonized cases.
- Screening high risk patients for C. auris colonization recommended.

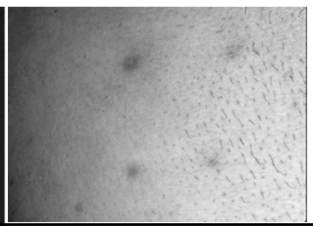
Echinocandins first choice for all Candida species, including C. parapsilosis, C. auris

Candida endophthalmitis:

"fluff balls" floating in the vitreous humor



Candida lesions in a neutropenic patient

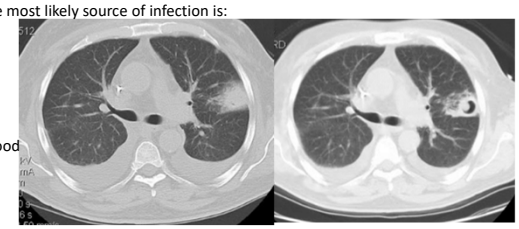


Candidiasis: key points

- Fundoscopy for retinal lesions in candidemia patients.
  - Intravitreal Rx may be needed
- Remove intravenous catheter with candidemia
- Candida auris hospital outbreaks. Spreads on hands, sufaces
- Fluconazole resistance in C. auris, C. krusei, C. glabrata
- Fungitell (1-3) beta-D-glucan positive in serum

Case 7
32 yr old male with allogeneic hematopoietic stem cell transplant recipient for AML, developed graft versus host disease , given high dose prednisone, discharged and re-admitted for fever not responding to antibacterial antibiotics. These two chest CT 's, were taken at admission and a week later while he was responding to voriconazole. The most likely source of infection is:

a. Dirt from his garden
b. His oral flora
c. Contaminated food
d. Intravenous catheter

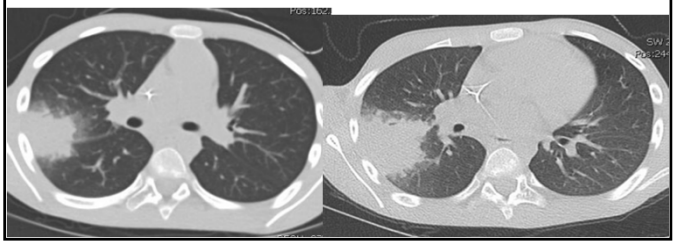


Aspergillus Pneumonia

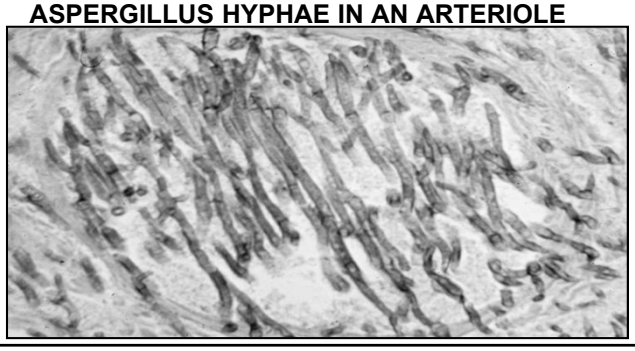
Sudden onset of a dense, well circumscribed lesion in a neutropenic patient should suggest a mould pneumonia, most commonly aspergillosis but mucormycosis gives same CT findings: halo sign early, crescent sign later
Septated hyphae invade blood vessels, infarct tissue.
Galactomannan useful in CSF, BAL, blood
- False positives
- False negatives with azole prophylaxis

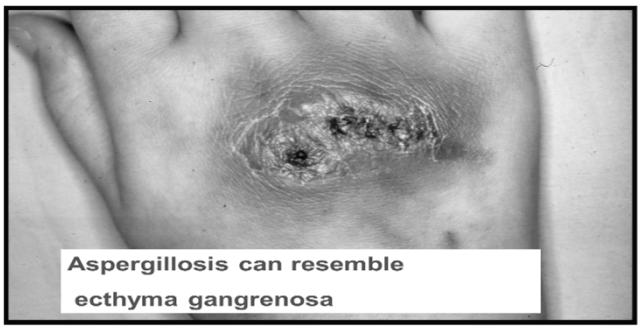
Rx. voriconazole, isavuconazole, posaconazole, ampho B

Two CT's showing transient worsening of CT despite clinical improvement . Note halo sign.



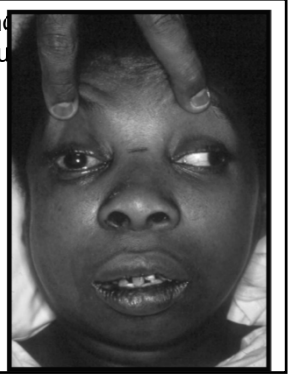
ASPERGILLUS HYPHAE IN AN ARTERIOLE





Mucormycosis mimics caverno
following sinu

CASE 8
25 YR OLD FEMALE ADMITTED WITH DIABETIC KETOACIDOSIS AND BLINDNESS IN HER RIGHT EYE. ON EXAM THE RIGHT EYE WAS FIXED IN POSITION AND PROPTOTIC. CT SHOWED DENSE MASS IN ADJACENT ETHMOID SINUS WITH EXTENSION INTO THE ORBIT. SURGICAL EXPLORATION OF THE SINUS SHOWED BROAD, ASEPTATE HYPHAE. THE FUNGUS WAS LIKELY:
A. RHIZOPUS
B. FUSARIUM
C. ASPERGILLUS
D. SCEDOSPORIUM
E. CANDIDA

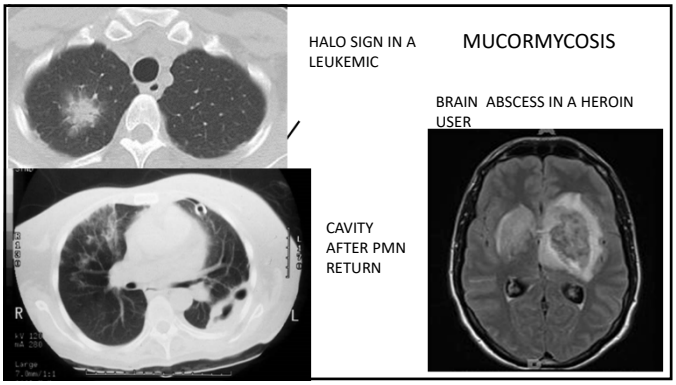


51 – Fungal Diseases in Normal and Abnormal Hosts

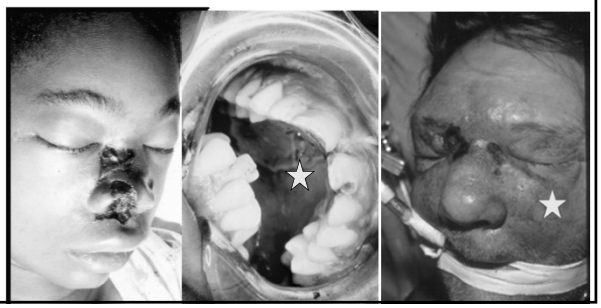
Speaker: John Bennett, MD

MUCORMYCOSIS

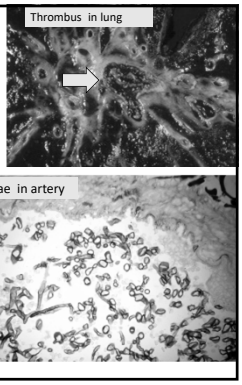
- Infection acquired by inhaling spores into lung or paranasal sinus
- Rhizopus, Rhizomucor, Mucor, Cunninghamella, Apophysomyces, Saksenaea
- Broad, flexible nonseptate hyphae, right angle branching
- Poorly controlled diabetes melitus, Prolonged neutropenia, corticosteroids
  - India: COVID-19+ corticosteroids+ poorly controlled diabetes mellitus
- Massive soft tissue trauma. IV drug abuse
- Hyphae invade blood vessels, causes infarction and necrosis. May form cavity if PMN's return.
- Negative beta d glucan, negative galactomannan
- Rx. Ampho B. Posaconazole f/u. Isavuconazole? Surgical debridement
  Control diabetes. Decrease immunosuppression.



MUCORMYCOSIS
LOCAL EXTENSION FROM PARANASAL SINUS



Mucormycosis: Vascular invasion



MYCOSES WORTH MENTIONING

- SCEDOSPORIUM APIOSPERMUM: IMMUNOSUPPRESSED HOST CLINIALLY RESEMBLING ASPERGILLOSIS . BRAIN ABSCESS AFTER NEAR DROWNING IN POLLUTED WATER. AMPHOTERICIN B RESISTANT
- TRICHOSPORONOSIS: LIKE CANDIDIASIS BUT ECHINOCANDIN RESISTANT
- PARACOCCIDIOIDOMYCOSIS: RURAL CENTRAL AND SOUTH AMERICA. MAY APPEARS DECADES AFTER LEAVING ENDEMIC AREA.
- TALAROMYCOSIS (FORMERLY PENICILLIUM MARNEFFEI). SOUTHEAST ASIA, AIDS, DISSEMINATED INFECTION WITH SKIN LESIONS. YEAST IN BIOPSY, MOLD IN CULTURE.

52

Penicillin Allergies

Dr. Sandra Nelson

52 – Penicillin Allergies

Speaker: Sandra Nelson, MD

Penicillin Allergies

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

6/30/2023

Disclosures of Financial Relationships with Relevant Commercial Interests

- **None**

Penicillin (PCN) Allergy: Premise

- 10% of the US population have reported penicillin allergy
  - Rash most common adverse drug reaction (ADR)
  - Others include "unknown", angioedema, GI symptoms, itching
  - More common in older adults and hospitalized patients
- Vast majority of patients with PCN allergy can safely receive penicillins (with appropriate evaluation and testing)
  - Reactions are mild drug rashes that do not always recur
  - True allergies often wane with time
  - Some reactions are not allergic

PCN Allergy: Consequences

- Alternative antimicrobial use
  - Less effective, more toxic, higher cost, broader spectrum
- Associated with:
  - increased risk of MRSA infection and VRE colonization
  - increased risk of *C. difficile* colitis
  - increased risk of surgical site infection
  - increased mortality
- An important target of stewardship efforts

Case #1

PREVIEW QUESTION

A 73-year-old woman undergoing chemotherapy for cholangiocarcinoma is hospitalized with bacteremia and sepsis due to ampicillin-susceptible *Enterococcus faecalis*. She has a history of allergy to penicillin that is listed in the records as rash; the family recalls that she went to the ED when the rash occurred several years earlier. She is delirious and not able to corroborate the history; no additional documentation of the reaction is available. Two of her daughters have allergies to penicillin.

Case #1: Vote

PREVIEW QUESTION

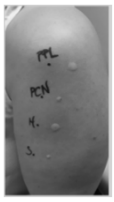
You are asked about optimal antibiotic treatment. What do you advise?

A. Administer IV ampicillin without prior testing
B. Skin test for penicillin reaction; if negative then administer full dose ampicillin
C. Skin test for penicillin reaction; if negative then administer test dose ampicillin followed by full dose ampicillin
D. Desensitize to ampicillin
E. Administer vancomycin

52 – Penicillin Allergies
Speaker: Sandra Nelson, MD

Options for Approaching PCN Allergy

1. Monitored oral challenge
   - Low-risk reactions (remote rash, pruritus)
2. Penicillin skin testing
   - Epicutaneous and intradermal administration of PPL (penicilloyl polylysine, Pre-Pen) and penicillin G
   - History of IgE mediated reaction
   - May also be used with unknown reaction or vague history
   - Followed by test dose of implicated drug or desired drug



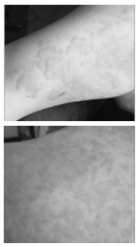
Shenoy JAMA 2019;321:188

Options for Approaching PCN Allergy

3. Graded challenge (also called test dose procedure)
   - 1/4th to 1/10th dose, followed by full dose 30-60 minutes later
   - Used as a first step if suspicion for immediate reaction is low
   - After negative PCN skin testing
4. Desensitization
   - Administration of increasing concentrations every 15-30 minutes until therapeutic dose reached
   - Used for positive skin test and/or confirmed immediate reaction when a penicillin is the best therapy for an important infection
   - Desensitization wanes with missed doses (3 half-lives)
5. Use of alternate therapy

Deciphering Cutaneous Reactions

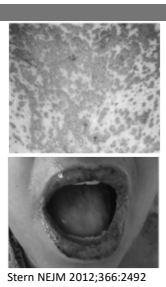
- IgE Mediated Reactions (hives)
  - Occur within minutes to hours, resolve within 24 hours
    - ➡ skin testing appropriate
  - if positive – desensitize or use alternate therapy
  - If negative – graded challenge (test dose)
- Benign T-cell mediated
  - morbilliform or maculopapular
  - Usual onset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



Shenoy JAMA 2019;321:188

Deciphering Cutaneous Reactions

- Severe cutaneous reactions
  - DRESS and SJS/TEN
  - Usual onset days to weeks
  - Blistering, mucosal involvement, severe skin desquamation, organ involvement
    - ➡ avoid any beta-lactam
- Vague or unknown skin reaction
  - Evaluate risk of severe cutaneous reaction
  - Assume possibly IgE mediated
    - ➡ skin test then test dose



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

Other types of penicillin allergy

- IgE Mediated reactions: anaphylaxis, angioedema, bronchospasm
  - ➡ Penicillin skin testing followed by graded challenge
- Antibody-mediated reactions: hemolytic anemia, neutropenia, thrombocytopenia
  - ➡ No testing; if severe avoid re-use
- Immune complex: serum sickness, vasculitis
  - ➡ No testing; generally avoid re-use
- Cell-mediated: interstitial nephritis, hepatitis
  - ➡ Varies; for severe reactions and organ involvement avoid re-use

Case #2

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

Case #2: Vote

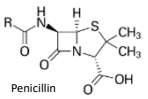
What do you do counsel?

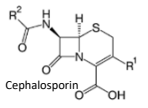
A. Administer clindamycin
B. Administer cefazolin
C. Administer cefazolin after intraoperative test dose
D. Administer ceftriaxone
E. Administer vancomycin

MASSACHUSETTS GENERAL HOSPITAL HARVARD MEDICAL SCHOOL 15

PCN Allergy and other beta-lactams

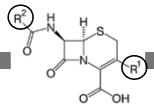
- Cephalosporins:
  - Significant cross reactivity rare, higher with earlier generation cephalosporins
  - IgE mediated PCN allergy:
    - use 3rd/4th gen (graded challenge or test dose)
    - use 1st/2nd after PCN skin testing
  - Mild delayed drug rash:
    - any cephalosporin OK
  - Avoid if severe reaction to PCN
- Carbapenems <1%
- Aztreonam: no cross reactivity in PCN-allergic





MASSACHUSETTS GENERAL HOSPITAL HARVARD MEDICAL SCHOOL 17

Cephalosporin Allergy



- Allergy often arises from side chains
  - More common than beta-lactam ring
- Probability of reaction higher when cephalosporins with similar side chains used (R1 > R2)
- Side chain tables are available to guide cross-reactivity

Similar Side Chain Groups (R1)
Amoxicillin, Cefadroxil, Cefprozil
Ampicillin, Cefaclor, Cephalexin
Cefepime, Ceftriaxone, Cefotaxime, Cefpodoxime
Ceftazidime and Aztreonam

MASSACHUSETTS GENERAL HOSPITAL HARVARD MEDICAL SCHOOL 18

A few more testable points

- Selective allergy to the aminopenicillins occurs
  - A patient that tolerates PCN may still be allergic to aminopenicillins
  - A patient that tolerates aminopenicillins is not allergic to PCN.
- Cefazolin has different side chains from all other cephalosporins
- Ceftazidime does not share side chains with ceftriaxone or cefepime
- Aztreonam can be safely used in individuals with beta-lactam allergy except for those allergic to ceftazidime

MASSACHUSETTS GENERAL HOSPITAL HARVARD MEDICAL SCHOOL 19

Thank you and good luck!

MASSACHUSETTS GENERAL HOSPITAL HARVARD MEDICAL SCHOOL 19

53

Kitchen Sink: Syndromes Not Covered Elsewhere

Dr. Stacey Rose

53 – Kitchen Sink: Syndromes Not Covered Elsewhere

Speaker: Stacey Rose, MD

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

Kitchen Sink: Syndromes Not Covered Elsewhere

Stacey R. Rose, MD, FACP, FIDSA
Associate Professor of Medicine, Infectious Diseases Section
Associate Director, Center for Professionalism
Baylor College of Medicine

6/27/2023

IDBR INFECTIOUS DISEASE BOARD REVIEW AUGUST 19-23 2023

Disclosures of Financial Relationships with Relevant Commercial Interests

- **Consultant: Pathogenomix, GlaxoSmithKline**

Session plan

- Case-based discussions of topics not extensively covered in other sessions
- Highlight points likely to be assessed on ID Boards (rather than comprehensive overview)

3

Question 1

- A 51 year-old male with past medical history significant for insulin dependent diabetes presents with a six-month history of progressive athralgias, abdominal pain, diarrhea, weight loss, and low-grade fevers.
- Work up thus far:

Negative blood cultures x 2
Negative Rheumatoid factor
Normal metabolic panels
Mild normocytic anemia

4

Question 1

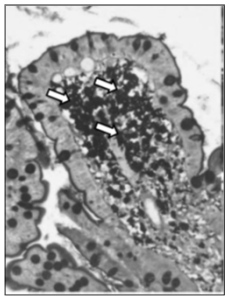
- Which of the following tests will most likely yield the diagnosis?

a) Anti-streptolysin O Antibody
b) Anti-nuclear Antibody
c) Stool ova and parasite
d) Duodenal biopsy

5

Whipple's disease

- Caused by *Trophyrema whipplei* (gram variable bacterium, difficult to cultivate)
- More common in middle aged, Caucasian men
- Diagnosis often delayed due to indolent clinical presentation
- Most commonly diagnosed via duodenal biopsy, stained with PAS
- PCR increasingly used



Periodic acid-Schiff-diastase (PAS-D)-stained duodenal biopsy specimens with PAS-D-positive granules in the foamy macrophages (arrows).

Dolmans RAV, Boel CHE, Lacle MM, Kusters JG. 2017. Clinical manifestations, treatment, and diagnosis of Tropheryma whipplei infections. Clin Microbiol Rev 30:529–555.

6

Whipple's: clinical presentations

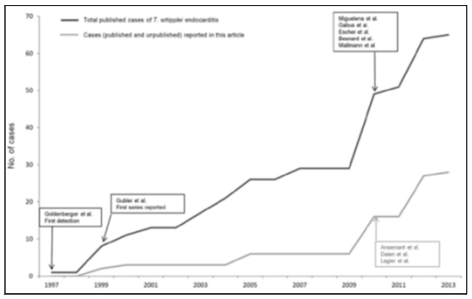
TABLE 1 Clinical manifestations of *Tropheryma whipplei* infection[a]

Classic Whipple's disease (% incidence)	Chronic localized infections[b]	Acute infections[b]
Weight loss (79–99)	Endocarditis	Gastroenteritis
Gastroenteritis (63–85)	Encephalitis	Pneumonia
Abdominal pain (23–60)		Bacteremia
Arthritis (20–83)		
Neurological symptoms (6–63)		

Dolmans RAV, Boel CHE, Lacle MM, Kusters JG. 2017. Clinical manifestations, treatment, and diagnosis of Tropheryma whipplei infections. Clin Microbiol Rev 30:529–555.

7

Whipple's endocarditis



- Increasingly recognized (molecular diagnostics; part of 2023 Duke's criteria)
- Consider in patients with arthralgias plus culture negative endocarditis

Fenollar F, Célard M, Lagier JC, Lepidi H, Fournier PE, Raoult D. Tropheryma whipplei endocarditis. *Emerg Infect Dis*. 2013

8

Whipple's: treatment

No gold standard

Options:

- Ceftriaxone or meropenem plus prolonged co-trimoxazole (~1 year)

OR

- Doxycycline plus hydroxychloroquine (12-18 mos)

Symptoms improve, but relapse is common without prolonged treatment / suppression

Dolmans RAV, Boel CHE, Lacle MM, Kusters JG. Clinical manifestations, treatment, and diagnosis of Tropheryma whipplei infections. Clin Microbiol Rev 2017.
Principles and Practice of Infectious Diseases, 9th ed

9

- Cause: *Trophyrema Whipplei*
- Epidemiology: middle aged, Caucasian males
- Clinical presentation: classic – ***arthralgia, diarrhea, weight loss***
- Localized infection e.g. ***endocarditis*** (increasingly recognized)
- Diagnosis with ***duodenal biopsy*** (***PAS*** stain; foamy macrophages) or ***PCR*** of blood or infected tissue
- Prolonged treatment needed to prevent relapse

Whipple's disease

Take home points

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Question 2

IDBR 2023 PREVIEW QUESTION

- A 20 year-old female school teacher presents with fever and pain / swelling in knees, elbows and wrists. The pain seems to move from joint to joint.
- She reports being ill ~3 weeks prior with sore throat and headache which resolved without specific treatment.
- She has no rash or lymphadenopathy.
- She denies travel. She is sexually active with one male partner, using barrier protection (condoms).
- Labs are notable for elevated ESR and CRP and + ASO titer; pregnancy and HIV tests (4th generation Ag/Ab) are negative.

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Question 2

IDBR 2023 PREVIEW QUESTION

Which of the following is the best explanation for her symptoms?

a. Acute HIV infection
b. Mononucleosis due to Epstein Barr Virus
c. Acute rheumatic fever
d. Lemierre's syndrome

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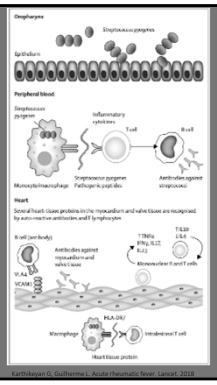
Explanation

- ✗ Acute HIV – joint symptoms are not prominent with acute HIV infection; HIV 4th generation testing (Ag / Ab) should detect early HIV infection
- ✗ Mononucleosis due to EBV – joint pains are not characteristic; no mention of lymphadenopathy
- ✓ **Acute Rheumatic Fever – multisystem disease following group A streptococcus pharyngitis; meets definition based on Jones criteria**
- ✗ Lemierre's – septic thrombophlebitis of internal jugular vein following pharyngitis, typically caused by *Fusobacterium necrophorum*. Joint pains are not characteristic; no neck swelling.

13



Acute Rheumatic Fever

- Rare in US (0.5 per 100K per year), but remains common worldwide (0.5 million per year)
- Affects ***children / young adults***
- Recurrence common
- *Pathogenesis*: immune response following *Streptococcus pyogenes* infection (pharyngitis; impetigo); leads to systemic manifestations (**arthritis, carditis, chorea, skin)**

Karthikeyan G, Guilherme L. Acute rheumatic fever. Lancet. 2018

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REVISED JONES CRITERIA

For patients with evidence of prior GAS infection*,

Acute Rheumatic fever =

2 MAJOR

OR

1 MAJOR plus 2 MINOR

Major	Minor
Arthritis (usually migratory polyarthritis)	Arthralgia
Carditis (clinical or subclinical)	Fever
Chorea	Elevated ESR or CRP
Erythema marginatum	Prolonged PR interval (unless carditis is a major criterion)
Subcutaneous nodules	

*e.g. rapid strep test; culture; anti-streptolysin-O titer (ASO)

Revision of the Jones Criteria for the diagnosis of acute rheumatic fever in the era of Doppler echocardiography: a scientific statement from the American Heart Association. *Circulation*. 2015

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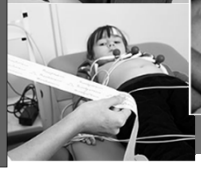
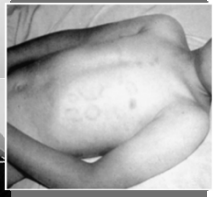
Revision of the Jones Criteria for the diagnosis of acute rheumatic fever in the era of Doppler echocardiography: a scientific statement from the American Heart Association. *Circulation*. 2015

Recognizing Acute Rheumatic Fever

- **Timing**: average 19 d after GAS infection
- **Arthritis**: migratory, polyarthritis involving large joints (knees, ankles, elbows, wrists)
- **Carditis**: wide range of effects – e.g. pericarditis, systolic dysfunction, valvular disease
- **Chorea**: late manifestation; involuntary movements
- **Skin**: Subcutaneous nodules; erythema marginatum (blanches; transient) – rare but specific

https://www.cdc.gov/groupastrep/diseases-public/rheumatic-fever.html

Karthikeyan G, Guilherme L. Acute rheumatic fever. *Lancet*. 2018.
Principles and Practice of Infectious Disease, 9th ed.

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Treatment and prophylaxis of Acute Rheumatic Fever

Primary episode	Secondary prophylaxis
IM benzathine penicillin x 1 or Oral penicillin x 10 d	IM benzathine penicillin q 4 weeks

Goal: *to prevent rheumatic heart disease*

Duration of ppx *varies by severity of primary illness*

Contemporary Diagnosis and Management of Rheumatic Heart Disease: Implications for Closing the Gap: A Scientific Statement From the American Heart Association. *Circulation*. 2020
Principles and Practice of Infectious Diseases, 9th ed.

CATEGORY	DURATION AFTER LAST ATTACK
Rheumatic fever with carditis and residual heart disease (persistent valvular disease[a])	10 yr or until age 40 yr, whichever is longer; sometimes lifelong prophylaxis (see text)
Rheumatic fever with carditis but no residual heart disease (no valvular disease[a])	10 yr or until age 21 yr, whichever is longer
Rheumatic fever without carditis	5 yr or until age 21 yr, whichever is longer

Duration of secondary prophylaxis following acute rheumatic fever:
longest if carditis and residual valvular disease

Principles and Practice of Infectious Diseases, 9th ed.

- Cause: immune dysregulation following *S. pyogenes* infection
- Epidemiology: children / young adults; rare in US
- Clinical presentation: ~3 weeks following GAS infection
  - Major: *migratory polyarthritis, carditis, chorea, subcutaneous nodules, erythema marginatum*
  - Minor: *fever, arthralgia, elevated ESR/CRP; PR prolongation*
- Diagnosis based on Jones criteria = 2 major OR 1 major + 2 minor (plus e/o prior GAS infection e.g. ASO titer)
- Treatment and secondary ppx with IM Penicillin; duration based on carditis (10 yr or to age 40 if carditis + residual valvular disease)

Acute Rheumatic Fever

Take home points

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Question 3

IDBR 2023 PREVIEW QUESTION

- A 34 year-old male with a history of injection drug use presents to the emergency room with two days of progressive muscle weakness and blurry vision. He also complaints of difficulty swallowing.
- On examination, vital signs are normal, but the patient is noted to have ptosis and sluggish pupillary responses as well as slurred speech.

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Question 3

IDBR 2023 PREVIEW QUESTION

- Which of the following treatments are recommended?

A. Plasmapheresis
B. Naloxone
C. Tetanus antitoxin
D. Botulinum antitoxin

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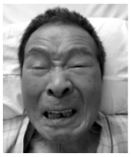
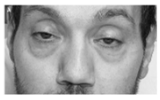
Explanation



Tetanus: sardonic smile



Botulism: ptosis

- Plasmapheresis – for Lambert-Eaton syndrome, immune attack of neuromuscular junction (chronic; associated with lung cancer)
- Naloxone – for opioid intoxication (respiratory suppression, *constricted* pupils)
- Tetanus antitoxin – for tetanus (rigid paralysis)
- Botulinum antitoxin – for botulism (flaccid paralysis)

https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(19)31137-7/fulltex
https://www.nejm.org/doi/pdf/10.1056/NEJMcm1003352

23

https://phil.cdc.gov/details.aspx?pid=2107

Botulism

- Caused by **Clostridium botulinum* (gram positive, strict anaerobe with subterminal spore; found in soil)
- Symptoms due to TOXINS which prevent release of acetylcholine in neuromuscular junction
- Leads to flaccid paralysis of motor and autonomic nerves, beginning with the cranial nerves (*descending* weakness)
- DX: culture or detection of toxin

**other neurotoxin producing species of Clostridium: C. butyricum, or C. baratii*

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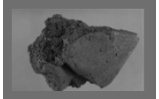
Botulism

Bioterrorism potential (aerosolization)

Foodborne

Infant



Wound (black-tar heroin)

Iatrogenic

Peak CM, Rosen H, Kamali A, et al. Wound Botulism Outbreak Among Persons Who Use Black Tar Heroin — San Diego County, California, 2017–2018. MMWR Morb Mortal Wkly Rep 2019.
https://www.cdc.gov/botulism/; *Principles and Practice of Infectious Diseases, 9th ed.*

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Botulism treatment

Supportive care	Antitoxin
• Ventilatory support for respiratory compromise • Wound debridement	• Botulinum anti-toxin (BAT) to prevent progression (for infant botulism syndrome, use Botulinum immune globulin (BabyBIG)

Rao AK, Sobel J, Chatham-Stephens K, Luquez C. Clinical Guidelines for Diagnosis and Treatment of Botulism, 2021. *MMWR Recomm Rep.* 2021.
https://www.cdc.gov/botulism/; *Principles and Practice of Infectious Diseases, 9th ed.*

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- Cause: *Clostridium botulinum* toxin impedes acetylcholine release from neuromuscular junction
- Epidemiology: food (home canned veggies / fruits / fish); infant (honey); wound (black-tar heroin); iatrogenic (rare)
- Clinical presentation: *descending flaccid paralysis*, starting with *cranial nerves* (ptosis, blurred vision, slurred speech)
- Diagnosis: clinical; confirmed by culture or ID of toxin
- Treatment: *antitoxin* & supportive care; wound debridement

Botulism

Take home points

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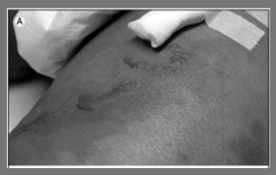
Question 4



- A 44 year-old male with a history of cirrhosis due to Hepatitis B and alcoholism presents with fever, lethargy and leg swelling. On exam, he is febrile, hypotensive and tachycardic. Skin exam is as pictured.

Lancet Infect Dis. 2008 Jun;8(6):399.

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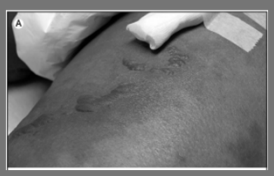
Question 4



Lancet Infect Dis. 2008 Jun;8(6):399.

- The patient's clinical syndrome was most likely caused by which of the following exposures?

A. Rat bite
B. Tick bite
C. Consumption of raw oysters
D. Consumption of raw egg

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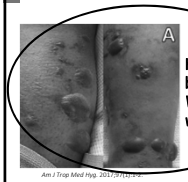
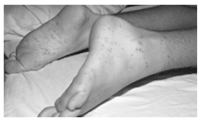
Explanation



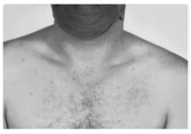
Hemorrhagic bullae from *Vibrio vulnificus*

Am J Trop Med Hyg. 2021;97(1):15.



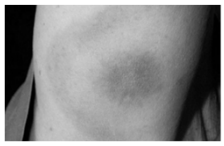
Petechial rash from *Streptobacillus moniliformis* (rat bite fever); fever, rash, migratory arthritis

CMAJ. 2006 Aug 15;175(4):354.



Rose spots from *Salmonella typhi*

https://www.cdc.gov/vaccines/vpd/typhoid/public/photos.html



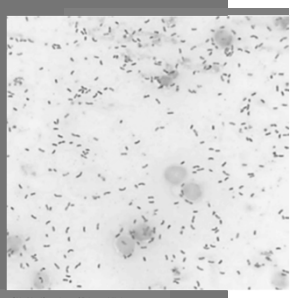
Erythema migrans due to *Borrelia burgdorferi* (tick borne)

https://www.cdc.gov/lyme/signs_symptoms/rashes.html

30

53 – Kitchen Sink: Syndromes Not Covered Elsewhere

Speaker: Stacey Rose, MD



Skin Manifestations of Primary *Vibrio vulnificus* Septicemia. *Am J Trop Med Hyg.* 2017.

Vibrio vulnificus

- Gram-negative, curved bacillus
- Halophilic (salt loving) – ***brackish water***
- Cause: ***consumption of raw seafood (oysters) or contamination of open wound***
- At risk: ***liver disease*** (cirrhosis); iron overload; renal disease; immunosuppression
- High mortality

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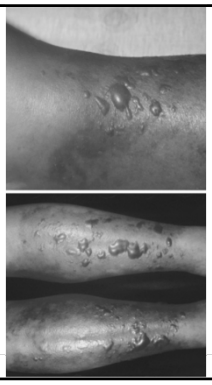
Clinical presentation and treatment



- Abrupt onset
- Fever, hypotension
- Rapidly progressive skin lesions: erythema → ***hemorrhagic bullae*** → necrosis
- Bacteremia common
- Treatment:
  - 3rd generation cephaloporin *plus* doxycycline OR fluoroquinolone
  - Debridement (for necrotizing fasciitis)

Principles and Practice of Infectious Diseases, 9th ed.

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- Epidemiology: consumption of raw oysters; contamination of wound (organism lives in warm, brackish water)
- At risk: liver disease, iron overload states (also chronic kidney disease; diabetes or other immune suppression)
- Clinical presentation: rapidly progressive skin lesions with ***hemorrhagic bullae; fever, hypotension, sepsis***
- Diagnosis: clinical; blood cultures usually positive
- Treatment: 3rd generation cephalosporin plus doxycycline or fluoroquinolone; debridement

Vibrio vulnificus

Take home points

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Question 5

2023 PREVIEW QUESTION

- A 23-year-old female presents with a non-productive cough for 2 weeks. She describes spells during which she coughs repeatedly for several minutes. On two occasions she vomited after coughing.
- She reports episodes of sweating but has had no fever or other constitutional symptoms.
- She has tried several cough medicines, but nothing seems to help.
- She works as a nurse in a pediatric intensive care unit, and would like guidance for when she can return to work.

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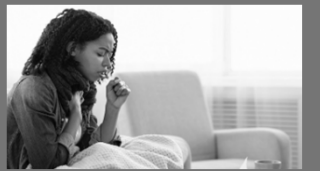
Question 5

2023 PREVIEW QUESTION



- Which of the following would you recommend for this patient?

A. Azithromycin, with return to work after 5 days

B. Azithromycin, with return to work after first dose

C. No treatment, with return to work after 5 days

C. No treatment; can return to work immediately

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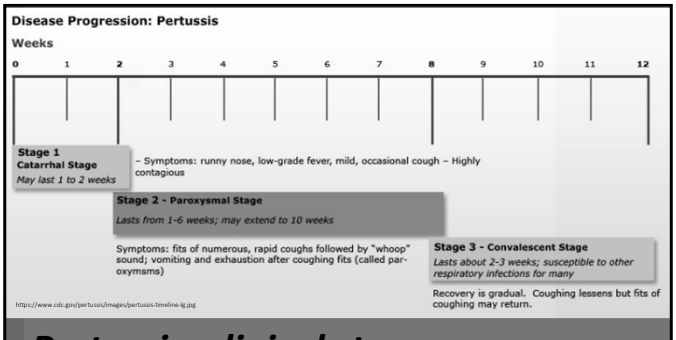


Pertussis: clinical stages

Pertussis diagnosis – requires clinical suspicion

Clinical case criteria (in absence of alternate dx):
- cough illness lasting ≥2 weeks, with at least one of the following:
  - Paroxysms of coughing; **OR**
  - Inspiratory whoop; **OR**
  - Post-tussive vomiting; **OR**
  - Apnea (with or without cyanosis)

Polymerase chain reaction (PCR) is most sensitive and specific
- Nasopharyngeal swab / aspirate
- Best if sent within first 3 weeks of illness

https://www.cdc.gov/nndss/conditions/pertussis/case-definition/2020/; https://www.cdc.gov/pertussis/clinical/diagnostic-testing/diagnosis-pcr-bestpractices.html
Clinical evaluation and validation of laboratory methods for the diagnosis of Bordetella pertussis infection: Culture, polymerase chain reaction (PCR) and anti-pertussis toxin IgG serology (IgG-PT). *PLoS One*. 2018.

37

Treatment and post exposure prophylaxis

- TREAT with **macrolide** (e.g. azithromycin) if **within 3 weeks of onset**
- Treat within 6 weeks of onset for infants or pregnant women

- **POST EXPOSURE PROPHYLAXIS (PEP) given to household members and contacts at risk of severe infection (within 3 weeks of exposure)**

https://www.cdc.gov/pertussis/
Decker MD, Edwards KM. Pertussis (Whooping Cough). *J Infect Dis*. 2021.

38

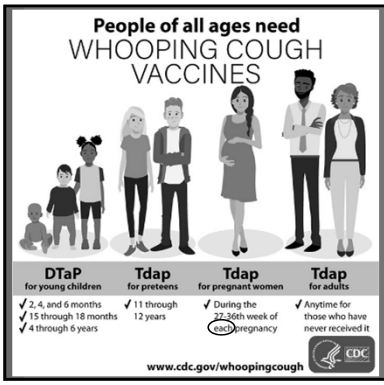
Pertussis: recommendations for health care workers (HCW)

Symptomatic infection: exclude from work for 21 days from onset of cough OR until 5 days after the start of effective antimicrobial therapy

Exposure: regardless of vaccination status, administer post-exposure prophylaxis if likely to interact with persons at high risk of complications

Recommended antimicrobial agents for the treatment and postexposure prophylaxis of pertussis: 2005 CDC Guidelines. *MMWR Recomm Rep*. 2005..
https://www.cdc.gov/infectioncontrol/guidelines/healthcare-personnel/selected-infections/pertussis.html

39



Pertussis Vaccination

- Epidemiology: infants > adolescents
- ***High risk for severe disease: infants, pregnant women***, lung disease
- Clinical presentation: ***cough*** lasting 2+ weeks plus ***paroxysmal cough***, ***inspiratory whoop***, ***post-tussive vomiting or apnea***
- Diagnosis: clinical; PCR
- Treat with ***macrolide within 3 wks*** of onset (6 wks if high risk)
- Post-exposure prophylaxis: (within 3 wks of exposure) for *household contacts / high risk / HCW* likely to interact with high risk patients
- HCW can return to work after 5 d of effective treatment or 21 d after cough onset

Bordatella pertussis

Take home points

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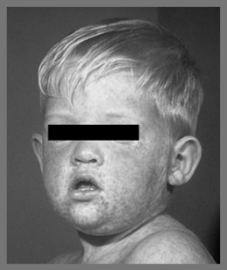
Question 6



- A 25-month old child is brought to the emergency room for ***fever, rash and fussiness***. The rash ***started on the face and spread to trunk*** and extremities within 1-2 days.
- 10 days ago, the family returned to the United States following a 1-month trip to Tanzania (where the parents conduct research as university professors).
- The child's 4-year old sibling is also ill, with cough and watery eyes, but does not have a rash.
- The parents do not believe in vaccination for their children due to fear of adverse effects (autism).

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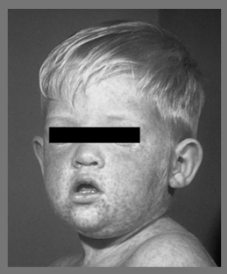
53 – Kitchen Sink: Syndromes Not Covered Elsewhere

Speaker: Stacey Rose, MD

Question 6



- Which of the following would you recommend to reduce further spread of this patient's illness?

A. Isolate the patient (airborne precautions)
B. Vaccinate exposed, non-immune persons
C. Treat the patient with acyclovir to reduce infectivity
D. Both A & B
E. All of the above

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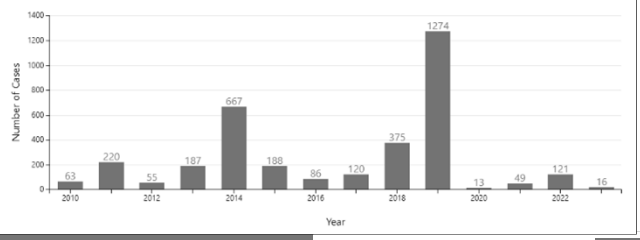
Measles (Rubeola) in the US

Mostly in unvaccinated individuals, related to international travel or an imported case

Number of measles cases reported by year

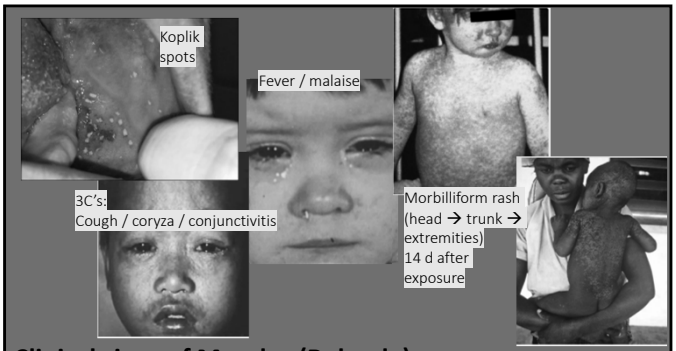
2010-2023* (as of June 8, 2023)



https://www.cdc.gov/measles/cases-outbreaks.html

44

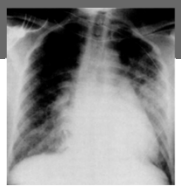
Clinical signs of Measles (Rubeola)



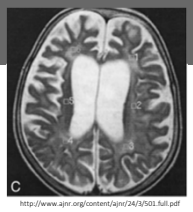
Principles and Practice of Infectious Diseases, 9th ed.
https://www.cdc.gov/measles/symptoms/photos.html

45

Complications of measles



Chest. 1993 May;103(5):1625-6



http://www.ajnr.org/content/ajnr/24/3/501.full.pdf

Acute

- 1 of 1000 children – death from respiratory / neurologic complications

Delayed

- rare but fatal - Subacute Sclerosing Pan-Encephalitis (SSPE)
- 7 yrs after infection; degenerative disease, seizures

Principles and Practice of Infectious Diseases, 9th ed.
https://www.cdc.gov/measles/

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Diagnosis

Don't wait for confirmation: isolate patients with suspected infection (airborne)

Clinical – high suspicion in unvaccinated individuals

Serum: measles-specific IgM antibody

*Respiratory specimen (nasopharyngeal swab): measles RNA by real-time polymerase chain reaction (RT-PCR)

*may also be detected in urine

https://www.cdc.gov/measles/

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Prevention: Measles-mumps-rubella (MMR) Vaccination

CHILDREN
1st dose: 12-15 mos
2nd dose: 4-6 years

ADULTS born after 1957 without evidence of immunity (at least one dose)

COLLEGE STUDENTS without evidence of immunity
(two doses, 28 d apart)

INTERNATIONAL TRAVELERS (6 mos and older) without evidence of immunity

Principles and Practice of Infectious Diseases, 9th ed.
https://www.cdc.gov/measles/

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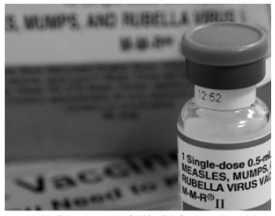
53 – Kitchen Sink: Syndromes Not Covered Elsewhere

Speaker: Stacey Rose, MD

Immunity and post exposure prophylaxis

Who is immune to measles?	What is the recommendation for PEP?
• written documentation of adequate vaccination • Lab evidence of immunity • Lab confirmation of measles infection • Born before 1957	• Non-immune persons with measles exposure should receive ***either*** **MMR vaccine** (within 72 hours of exposure) **or Immune globulin (IG)** within 6 days of exposure • **Do not co-administer** MMR vaccine and IG (invalidates vaccine)



https://www.washingtonpost.com/health/2019/04/09/how-does-measles-spread-other-frequently-asked-questions-about-measles/

https://www.cdc.gov/measles/; Principles and Practice of Infectious Diseases, 9th ed.

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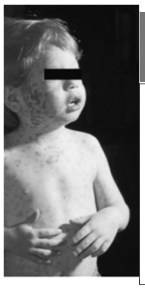
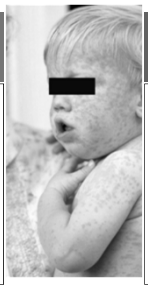
"German measles" (Rubella) vs. Measles (Rubeola)



German Measles (Rubella)	Measles (Rubeola)
• Caused by RNA virus of *Togaviridae* family • Often **mild** / asymptomatic • Viral prodrome → maculopapular rash which spreads from head to extremities, +/- **arthritis** • Transmitted in utero (**congenital** rubella): deafness, cataracts, glaucoma, heart disease, cognitive defects	• Caused by RNA virus of Paromyxovirus family • **Severe** disease with complications including death • Viral prodrome → **cough / coryza / conjunctivitis, fever, Koplik spots** → maculopapular rash which spreads from head to extremities



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- Cause: Rubeola (RNA virus of Paramyxovirus family)
- Epidemiology: worldwide distribution; *in US, seen in unvaccinated persons due to travel or exposure to imported case*
- Clinical presentation: three C's (*cough, coryza, conjunctivitis*), Koplik spots, morbilliform rash spreading from head → trunk → extremities (14 d after exposure)
- Diagnosis: clinical; serum IgM; PCR on respiratory swab (or urine)
- Treatment: supportive care, Vit A for severe cases in children
- Post-exposure ppx: vaccination (within 72 h) or IG (within 6 days)

Measles (Rubeola)

Take home points

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Question 7

- A 19 year-old college student, previously healthy, complained of abdominal pain and nausea after eating leftovers from a restaurant.
- Within several hours, his symptom progressed to include weakness, headache and neck stiffness.
- Five hours later, he had developed purplish skin discolorations and a friend brought him to the emergency room for evaluation.

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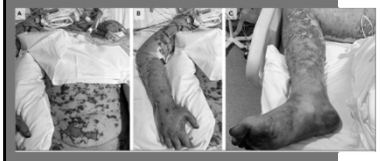
Question 7



- Upon arrival to the hospital, he was noted to be febrile (40.4 degrees Celsius), tachycardic (HR 166), and tachypneic (RR 28), with BP 120/53, and with rapidly progressive reticular, purpuric rash.
- Within 24 hours, gram stain of blood cultures showed gram-negative diplococci.

N Engl J Med. 2021 Mar 11;384(10):953-963.

53

Question 7

- Based on the presumed diagnosis, who should receive post-exposure prophylaxis?

A. All residents in the student's dormitory
B. Nurse who started the patient's IV
C. Physician who emergently intubated the patient
D. Pharmacist who delivered medications to the room

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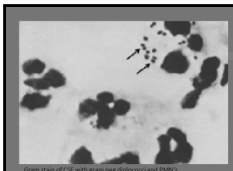
53 – Kitchen Sink: Syndromes Not Covered Elsewhere

Speaker: Stacey Rose, MD



Gram stain of CSF with gram neg diplococci and PMN's
https://www.cdc.gov/meningitis/lab-manual/chpt06-culture-id.html

Principles and Practice of Infectious Diseases, 9th ed

Invasive meningococcal disease (*N. meningitidis*)

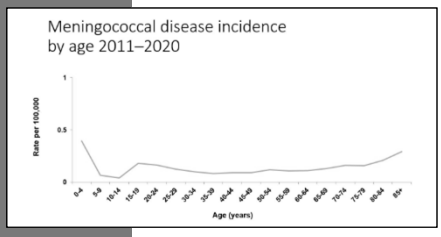
- Main manifestations:
  - *meningococcemia*
  - *acute meningitis*
- **Petechial or purpuric rash** in 40-80% of meningococcemia cases
- Fulminant disease **can progress to death within hours**
- Treat with 3rd generation cephalosporin (**ceftriaxone or cefotaxime**) and supportive care

Principles and Practice of Infectious Diseases, 9th ed.
https://www.cdc.gov/meningococcal/clinical-info.html

55

Epidemiology

- In US, infants, young adults, and adults >80 years of age have the highest rates of meningococcal disease



https://www.cdc.gov/meningococcal/surveillance/index.html

Transmission and risk factors

TRANSMISSION: person to person (respiratory droplets, oral secretions) from asymptomatic carriage or invasive disease

HOST / IMMUNE factors: asplenia; terminal complement deficiencies (native or acquired, such as use of complement inhibitors: eculizumab or ravulizumab); HIV

BEHAVIORAL / ENVIRONMENTAL factors: crowded conditions (college dorms, military barracks; Hajj and Umrah pilgrimages); daycare / preschool facilities; microbiologists; men who have sex with men (MSM)

https://www.cdc.gov/meningococcal/about/risk-community.html

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Detection of Ciprofloxacin-resistant, β-lactamase-producing *Neisseria meningitidis* Serogroup Y Isolates, United States, 2019–2020

HAN HEALTH ALERT NETWORK | This is an official CDC HEALTH ADVISORY

JOURNAL ARTICLE

Antimicrobial Susceptibility Survey of Invasive *Neisseria meningitidis*, United States 2012–2016

Caelin C Potts, Lorraine D Rodriguez-Rivera, Adam C Retchless, Fang Hu, Henju Marjuki, Amy E Blain, Lucy A McNamara, Xin Wang

The Journal of Infectious Diseases, Volume 225, Issue 11, 1 June 2022, Pages 1871–1875, https://doi.org/10.1093/infdis/jiac046

Treatment

First line: 3rd generation cephalosporin

Though rates of resistance remain low in the US, susceptibility testing recommended before changing to penicillin or ampicillin to complete therapy

Chemoprophylaxis for:

Drug	Considerations
Ciprofloxacin	Single dose
Rifampin	Multiple doses required; drug interactions
Ceftriaxone	Recommended in pregnancy
Azithromycin	Less data; may be used if known ciprofloxacin resistance

Household members
Childcare center contacts
Anyone directly exposed to an infected person's oral secretions (kissing; mouth to mouth resuscitation; intubation) within 7 d before symptom onset
HCW with exposure to respiratory secretions of infected patient

https://www.cdc.gov/vaccines/pubs/surv-manual/chpt08-mening.html
https://www.cdc.gov/meningococcal/surveillance/index.html

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Meningococcal Vaccination

- Recommendations revised in 2020

Summary:

- MenACWY for all adolescents (11-12 yrs) plus persons at increased risk due to host or environmental factors
- MenB for those at increased risk due to host or environmental factors; shared decision making for others

https://www.cdc.gov/vaccines/vpd/mening/public/index.html

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53 – Kitchen Sink: Syndromes Not Covered Elsewhere

Speaker: Stacey Rose, MD

- Epidemiology:
  - Host (*asplenia*; *complement deficiencies*; *complement inhibitors* – eculizumab or ravulizumab)
  - Environmental (crowded conditions – dorms, barracks, day care)
  - Person to person transmission from oral / respiratory droplets
- Clinical presentation: *acute meningitis* or *meningococcemia*; rapidly progressive, *rash with petechiae / purpura*
- Treatment: *ceftriaxone or cefotaxime*; immunize for prevention and during outbreaks
- Chemoprophylaxis for close contacts within 7 d of exposure: *ciprofloxacin* (single dose), *rifampin* (multiple doses), *ceftriaxone* (pregnancy), *azithromycin* (if known resistance to ciprofloxacin)

Invasive meningococcal disease (*Neisseria meningitidis*)

Take home points

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Question 8

- A 34 year-old motorcyclist is involved in a severe motor vehicle accident, resulting in laceration of the spleen and requiring splenectomy.

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Question 8

https://www.nationalgeographic.com/animals/mammals/facts/prairie-dogs

- Post-splenectomy, the patient is at increased risk of severe disease due to which of the following microorganisms?

A. *Helicobacter pylori*
B. *Capnocytophaga canimorsus*
C. *Candida glabrata*
D. *Clostridium difficile*

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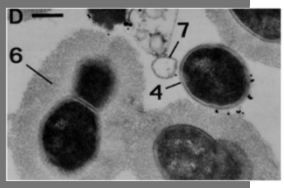
Splenectomy and infection risk



Skov Sørensen et al. (1988) Infect Immun 56: 1890-1896

Why: reduced clearance of encapsulated organisms; impaired humoral immunity

On the boards, look for…
- *Streptococcus pneumonia*
- *Hemophilus influenza type B*
- *Neisseria meningitidis*
- *Capnocytophaga canimorsus (dog bite)*
- *Babesia microti (tick borne)*
- *Bordatella holmesii*
- *Salmonella typhi*

Rubin LG, Schaffner W. Clinical practice. Care of the asplenic patient. N Engl J Med. 2014

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Strategies to reduce infection risk in asplenia

Vaccination for encapsulated organisms

- Pneumococcus
- Meningococcus
- Hemophilus influenza type B

Penicillin prophylaxis

- Children < 5 years
- Older children / adults within 1-2 years of splenectomy
- Any age: secondary prevention (lifelong) following sepsis

Rubin LG, Schaffner W. Clinical practice. Care of the asplenic patient. N Engl J Med. 2014

65

- Increased risk for infection with encapsulated organisms (and others)…
  - *S. pneumoniae; N. meningitidis; HIB; Capnocytophaga; Babesia; Salmonella typhi*
- Reduce risk of infection via:
  - Immunizations
  - PCN ppx if < 5 yrs old; recent splenectomy; h/o sepsis

Infection in asplenia

Take home points

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Question 9

- A 19 year-old male with no past medical history presents with acute onset of pain that started in the periumbilical region and moved to the lower region.
- Physical exam is notable for point tenderness in the right lower quadrant.
- Appendicitis is diagnosed based on clinical findings and imaging results.
- The patient wants to avoid surgery if at all possible.

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Question 9

You note that antibiotic therapy for uncomplicated appendicitis has become accepted practice by some physicians, and offer to counsel him regarding risks and benefits.

Which of the following is a recognized **disadvantage** of this approach, when compared to immediate surgery?

A. Risk of *C. difficile* within 30 days
B. Risk of bowel obstruction in 1 year
C. 20% risk of intra-abdominal abscess within 30 days
D. 30-50% risk of subsequent appendectomy within 4 years

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Appendicitis: to cut or not to cut…

In several studies, non-operative management (antibiotics alone) was "non-inferior" to operative management for **acute, uncomplicated appendicitis**

Features that may prompt ***OPERATIVE*** management:

- Appendicolith (+/-)
- Perforation
- Abscess
- Suspicion of tumor
- Peritonitis
- Serious systemic illness

CODA: N Engl J Med. 2020; APPAC: JAMA. 2018; Pediatr Surg Int. 2020

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Risks and benefits

30-50% of patients initially managed with antibiotics required appendectomy within 5 years

Long term follow up suggests overall equivalent patient satisfaction

Recommendation: shared decision-making

Quality of Life and Patient Satisfaction at 7-Year Follow-up of Antibiotic Therapy vs Appendectomy for Uncomplicated Acute Appendicitis: A Secondary Analysis of a Randomized Clinical Trial. JAMA Surg. 2020

70

- Non-operative management of acute appendicitis may be considered if ***uncomplicated***
  - Features which should prompt immediate surgery: perforation; abscess; suspected tumor; peritonitis; systemic illness
- Up to 50% will require subsequent appendectomy; shared decision-making recommended to discuss risks and benefits
- *ID board potential* – recognize when an operation is NEEDED

Appendicitis

Take home points

71

53 – Kitchen Sink: Syndromes Not Covered Elsewhere

Speaker: Stacey Rose, MD

Kitchen Sink summary - 1

Whipple's:
- Classic: arthralgia, diarrhea, weight loss
- Dx with duodenal bx (PAS+, foamy macrophages)
- or PCR of tissue (heart valve for endocarditis)

Acute Rheumatic fever:
- Kids / young adults with migratory polyarthritis, carditis, chorea, subcutaneous nodules, erythema marginatum following GAS pharyngitis
- Monthly IM penicillin prophylaxis for 10 years or to age 40 if carditis + residual valvular disease

https://www.cdc.gov/groupastrep/diseases-public/rheumatic-fever.html

Kitchen Sink summary - 2

Botulism:
- Due to *C. botulinum* toxin
- Food; infant; wound (black-tar heroin); iatrogenic
- Descending flaccid paralysis (starts with cranial nerves)
- Antitoxin / supportive care

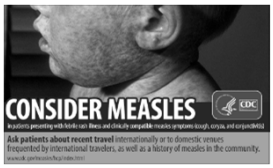
***Vibrio vulnificus*:**
- Liver disease at risk
- Exposure to raw seafood or contaminated wound (brackish water)
- Rapidly progressive, hemorrhagic bullae / sepsis
- Ceftriaxone plus FQ or doxy; debridement

https://www.cdc.gov/vibrio/wounds.html

Kitchen Sink summary - 3

Pertussis
- Clinical diagnosis: 2+ weeks of cough plus paroxysms, inspiratory whoop, post-tussive emesis, apnea
- Macrolide if within 3 weeks of onset or as PEP for contacts at risk of severe disease

Measles
- unvaccinated + travel history
- 3 C's – coryza, cough, conjunctivitis
- Koplik spots
- Rash spreads from head to trunk to extremities
- Contagious and severe
- Later – SSPE (degenerative neurologic dz / seizures)

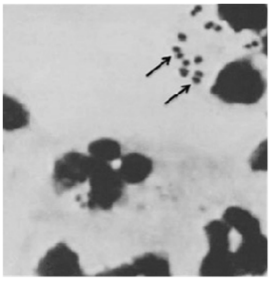


https://www.cdc.gov/measles/consider-measles-infographic.html

Kitchen Sink summary - 4

Invasive meningococcal disease
- Host (asplenia/ complement deficiency); environmental (crowded conditions) risks
- Rapidly progressive; meningitis; purpuric rash
- Rx: 3rd gen cephalosporin
- Ppx for close contacts (cipro; rifampin; ceftriaxone; azithro?)
- No rx for asx carriage

Asplenia
- Increased risk of infection with encapsulated organisms
- If prompt says asplenia, think…
  - S. pneumoniae
  - N. meningitidis
  - H. influenzae type B
  - Capnocytophaga
  - Babesia
  - Salmonella typhi
- Prevent infection with immunizations and
- PCN prophylaxis (if < 5 yrs old; recent splenectomy; prior episode of sepsis)



https://www.cdc.gov/meningitis/lab-manual/chpt06-culture-id.html

Kitchen Sink summary - 5

Appendicitis
- Non operative management may be reasonable for uncomplicated cases
- Identify features that should prompt surgery:
  - Appendicolith +/-
  - perforation
  - Abscess
  - Suspicion of tumor
  - Peritonitis
  - Systemic illness

Questions?

Stacey Rose, MD, FACP, FIDSA
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OL1

Bootcamp: HIV

Dr. Roy Gulick

IDBR INFECTIOUS DISEASE BOARD REVIEW AUGUST 19-23 2023

Bootcamp: HIV

Roy M. Gulick, MD, MPH
Chief, Division of Infectious Diseases
Rochelle Belfer Professor in Medicine
Weill Cornell Medicine

6/15/2023

IDBR INFECTIOUS DISEASE BOARD REVIEW AUGUST 19-23 2023

Disclosures of Financial Relationships with Relevant Commercial Interests

- **No pharmaceutical or device company relationships**
- **Co-Chair, U.S. DHHS Adult and Adolescent ART Treatment Guidelines Panel**

ID Boards – Medical Content: 15% HIV

- Epidemiology (<2%)
- Pathogenesis (<2%)
- Lab testing (<2%)
- HIV Treatment Regimens (4.5%)
- Opportunistic Infections (5%)
- Malignancies (<2%)
- Other complications of HIV (2%)
- Related issues (<2%)

Morbidity and Mortality Weekly Report (MMWR): 1981

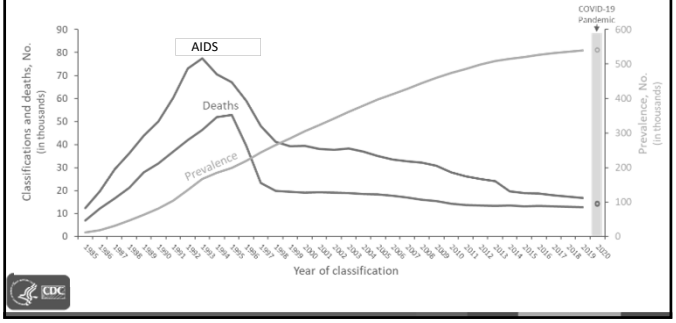
1981 June 5;30:250–2

Pneumocystis Pneumonia – Los Angeles

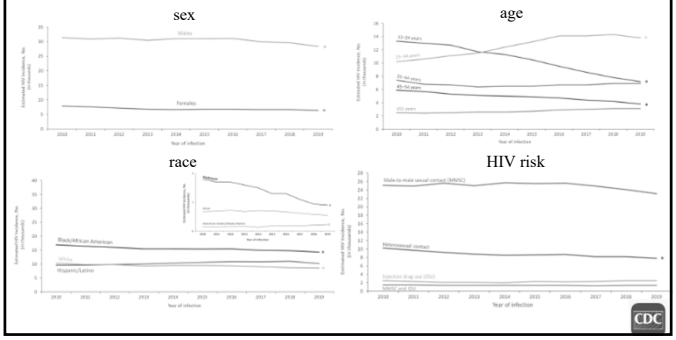
In the period October 1980-May 1981, 5 young men, all active homosexuals, were treated for biopsy-confirmed *Pneumocystis carinii* pneumonia at 3 different hospitals in Los Angeles, California. Two of the patients died. All 5 patients had laboratory-confirmed previous or current cytomegalovirus (CMV) infection and candidal mucosal infection. Case reports of these patients follow.

2022: >79 million people infected globally; ~1/2 have died

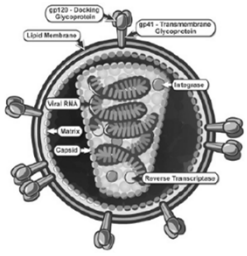
AIDS, Deaths, and Diagnosed HIV Infection Ever Classified 1985–2020 — US and 6 Dependent Areas



HIV Incidence ≥13 Years Old 2010–2019—U.S.



Human Immunodeficiency Virus (HIV)



- formerly HTLV-III; isolated 1983-4
- human retrovirus – outer glycoprotein coat, inner protein coat and genetic material: RNA (2 strands)
- types: HIV-1 and HIV-2
- subtypes (clades): B most common in North America and Europe
- zoonosis from primates (~1900)
- target cell: CD4+ T-lymphocyte

Question 1

Which is the current sequence of initial and confirmatory HIV diagnostic testing?

A. ELISA, followed by Western Blot
B. ELISA, followed by HIV RNA
C. ELISA, followed by immunoassay
D. HIV RNA, followed by Western Blot
E. HIV RNA, followed by ELISA
F. HIV RNA, followed by immunoassay

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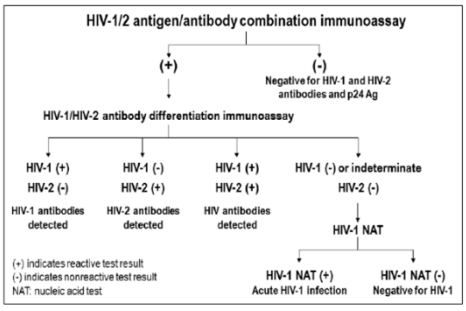
E. HIV RNA, followed by ELISA
F. HIV RNA, followed by immunoassay

HIV Testing

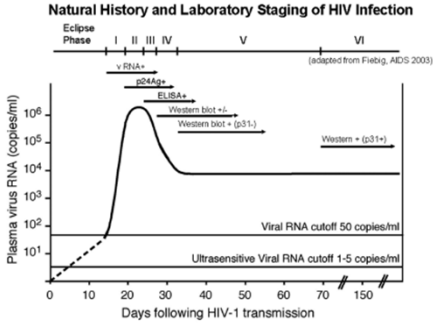
- HIV antibody testing (indirect)
  - Screening test: HIV-1, HIV-2 antibodies by ELISA
  - If repeatedly positive, proceed to confirmatory test
    - Immunoblot or 2nd HIV rapid test
  - 20-minute oral test and 1-minute blood test
- HIV viral testing (direct)
  - p24 antigen
  - viral culture
  - HIV RNA (viral load)
- Newer combination antibody + antigen test
  - window period 3 months → 2 weeks

Recommended Laboratory HIV Testing Algorithm for Serum or Plasma Specimens



CDC 2014

Natural History and Laboratory Staging of HIV Infection



Cohen JID 2010;202:S270

Question 2

Who should NOT be routinely offered HIV testing?

A. 32 year old pregnant woman in a stable relationship
B. 23 year old sexually active monogamous gay man
C. 75 year old former injection drug user
D. 10 year old pre-pubescent girl
E. All of them should be routinely offered HIV testing

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D. 10 year old pre-pubescent girl
E. All of them should be routinely offered HIV testing

U.S. Preventive Services Task Force (UPSTF)

Recommendations

- Screen adolescents and adults ages 15 to 65 for HIV infection.
- Screen all pregnant women.
- Younger adolescents and older adults who are at increased risk should also be screened.
- This is a grade A recommendation ("high certainty that the net benefit is substantial").
- Federal Rule: Private Insurance and Medicare must offer A or B services without a co-pay.

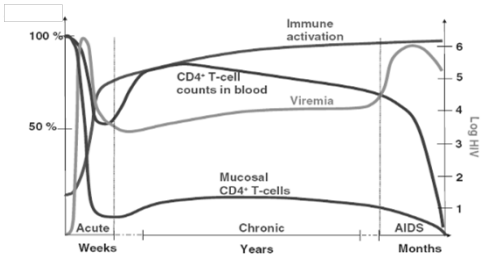
Ann Intern Med 2013;159:1-36

HIV Transmission Risks

Exposure from HIV+ source	Risk per exposure (%)	Risk per exposure (number)
Blood transfusion	93%	9/10
Needle-sharing injection drug use	0.6%	1/167
Percutaneous needle stick	0.2%	1/500
Receptive anal sex	1.4%	1/70
Insertive anal sex	0.1%	1/1000
Receptive penile-vaginal sex	0.08%	1/1250
Insertive penile-vaginal sex	0.04%	1/2500
Oral sex	low	very low
Mother-to-child	23%	1/4

Patel AIDS 2014;28:1509

Time Course of HIV Infection



Grossman Nature Medicine 2006;12:289-295

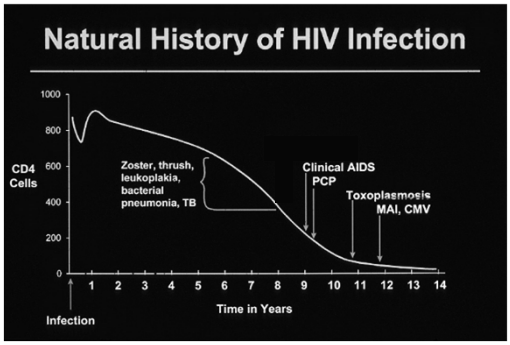
CDC Adult AIDS Case Definition

- 1982: "AIDS" -- list of diseases (definitive diagnosis) and disqualifying conditions
- 1985: HIV antibody testing added to definition
- 1987: presumptive diagnoses with a positive HIV antibody added
- 1993: CD4 <200 (without symptoms) and other diagnoses added

Opportunistic Infections (OI)

- Definition: Infection caused by an organism capable of causing disease only in a host whose resistance is lowered (by other diseases or by drugs)
- AIDS-related:
  - Bacterial: MAC, tuberculosis
  - Fungal: PCP, Cryptococcus, Histoplasma
  - Viral: CMV
  - Parasitic: Toxoplasma
  - Malignancies: Kaposi's sarcoma, NH-lymphoma

Natural History of HIV Infection



Goal of Antiretroviral Therapy

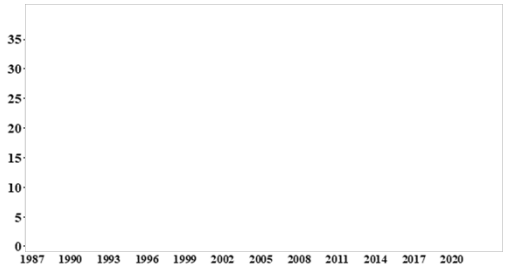
- to suppress HIV RNA (viral load level) as low as possible, for as long as possible
- to preserve or enhance immune function
- to delay clinical progression of HIV disease and prolong healthy survival

When to start ART?

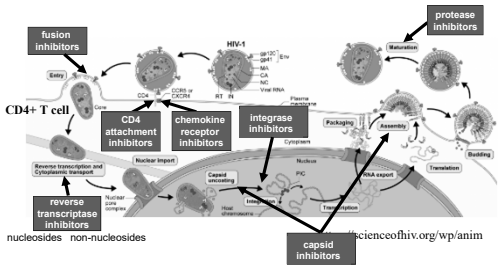
Guidelines	AIDS/ symp-toms	CD4 <200	CD4 200-350	CD4 350-500	CD4 >500
US DHHS '23 www.clinicalinfo.hiv.gov					
IAS-USA '23 JAMA 2023;329:63-84					

U.S. DHHS HIV Treatment Guidelines (3/23):
- ART is recommended for all persons with HIV to ↓ morbidity and mortality **(AI)** and to prevent transmission of HIV to others **(AI)**.
- Initiate ART immediately (or as soon as possible) after HIV diagnosis.

Antiretroviral Drug Approval: 1987 - 2023



Life Cycle of HIV



Approved ART: 2023*

nucleoside/tide RTIs (NRTIs)
- zidovudine (ZDV, AZT)
- lamivudine (3TC)
- abacavir (ABC)
- emtricitabine (FTC)
- tenofovir (TAF, TDF)

NNRTIs
- nevirapine (NVP)
- efavirenz (EFV)
- etravirine (ETR)
- rilpivirine (RPV)
- doravirine (DOR)

protease inhibitors (PIs)
- saquinavir (SQV)
- ritonavir (RTV)
- indinavir (IDV)
- nelfinavir (NFV)
- lopinavir/r (LPV/r)
- atazanavir (ATV)
- tipranavir (TPV)
- darunavir (DRV)

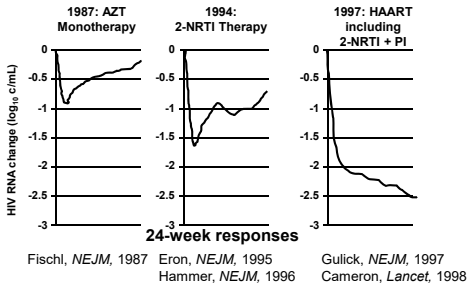
integrase inhibitors (IIs)
- raltegravir (RAL)
- elvitegravir (EVG)
- dolutegravir (DTG)
- bictegravir (BIC)
- cabotegravir (CAB)

entry inhibitors (EIs)
- enfuvirtide (T-20, fusion inhibitor)
- maraviroc (MVC, CCR5 antagonist)
- ibalizumab (IBA, CD4 post-attachment inhibitor)
- fostemsavir (FTR, CD4 attachment inhibitor)

capsid inhibitors (CIs)
- lenacapavir (LEN)

*ddI, ddC, d4T, DLV, and APV (and FPV 1/24) discontinued from market

Antiretroviral Activity: 1987-1997



Fischl, *NEJM,* 1987 Eron, *NEJM,* 1995 Hammer, *NEJM,* 1996 Gulick, *NEJM,* 1997 Cameron, *Lancet,* 1998

Question 3

Which class of ART is recommended for initial HIV treatment for most patients?

A. All nucleoside analog (NRTI) regimen
B. Non-nucleoside (NNRTI)-based regimen
C. Protease inhibitor (PI)-based regimen
D. Integrase inhibitor (INSTI)-based regimen
E. Entry inhibitor (EI)-based regimen

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What to start?

Recommended regimens:

1 or 2 nucleoside analogues + integrase inhibitor
• bictegravir/tenofovir alafenamide (TAF)/emtricitabine (FTC)
• dolutegravir/abacavir/lamivudine
• dolutegravir + (FTC or lamivudine [3TC]) + (TAF or tenofovir disoproxil fumarate [TDF])
• dolutegravir/3TC

Alternative regimens: non-nucleoside (NNRTI)-, protease inhibitor (PI)-, and other integrase inhibitor (elvitegravir, raltegravir) -based

U.S. DHHS HIV Treatment Guidelines 3/23

Approved Single-Tablet ART Regimens

TDF/FTC/EFV (2006)
TDF/FTC/RPV (2011)
TDF/FTC/EVG/c (2012)
ABC/3TC/DTG (2014)
TAF/FTC/EVG/c (2015)
TAF/FTC/RPV (2016)

DTG/RPV (2017)*
TAF/FTC/BIC (2018)
TAF/FTC/DRV/c (2018)
TDF/3TC/DOR (2018)
DTG/3TC (2019)

*FDA approved for maintenance therapy

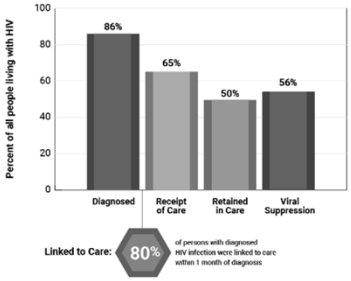
Cabotegravir (CAB)

- Integrase inhibitor similar to similar to dolutegravir
- Potent in people with HIV (5, 10, 30, 60 mg oral)
  Spreen HIV Clin Trials 2013;14:192
- Nanotechnology formulation; injectable
- Phase 3 studies of IM CAB/rilpivirine (RPV) for treatment switch demonstrated non-inferiority to standard oral treatment regimens
  - Orkin NEJM 2020;382:1124
  - Swindells NEJM 2020;382:1112
- U.S. FDA approved the combination of IM CAB + RPV monthly for switch treatment in 2021
  - For patients undetectable on ART without a history of virologic failure, drug resistance, or chronic HBV infection
  - 2022 FDA label amended for every other month dosing and optional lead-in dosing

FDA APPROVED

Overton Lancet 2021;396:1994 + Orkin Lancet HIV 2021;8:e668

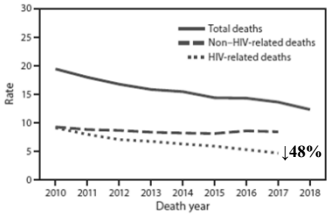
Prevalence-based HIV Care Continuum, U.S. and 6 Dependent Areas, 2018



www.hiv.gov

U.S. HIV Deaths: 2010-2018

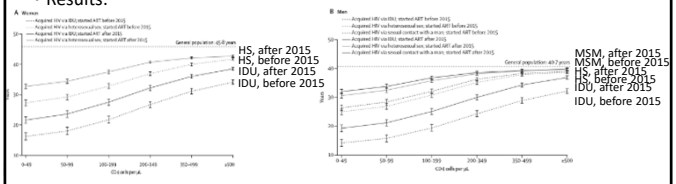
FIGURE 1. Age-adjusted rates* of total deaths,† human immunodeficiency virus (HIV)–related deaths,§ and non–HIV-related deaths among persons aged ≥13 years with diagnosed HIV infection — United States, 2010–2018¶



Bosh, MMWR 2020;69:1717-24

Life Expectancy of HIV on ART

- Goal: To estimate life expectancy of people with HIV on ART for ≥1 year after 2015 at age 40 in North America / Europe
- Study population: ART Cohort Collaboration + UK CHIC Cohort Study (N=206,891 with 5780 deaths)
- Results:

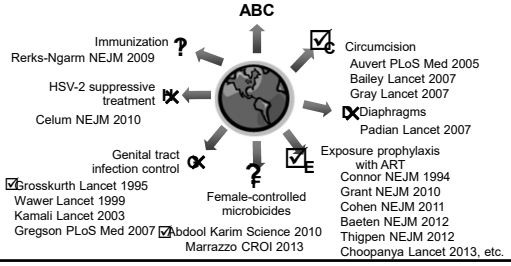


Trickey Lancet HIV 2023;10:e295-e307

HIV Prevention Strategies

Adapted from Ramjee *IAS Meeting* 2006, #TUPL02

Abstain, **B**e faithful, **C**ondoms,
Counseling & testing



Question 4

Which PrEP regimen is FDA-approved for at-risk men and women?

A. Daily tenofovir disoproxil fumarate (TDF)/emtricitabine (FTC)
B. Daily tenofovir alafenamide (TAF)/FTC
C. On-demand TDF/FTC
D. On-demand TAF/FTC
E. All of the above

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E. All of the above

HIV Prevention Strategy: PrEP

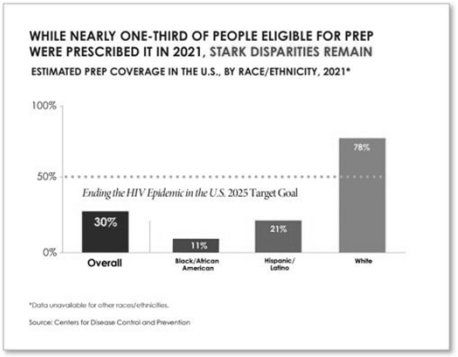
- Pre-exposure prophylaxis
- Strategy of administering HIV medications to uninfected, at-risk individuals
- Optimal drug candidates:
  - potent, safe, tolerable, and convenient
  - – = co-formulated tenofovir/FTC
- Potential concerns:
  - used widely for treatment; drug resistance; toxicities (kidney, bone); cost (>$10,000/year)
- 2012: FDA approves TDF/FTC for PrEP ♂♀
- 2019: FDA approves TAF/FTC for PrEP ♂
- 2021: FDA approves injectable CAB for PrEP ♂♀

Recent PrEP Studies

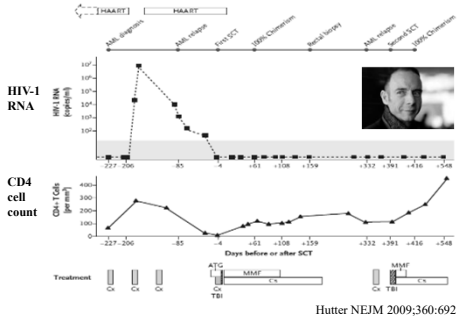
Study (reference)	Study population	Design	Results: Reduction in HIV Infection
PROUD McCormack Lancet 2015;387:54-60	544 HIV- MSM in UK	TDF/FTC (daily) immediate vs. delayed	TDF/FTC immediate: **86% reduction**
IPERGAY Molina NEJM 2015;373:2237	400 HIV- MSM in France and Canada	TDF/FTC (on demand) vs. placebo	TDF/FTC: **86% reduction**
HPTN 083 Landovitz NEJM 2022;385:595	4570 HIV- MSM and transgender women globally	TDF/FTC (daily) vs. CAB injections (every other month)	CAB non-inferior and **superior** to TDF/FTC
HPTN 084 Delany-Moretlwe Lancet 2022;399:1779	3224 HIV- at-risk women aged 18-45 in Sub-Saharan Africa	TDF/FTC (daily) vs. CAB injections (every other month)	CAB **superior** to TDF/FTC

Federal Plan to End AIDS by 2030

https://www.hiv.gov/ (2019)



HIV Cure (N=*1*) **5!**



Hutter NEJM 2009;360:692

Cure #2
London
Gupta, et al
Nature
2019;568: 244-248.

Cure #3
NYC
Hsu, et al
Cell
2023;186:1115-1126

Cure #4
City of Hope
IAS 2022

Cure #5
Dusseldorf
Jensen, et al
Nat Med 2023
(on line)

Conclusions

- HIV/AIDS is a worldwide pandemic.
- Routine HIV testing should be offered to ALL patients.
- Antiretroviral therapy (ART) ↓ HIV RNA, ↑ CD4 cell counts, prevents disease progression, and prolongs healthy survival.
- Current ART consists of 3-drug therapy and is increasingly available worldwide.
- Current life expectancy for HIV+ people on therapy approaches that of the general population.
- Prevention continues to be key.
- Cure research is in progress.

Acknowledgments

- Cornell HIV Clinical Trials Unit (CCTU)
- Division of Infectious Diseases
- Weill Cornell Medicine
- NY Presbyterian
- AIDS Clinical Trials Group (ACTG)
- Division of AIDS, NIAID, NIH
- The patient volunteers!

rgulick@med.cornell.edu

OL2

ID Bootcamp: Transplant

Dr. Camille Kotton

Online Only Lectures – Bootcamp: Transplant

Speaker: Camille Kotton, MD

Bootcamp: Transplant

Camille Nelson Kotton, MD, FIDSA, FAST
Clinical Director, Transplant and Immunocompromised Host
Infectious Diseases
Massachusetts General Hospital
Harvard Medical School

6/15/2023

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

Outline: What I Hope You Will Learn

- Type of immunosuppression seen with organ transplant
- Timeline of infection
- Prevention is paramount
  - Gaps in prophylaxis help develop the differential diagnosis
- Syndromes
- Diagnostics
  - Differential diagnosis is broad, imperative to obtain diagnosis
- Treatment – including drug interactions
- Latest strategies for prevention, recognition, diagnosis, and treatment
  - Guidelines
  - Best practices for safety and practice improvement
- **Bootcamp: meant as an introduction to subsequent similar talks**

The More Immunocompromised Host

- Hematopoietic stem cell transplant (HSCT) < 2 years
  - ↑ if graft versus host disease
- Solid organ transplant (SOT) < 1 year
  - ↑ if rejection
- AIDS with low CD4 counts
- Active leukemia or lymphoma, generalized malignancy, aplastic anemia, recent radiation tx
- Congenital immunodeficiency
- Immunosuppressive medications
- Chronic hepatic or renal disease, diabetes
- Autoimmune diseases

https://wwwnc.cdc.gov/travel/yellowbook/2022/travelers-with-additional-considerations/immunocompromised-travelers. Kotton, Kroger, Freedman

Definition: moderate and severe immunocompromising conditions and treatments (CDC)

Moderate and severe immunocompromising conditions and treatments include but are not limited to:

- Active treatment for **solid tumor and hematologic malignancies**
- Receipt of **solid-organ transplant** and taking immunosuppressive therapy
- Receipt of **CAR-T-cell therapy or hematopoietic cell transplant** (HCT) (within 2 years of transplantation or taking immunosuppression therapy)
- Moderate or severe **primary immunodeficiency** (e.g., DiGeorge syndrome, Wiskott-Aldrich syndrome)
- **Advanced or untreated HIV infection** (people with HIV and CD4 cell counts <200/mm3, history of an AIDS-defining illness without immune reconstitution, or clinical manifestations of symptomatic HIV)
- **Active treatment with high-dose corticosteroids (i.e., ≥20 mg prednisone or equivalent per day when administered for ≥2 weeks), alkylating agents, antimetabolites, transplant-related immunosuppressive drugs, cancer chemotherapeutic agents classified as severely immunosuppressive, tumor necrosis factor (TNF) blockers, and other biologic agents** that are immunosuppressive or immunomodulatory.

- https://www.cdc.gov/vaccines/covid-19/clinical-considerations/covid-19-vaccines-us.html#considerations-covid19-vax-immunocopromised

The More Immunocompromised Host

- **Transplant-related immunosuppressive drugs** (such as cyclosporine, tacrolimus, sirolimus, everolimus, azathioprine, and mycophenolate mofetil).
- **Cancer chemotherapeutic agents** are classified as severely immunosuppressive, as evidenced by increased rates of opportunistic infections and blunting of responses to certain vaccines among patient groups.[1]
- **High-dose corticosteroids**—Most clinicians consider a dose of either >2 mg/kg of body weight or ≥20 mg per day of prednisone or equivalent in people who weigh >10 kg, when administered for ≥2 weeks, as sufficiently immunosuppressive to raise concern about the safety of vaccination with live vaccines. Furthermore, the immune response to vaccines may be impaired. Clinicians should wait ≥1 month after discontinuation of high-dose systemic corticosteroid therapy before administering a live-virus vaccine.
- **Alkylating agents** (such as cyclophosphamide).
- **Antimetabolites** (such as azathioprine, 6-mercaptopurine, methotrexate), especially at higher doses.
- **Tumor necrosis factor (TNF) blockers** such as etanercept, adalimumab, certolizumab pegol, golimumab, and infliximab
- **Other biologic agents** that are immunosuppressive or immunomodulatory may result in significant immunocompromise. In particular, lymphocyte-depleting agents (thymoglobulin or alemtuzumab) and B cell–depleting agents (rituximab) are more significantly immunosuppressive. Consideration of the clinical context in which these were given is important, especially in hematologic malignancies.

https://wwwnc.cdc.gov/travel/yellowbook/2022/travelers-with-additional-considerations/immunocompromised-travelers. Kotton, Kroger, Freedman

The Less Immunocompromised Host

- Stem cell transplant recipients > 2 years post-transplant, not on immunosuppressive drugs, no graft versus host disease
- Chemotherapy for leukemia/lymphoma or cancer more than 3 months earlier with malignancy in remission
  - Those who have received immunotherapy with agents such as checkpoint inhibitors may need longer
- HIV patients with >500 CD4 lymphocytes
- Asplenia
- Nutritional deficiencies
- Steroid inhalers, topical steroids, intra-articular, bursal, or tendon injection of steroids, or on high-dose steroids over a month ago

https://wwwnc.cdc.gov/travel/yellowbook/2022/travelers-with-additional-considerations/immunocompromised-travelers, Kotton, Kroger, Freedman

Host considerations: *"Net state of immunosuppression"*
Dr. Robert Rubin, Massachusetts General Hospital

IMMUNOSUPPRESSION IS ADDITIVE

- Disease state may alter the immune system
  - Autoimmune diseases
  - Advanced organ failure
  - Other organ compromise: kidney, liver
- Comorbidities/conditions
  - Diabetes, obesity, malnutrition/weight loss
  - Hypogammaglobulinemia
  - Viral infections (HIV, CMV, EBV, HCV)
  - Altered microbiome
  - Advanced age
- Exogenous immunosuppression
  - Pre-transplant immunosuppression (i.e. autoimmune hepatitis)
  - Induction agents @ time of transplant
  - Chronic immunosuppression
  - Treatment of rejection

National Organ Transplant Data – USA

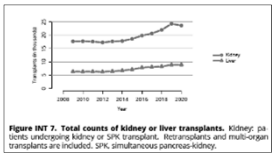


Figure INT 7. Total counts of kidney or liver transplants. Kidney: patients undergoing kidney or SPK transplant. Retransplants and multi-organ transplants are included. SPK, simultaneous pancreas-kidney.

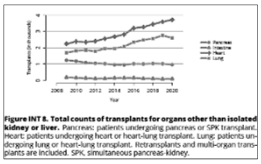


Figure INT 8. Total counts of transplants for organs other than isolated kidney or liver. Pancreas: patients undergoing pancreas or SPK transplant. Heart: patients undergoing heart or heart-lung transplant. Lung: patients undergoing lung or heart-lung transplant. Retransplants and multi-organ transplants are included. SPK, simultaneous pancreas-kidney.

>850,000 transplants done in USA since 1988

OPTN/SRTR 2020 Annual Data Report:
Introduction, AJT Feb 2022

National Organ Transplant Data – USA
>928,000 transplants done in USA since 1988

	To Date	2023	2022	2021	2020	2019	2018	2017	2016	2015	2014	2013
All Organs	928,235	7,153	42,888	41,356	39,036	39,719	36,530	34,770	33,610	30,974	29,540	28,956
Kidney	546,922	4,175	25,499	24,670	22,817	23,401	21,167	19,849	19,060	17,878	17,108	16,896
Liver	202,394	1,654	9,528	9,236	8,906	8,896	8,250	8,082	7,841	7,127	6,730	6,455
Pancreas	9,295	15	108	143	135	143	192	213	215	228	245	256
Kidney / Pancreas	27,199	124	810	820	827	872	835	789	798	719	709	762
Heart	88,197	706	4,111	3,818	3,658	3,552	3,408	3,244	3,191	2,804	2,655	2,531
Lung	49,255	454	2,692	2,524	2,539	2,714	2,530	2,449	2,327	2,057	1,925	1,923
Heart / Lung	1,475	16	51	45	58	45	32	29	18	15	24	23
Intestine	3,376	8	82	96	91	81	104	109	147	141	139	109

The COVID-19 pandemic didn't slow us down (much)!

*UNOS data downloaded 1 April 2023
https://optn.transplant.hrsa.gov/data/view-data-reports/national-data/#

Total number of HCTs performed in the United States, Center for International Blood and Marrow Transplant Research, 2016-2020

Donor Type	number	%
Autologous:	*66,458*	*59%*
Allogeneic:		
HLA-Matched Sibling	10,792	10%
Other Related Donor	10,037	9%
Unrelated	24,697	22%
Total	**111,984**	**100%**

https://bloodstemcell.hrsa.gov/data/donation-and-transplantation-statistics/transplant-activity-report#summary accessed 4 May 2023

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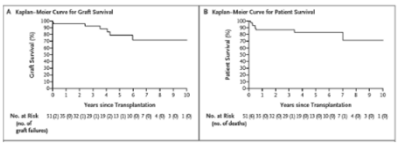
What's Trendy? (Might be on boards?)
Hepatitis C Donors and Organ Transplant

- Many programs are using hepatitis C positive donors into negative or positive recipients and treating after transplant
  - Yes, we are infecting people with hepatitis C
- Can be either HCV viral load and/or antibody positive
- For all organs, ~100% clearance
- Was often research protocol, now moving towards standard of care
- Need to have a good plan for medications (insurance)
- Trend towards shorter treatment protocols

Longer-Term Outcomes of *HIV-Positive–to–HIV-Positive Renal Transplantation*, Selhorst, Muller et al, NEJM 2018

- n=51
- 8 patients (16%) died after transplantation from non–graft-related causes
- No transmission of drug resistant virus
- **5-year overall survival and graft survival similar to the 3-year overall survival and graft survival observed among HIV-positive patients who received an organ from an HIV-negative donor in the United States**



HIV Organ Policy Equity (HOPE) Act: USA

- **Permits donated, HIV-positive organs to be used for transplantation in HIV-positive patients (only)**
  - Previously prohibited by federal law
- **An active program at multiple centers**
  - Previously research setting only, moving towards standard of care (kidney, liver)
  - Will remain research program for heart and lung transplant (for now)
- **+/- Half of organ donors have false positive testing**
  - Screening test positive, confirmatory test (done later, takes time) negative

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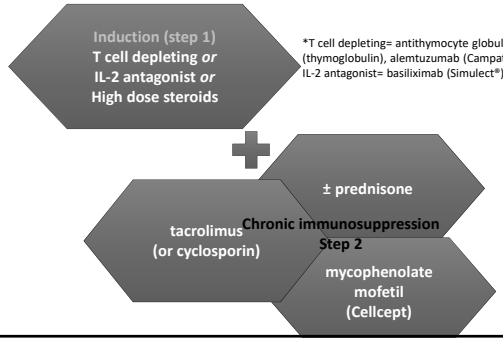
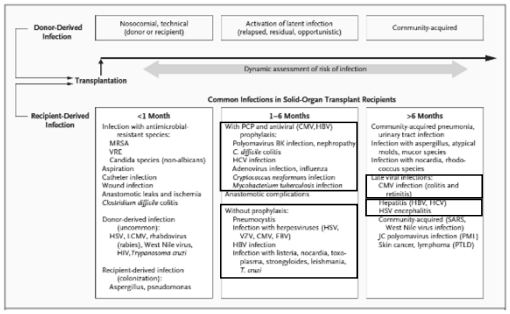
Common Immunosuppression after Organ Transplant



Timeline of Infection after Organ Transplantation



Fishman, Infection in Solid-Organ Transplant Recipients, NEJM 2007

Challenges w/ Current Antiviral Prophylaxis

Consider "net state of immunosuppression"

- **Optimizing the duration of prophylaxis** so as to minimize risk of active infection
  - Cellular immune assays for CMV – useful in CMV R+ (but lower rates of disease anyway), not in D+R-
  - "Treatment of rejection resets the prophylaxis clock to day 0"(Jay Fishman)
  - Absolute lymphocyte count
- Toxicity (especially with longer durations of prophylaxis (IMPACT trial)
  - Mostly leukopenia with valganciclovir - especially if prophylaxis dose too high
  - Risk of resistant virus - especially if prophylaxis dose too low
- Cost
- Treatment/secondary prophylaxis after ganciclovir resistance develops (<5% of patients)
  - Maribavir newly approved treatment option, no approved secondary prophylaxis options
- Phase 3 trial underway: Letermovir Versus Valganciclovir to Prevent Human Cytomegalovirus Disease in Kidney Transplant Recipients (MK-8228-002) ClinicalTrials.gov: NCT03443869

Common Immunosuppression after Stem Cell Transplant

- Chemotherapy
- Anti-graft versus host disease <u>prophylaxis</u>
  - Tacrolimus, cyclosporin
  - Methotrexate
  - Mycophenolate mofetil
  - Antithymocyte globulin (rabbit)
- Anti-graft versus host disease <u>treatment</u>
  - The first-line treatment of acute GVHD is methylprednisolone

Timeline of Infection after HSCT

Time Period	Pre-engraftment (day 0 to day 10-30*)	Early post-engraftment (to day 100)	Mid post-engraftment (to 1-2 years)	Late post-engraftment (after 1-2 years)
Infection risk factors	Neutropenia, Mucositis Venous catheters	Immunosuppression (aGVHD) Venous catheters	Immunosuppression (late aGVHD, cGVHD)	Immunosuppression (cGVHD)
Type of Infection	Chemotherapy-associated and Nosocomial infections	Opportunistic infections	Opportunistic and Community infections	Community-acquired infections
Bacterial	Gram positive cocci Gram negative rods	Encapsulated bacteria Listeria/Salmonella/Nocardia		
Viral	HSV			VZV
		BK virus hemorrhagic cystitis		EBV/PTLD
		CMV		
		HHV-6/Adenovirus reactivation		HBV reactivation (cAb+)
Fungal		Respiratory and enteric viral infections (influenza, RSV, parainfluenza, norovirus)		
	Candida			
	Aspergillus	Aspergillus and other molds (mucorales)		
Parasitic		Pneumocystis jirovecii pneumonia		
		Strongyloides hyperinfection		
		Toxoplasma reactivation		
	High risk	Moderate risk	Low risk	High risk, but prophylaxis usually given

Hammond SP, Marty FM. Timeline of infection after Hematopoietic Stem Cell Transplant. In:AST Handbook of Transplant Infections, D Kumar A Humar Eds. 2011;4.

Prevention & Prophylaxis

- Pre-immunosuppression evaluation**
  - Vaccines
  - Screening for latent infections
  - Plan for chronic infections
  - Optimize diabetes, stop smoking/marijuana use, etc
  - Education
- Management: peritransplant/initiation of immunomodulatory
- Prophylaxis and/or screening after transplant/immunomodulatory therapy started

48yo man referred for routine pre-kidney transplant evaluation, originally from rural El Salvad

Treponemal antibody positive, **RPR 1:16**, never treated, diagnosis = late latent syphilis, treated with weekly benzathine penicillin x 3

***Strongyloides* antibody positive**, 18% eosinophils, diagnosis = indolent strongyloidiasis, treated ivermectin daily x 2, repeated 2 weeks later

Hepatitis B core antibody positive, surface antibody negative, diagnosis = prior hepatitis B exposure, plan to monitor with HBV DNA (viral load) q 3 months after transplant

TSPOT TB positive (high number spots both ELISpot panels),scattered calcified granulomas on chest CT, diagnosis = latent tuberculosis, I with isoniazid/vitamin B6 x 9 months

Chagas antibody positive, diagnosis = chronic, late Chagas disease, plan to monitor with Chagas DNA (PCR, parasite load) q month x 3 after transplant then less ofte

Poorly vaccinated, plan for: COVID-19 bivalent booster PCV20 (pneumococcal), Tdap Quadrivalent influenza vaccine Shingrix x 2 (shingles)

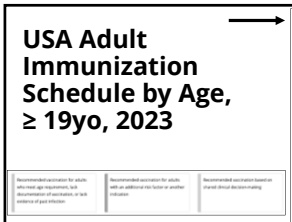
Pre-Immunosuppression Evaluation (MGH)

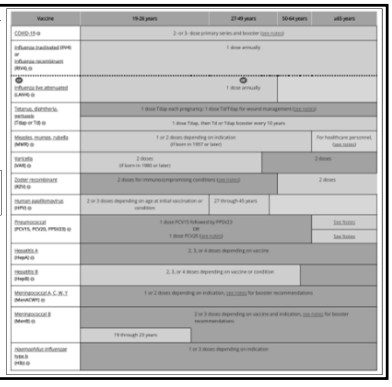
	Everyone	If risk factors
Hepatitis B surface antigen	x	
Hepatitis B core antibody (IgG not IgM)	x	
Hepatitis B surface antibody	x	
Hepatitis C	x	
HIV	x	
Tuberculosis screening	x	
Coccidioides serology		x
Strongyloides serology		x
Trypanosoma cruzi (Chagas disease)		x

Pre-Solid Organ Transplant Evaluation (MGH)

	Everyone	Vaccinate if neg	If risk factors
Hepatitis A	x	x	
Hepatitis B surface antigen	x		
Hepatitis B core antibody (IgG not IgM)	x		
Hepatitis B surface antibody	x	x	
Hepatitis C	x		
HIV	x		
Tuberculosis screening	x		
Varicella	x	x	
Cytomegalovirus	x		
Mumps-measles-rubella	x	x	
Syphilis antibody	x		
Coccidioides antibody			x
Strongyloides serology			x
Trypanosoma cruzi (Chagas disease)			x

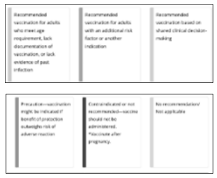
USA Adult Immunization Schedule by Age, ≥ 19yo, 2023

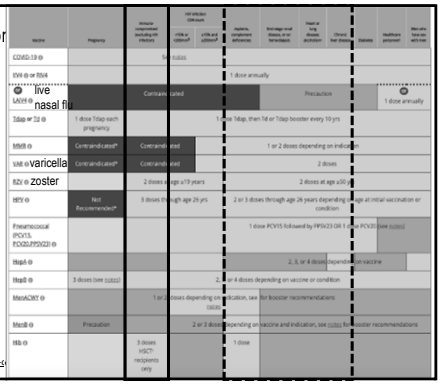




https://www.cdc.gov/vaccines/schedules/hcp/imz/adult.html

USA Adult Immunizatio Schedule by Condition, ≥19yo, 2023





https://www.cdc.gov/vaccines/schedules/hcp/imz/adult-c

CDC: Who Should Get Tested for TB

- TB tests are generally not needed for people with a low risk of infection
- Certain people should be tested for TB bacteria because they are more likely to get TB disease, including:
  - People who have spent time with someone who has TB disease
  - **People with HIV infection or another medical problem that weakens the immune system**
  - People who have symptoms of TB disease (fever, night sweats, cough, and weight loss)
  - People from a country where TB disease is common (most countries in Latin America, the Caribbean, Africa, Asia, Eastern Europe, and Russia)
  - People who live or work somewhere in the US where TB disease is more common (homeless shelters, prison or jails, or some nursing homes)
  - People who use illegal drugs

www.cdc.gov/tb/topic/testing/

Latent TB Screening

- Medical history
- Epidemiologic risk factors
- TB skin test (TST)
- Interferon gamma release assay (IGRA) (blood test) (sometimes preferentially vs TST, IDSA guidelines 2016)
  - T-SPOT.®*TB*
  - QuantiFERON®-TB Gold
- Radiographic findings
  - Old granulomatous disease, apical scarring

T-SPOT.®*TB* and QuantiFERON®-TB Gold

- Enumerates effector T-cell response to stimulation with a combination of peptides simulating ESAT-6 and CFP10 (+ TB7.7 for QFN) antigens
- Detects prior exposure to:
  - *M. tuberculosis* complex organisms (*M. tuberculosis, M. bovis, M. africanum, M. microti, M. canetti)*
  - *M. kansasii, M. szulgai,* and *M. marinum*
- Not + with prior BCG vaccine (bacille Calmette–Guérin)
- Interpret test correctly:
  - If either test or PPD positive, take as positive
  - Borderline results = partway b/w + and negative
  - **Indeterminate results = assay did not work**

Your patient has latent TB. Should and when should you start chemoprophylaxis? When can immunosuppressive medications be started?

A. Start TB chemoprophylaxis ASAP as per guidelines. (Ensure no active TB, pulmonary or extrapulmonary.) Can start immunosuppression any time.
B. Avoid TB chemoprophylaxis. Too many side effects, and too much hassle.
C. Most of my patients had BCG vaccine as children, and test false + as older adults. I don't give TB chemoprophylaxis.

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C. Most of my patients had BCG vaccine as children, and test false + as older adults. I don't give TB chemoprophylaxis.

Excellent Prophylaxis is Paramount… and provides important clues on boards questions

- Antivirals
- Pneumocystis/Toxoplasmosis
- Antifungals

Prophylaxis: Solid Organ Transplant Massachusetts General Hospital

CMV/Herpes Antiviral Prophylaxis

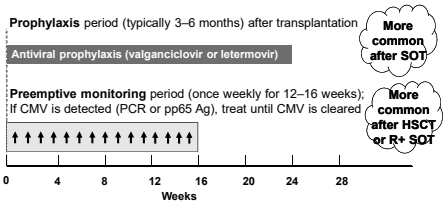
- Valganciclovir if any CMV risk (if either donor and/or recipient are CMV positive)
  - Prevents CMV, herpes, varicella/zoster
- Acyclovir/valacyclovir/famvir **if no CMV risk**
  - Prevents herpes, varicella/zoster
- Duration varies, 3-6 months is common (longer for lung transplant)
- Main side effect is leukopenia and cost with valganciclovir

Donor CMV Antibody	Recipient CMV Antibody	Prophylaxis	Duration
+	+	Valganciclovir	Antithymocyte globulin and D+R- → 6 months
-	+		
+	-		All others 3 months
-	-	ACV/Famvir/ValACV	

Anti-*Pneumocystis*/anti-bacterial

- Trimethoprim-sulfamethoxazole x 6-12 months (longer for heart/lung transplants)
- *or* dapsone or atovaquone if true allergy

CYTOMEGALOVIRUS PREVENTION: Prophylaxis vs. Preemptive Therapy

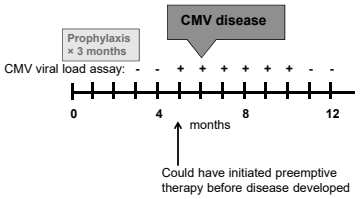


Humar A, Snydman D; AST Infectious Diseases Community of Practice. *Am J Transplant.* 2009;9 (Suppl 4):S78-S86.

Hybrid Strategy for SOT: CMV Surveillance After Prophylaxis

Consider "net state of immunosuppression"

- Weekly monitoring after end of prophylaxis, for ~12 weeks
- High risk (D+/R-) may be highest yield population (for late disease)
  - Other high-risk groups (potent immunosuppression)
- Guidelines experts use approach, not strongly evidence-based



Kotton CN et al, The Third International Consensus Guidelines on The Management of Cytomegalovirus In Solid Organ Transplantation, Transplantation 2018

Antiviral Prophylaxis: Stem Cell Transplant

- Acyclovir/valacyclovir/famvir for everyone
  - Prevents herpes, varicella/zoster
  - Duration varies a lot across programs, 6-12+ months is common
- **Letermovir** x 100 days if higher CMV risk
  - if recipient is CMV positive – opposite of solid organ (D-R+ is high risk after HSCT)
  - Prevents CMV, NOT herpes, varicella/zoster
  - Decreased mortality
  - If small viral load "blips", carry on and retest a week later – only stop therapy if high blips (>1,000 IU/ml)
  - Main side effect is cost

Antiviral Prophylaxis/Treatment Agents

Antiviral agent	CMV	HSV	Varicella	BK	Adeno-virus	EBV
Commercially available						
ganciclovir IV/valganciclovir PO	x	x	x			
acyclovir/valacyclovir/famciclovir*	high dose +/-	x	x			
letermovir	x					
maribavir	x					*in vitro*
foscarnet**	x	x	x			
cidofovir**	x	x	x	poor	+/- (IC50)	
Novel/investigational antiviral agents (SOT)						
brincidofovir (not available)	*x*	*x*	*x*	*x*	*x*	*x*

*acyclovir/valacyclovir/famciclovir and letermovir for prophylaxis only
**foscarnet, cidofovir not usually used for prophylaxis

Pneumocystis/Toxoplasmosis

- First line:
  - Bactrim SS daily or DS three times a week
- Second line (only if real Bactrim allergy or intolerance) alternatives:
  - Atovaquone (Mepron) 1500 mg QD
  - Dapsone 100 mg QD
    - √ G6PD
    - watch for methemoglobinemia, low white blood cell count
  - Pentamidine IV q month (does not cover Toxoplasmosis)
- Duration variable, usually until end of PPx

Approach to Toxoplasmosis prophylaxis

- Toxoplasmosis risk highest in Donor +/Recipient seronegative = 50-75% risk of symptomatic infection without prophylaxis within 3 months of heart transplant (much lower with other organs)
- ~7% of Americans age 12-49y are seropositive (https://www.ncbi.nlm.nih.gov/pubmed/25012250).
- Infection more common in patients from endemic regions (e.g., France, Caribbean)
- Can present in any organ system (CNS abscess, pneumonia, myocarditis, disseminated disease)
- Very rare with good prophylaxis

Duration of prophylaxis based on serologic combinations (MGH)			Prophylaxis
Serologies	Risk group	Duration of therapy	
D+/R-	Highest risk	Lifetime, if possible (otherwise discuss with infectious disease)	First line: FIRST YEAR: -Bactrim DS 1 tab QD x 1 year (for D+/R-) -Can dose reduce the DS to SS if CrCl<30 -Bactrim SS 1 tab QD (for all other serology; no need to dose reduce this dosage with renal failure/HD) AFTER FIRST YEAR: Bactrim SS 1 tab QD (see columns to left) Second line (only if real Bactrim allergy): Atovaquone (mepron) 1500 mg QD Third line (both Bactrim and mepron allergy): Dapsone 100 mg QD √ G6PD and watch for MetHgb
R+ (regardless of donor status)	Moderate risk	Can stop at one year, or when on low-dose prednisone 5 mg a day, whichever is later/longer.	
D-/R-	Lowest risk		

Antifungal Prophylaxis: Solid Organ Transplant

Organ	Common Practice	Comments
Kidney, liver, heart	None for most; some programs give fluconazole/echinocandins peri-liver	Some Nystatin swish and swallow
Pancreas	Fluconazole post-op for variable time, < 1 month	
Lung	Voriconazole, posaconazole, itraconazole for variable times after transplant	Voriconazole and augmented skin cancer, osteitis risks a major concern
Intestinal transplant, Composite tissue	Often longer courses of fluconazole/echinocandins	

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Antifungal Prophylaxis: Hematopoietic Stem Cell Transplant

- Fluconazole often used in first 100 days after HSCT
  - Generally for higher risk receipts
  - Classic population for *C. krusei,* R to fluconazole
- Posaconazole generally reserved for higher risk patients
  - Only FDA approved agent for this indication
- Voriconazole – higher risk of mucormycosis seen

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Sources of Infection after Transplant

- Community-acquired
- Nosocomial
- Prior colonization
  - + Intraoperative *Aspergillus* culture w/ cystic fibrosis & lung transplant → OR 4.36 invasive aspergillosis (Luong *et al*, Transplantation 2014)
- Emerging
- Donor-derived infection
  - Organ graft, blood products

Ten years of donor-derived disease: A report of the disease transmission advisory committee *Am J Transplant.* 2021;21:689–702

Daniel R. Kaul[1] | Gabe Vece[2] | Emily Blumberg[3] | Ricardo M. La Hoz[4] | Michael G. Ison[5] | Michael Green[6] | Timothy Pruett[7] | Michael A. Nalesnik[8] | Susan M. Tlusty[3] | Amber R. Wilk[2] | Cameron R. Wolfe[9] | Marian G. Michaels[4]

- The Organ Procurement and Transplantation Network (OPTN) created The Disease Transmission Advisory Committee (DTAC) to review and classify reports of potential disease transmission to inform national policy and improve patient safety.
- January 1, 2008 to December 31, 2017, DTAC received 2185 reports
  - 335 (15%) classified as a proven/ probable donor transmission event
- ~2/3 infection, ~1/3 malignancy
- **Overall risk 17.8/10,000 or 0.178%**
- **All types of infections (!)**
- **Note: initial trigger is transplant center reporting to local organ bank (you!)**

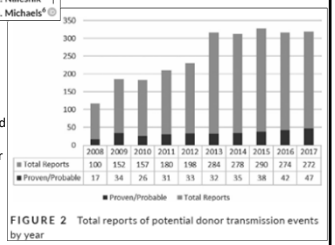
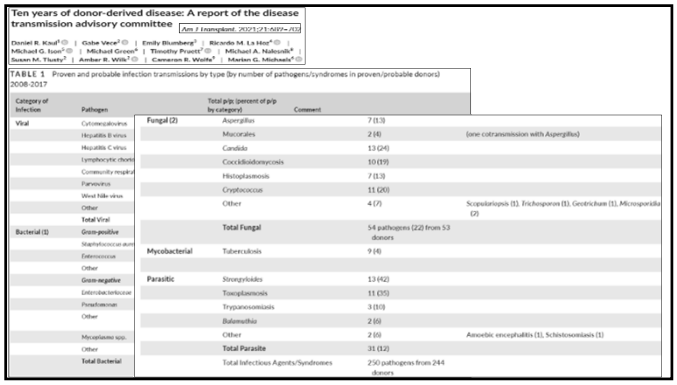


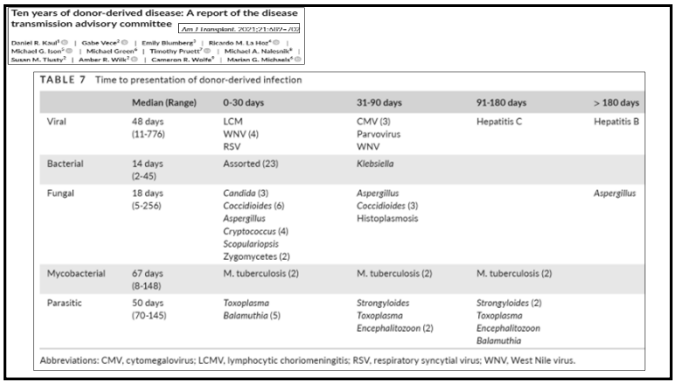
FIGURE 2 Total reports of potential donor transmission events by year


Ten years of donor-derived disease: A report of the disease transmission advisory committee

Am J Transplant. 2021;21:497–513

TABLE 1 Proven and probable infection transmissions by type (by number of pathogens/syndromes in proven/probable donors) 2008-2017

Category of infection	Pathogen		Total p/p (percent of p/p by category)	Comment
Viral	Cytomegalovirus			
	Hepatitis B virus			
	Hepatitis C virus			
	Lymphocytic choriomeningitis virus			
	Community respiratory virus			
	Parvovirus			
	West Nile virus			
	Other			
	Total Viral			
Bacterial (1)	*Gram-positive*			
	Staphylococcus aureus			
	Enterococcus			
	Other			
	Gram-negative			
	Enterobacteriaceae			
	Pseudomonas			
	Other			
	Mycoplasma spp.			
	Other			
	Total Bacterial			
		Fungal (2)	Aspergillus	7 (13)	
			Mucorales	2 (4)	(one cotransmission with *Aspergillus*)
			Candida	13 (24)	
			Coccidioidomycosis	10 (19)	
			Histoplasmosis	7 (13)	
			Cryptococcus	11 (20)	
			Other	4 (7)	Scopulariopsis (1), *Trichosporon* (1), Geotrichum (1), Microsporidia (2)
			Total Fungal	54 pathogens (22) from 53 donors	
		Mycobacterial	Tuberculosis	9 (4)	
		Parasitic	*Strongyloides*	13 (42)	
			Toxoplasmosis	11 (35)	
			Trypanosomiasis	3 (10)	
			Balamuthia	2 (6)	
			Other	2 (6)	Amoebic encephalitis (1), Schistosomiasis (1)
			Total Parasite	31 (12)	
			Total Infectious Agents/Syndromes	250 pathogens from 244 donors	


Ten years of donor-derived disease: A report of the disease transmission advisory committee

Am J Transplant. 2021;21:497–513

TABLE 7 Time to presentation of donor-derived infection

	Median (Range)	0-30 days	31-90 days	91-180 days	> 180 days
Viral	48 days (11-776)	LCM WNV (4) RSV	CMV (3) Parvovirus WNV	Hepatitis C	Hepatitis B
Bacterial	14 days (2-45)	Assorted (23)	*Klebsiella*		
Fungal	18 days (5-256)	*Candida* (3) *Coccidioides* (6) *Aspergillus* *Cryptococcus* (4) *Scopulariopsis* Zygomycetes (2)	*Aspergillus* *Coccidioides* (3) Histoplasmosis		*Aspergillus*
Mycobacterial	67 days (8-148)	M. tuberculosis (2)	M. tuberculosis (2)	M. tuberculosis (2)	
Parasitic	50 days (70-145)	*Toxoplasma* *Balamuthia* (5)	*Strongyloides* *Toxoplasma* *Encephalitozoon* (2)	*Strongyloides* (2) *Toxoplasma* *Encephalitozoon* *Balamuthia*	

Abbreviations: CMV, cytomegalovirus; LCMV, lymphocytic choriomeningitis; RSV, respiratory syncytial virus; WNV, West Nile virus.

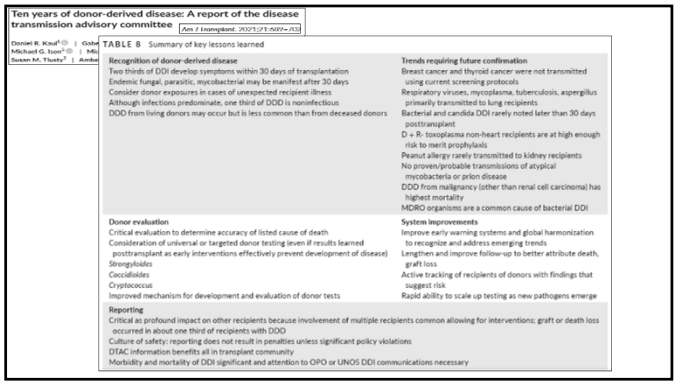

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TABLE 8 Summary of key lessons learned

Recognition of donor-derived disease
- Two thirds of DDI develop symptoms within 30 days of transplantation
- Endemic fungal, parasitic, mycobacterial may be manifest after 30 days
- Consider donor exposures in cases of unexpected recipient illness
- Although infections predominate, one third of DDD is noninfectious
- DDD from living donors may occur but is less common than from deceased donors

Trends requiring future confirmation
- Breast cancer and thyroid cancer were not transmitted using current screening protocols
- Respiratory viruses, mycoplasma, tuberculosis, aspergillus primarily transmitted to lung recipients
- Bacterial and candida DDI rarely noted later than 30 days posttransplant
- D + R- toxoplasma non-heart recipients are at high enough risk to merit prophylaxis
- Peanut allergy rarely transmitted to kidney recipients
- No proven/probable transmissions of atypical mycobacteria or prion disease
- DDD from malignancy (other than renal cell carcinoma) has highest mortality
- MDRO organisms are a common cause of bacterial DDI

Donor evaluation
- Critical evaluation to determine accuracy of listed cause of death
- Consideration of universal or targeted donor testing (even if results learned posttransplant as early interventions effectively prevent development of disease)
  - *Strongyloides*
  - *Coccidioides*
  - *Cryptococcus*
- Improved mechanism for development and evaluation of donor tests

System improvements
- Improve early warning systems and global harmonization to recognize and address emerging trends
- Lengthen and improve follow-up to better attribute death, graft loss
- Active tracking of recipients of donors with findings that suggest risk
- Rapid ability to scale up testing as new pathogens emerge

Reporting
- Critical as profound impact on other recipients because involvement of multiple recipients common allowing for interventions; graft or death loss occurred in about one third of recipients with DDD
- Culture of safety: reporting does not result in penalties unless significant policy violations
- DTAC information benefits all in transplant community
- Morbidity and mortality of DDI significant and attention to OPO or UNOS DDI communications necessary

Syndromes

CMV: the most common pathogen after transplant, one of the "*great masqueraders*"

- Asymptomatic viremia**
- CMV syndrome
- End organ disease:
  - Colitis
  - Pneumonitis
  - Retinitis
- Best diagnosed by CMV viral load
- Best treated with valganciclovir or ganciclovir IV
- Treat to resolution of infection and/or viral load – check weekly
- If low absolute lymphocyte count at end, consider secondary prophylaxis or monitoring

Pathogens Contribute to Infection Risk: Indirect Effects of CMV

General indirect effects–elevated risks
- Bacterial, fungal, viral infections
- Post-transplant lymphoma (PTLD)
- Cardiovascular events
- New-onset diabetes mellitus after transplantation
- Immunosenescence
- Acute rejection
- Mortality

Transplant-specific indirect effects
- Chronic allograft nephropathy and/or allograft loss after renal transplant
- Accelerated hepatitis C recurrence after liver transplant
- Hepatic artery thrombosis after liver transplant
- Allograft vasculopathy after cardiac transplant
- Bronchiolitis obliterans after lung transplant

Kotton, CMV: Prevention, Diagnosis and Therapy, AJT 2013

Management of mild to moderate CMV infection-I

Who to treat

If Donor positive/recipient seronegative (highest risk group), likely need to treat if CMV viral load > 500 IU/ml (start at lower level if very low lymphocyte count or potent immunosuppression)

If recipient seropositive, likely need to treat if CMV viral load > 1500 - 2000 IU/ml (start at lower level if very low lymphocyte count or potent immunosuppression)

If not starting treatment, recheck all a week later – follow closely to see if better or worse

Diagnostically

Check weekly CMV DNAemia (i.e. CMV viral load) on plasma (not whole blood); **trend until there are two negative/very low (<300 IU/ml) results**, then stop therapy; consider weekly monitoring after the end of treatment for 8-12 weeks so as to capture early recurrent disease (especially in high risk D+R- patients, or with higher immunosuppression).

Best to check CMV DNAemia with same specimen type, on same testing platform and at same lab, as whole blood can be +/- 10x higher (extremely variable) result c/w plasma and test results can vary significantly across different labs and testing platforms; best to pick one lab and use that for comparison.

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 some increase in the CMV viral load.

Consider checking total IgG level at the time of initiation of treatment. We would replete if the total IgG level was less than 400 with either CMV immunoglobulin or IVIG.

Management of mild to moderate CMV infection-II

Therapeutically

Start **valganciclovir** 900mg po q12 hours, renally adjusted as needed

Note: would use intravenous therapy if severe, ophthalmologic, refractory/resistant, or life-threatening disease. Consider using intravenous therapy with significant colitis with concern for malabsorption, or if viral load >100,000 IU/ml.

Consider lowering immunosuppression

If total IgG < 400, consider giving either CMV Ig 150mg/kg or IVIG (especially if severe or resistant disease)

References

Kotton CN, Kumar D, Caliendo AM, Huprikar S, Chou S, Danziger-Isakov L, Humar A; The Third International Consensus Guidelines on the Management of Cytomegalovirus in Solid Organ Transplantation. Transplantation Society International CMV Consensus Group*.Transplantation. 2018 Mar 29.

Are We There Yet? Impact of the First International Standard for Cytomegalovirus DNA on the Harmonization of Results Reported on Plasma Samples. Preiksaitis JK et al, Clin Infect Dis. 2016 Sep 1;63(5):583-9. doi: 10.1093/cid/ciw370.

Treatment of CMV: Massachusetts General Hospital

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

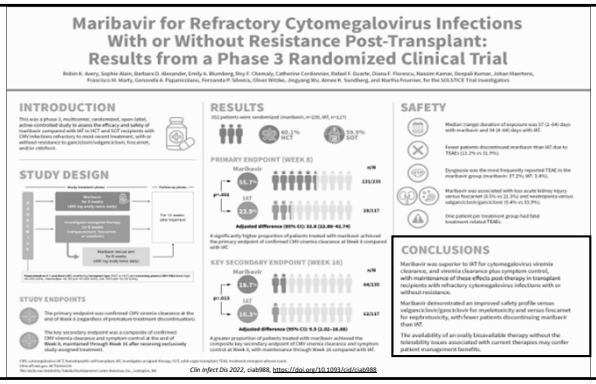
Check weekly CMV DNAemia (i.e. CMV viral load) on plasma (vs whole blood).
Trend weekly until there are one-two negative/very low (<200 IU/ml) results, then stop therapy.

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.)

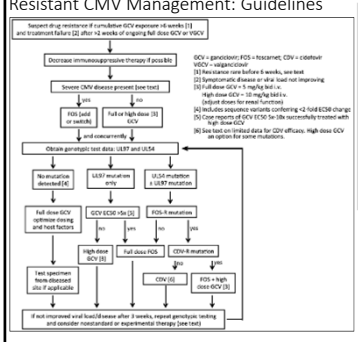
Consider weekly monitoring after the end of treatment for 8-12 weeks so as to capture early recurrent disease vs restarting prophylaxis (especially in high risk D+R- patients, or with higher immunosuppression).

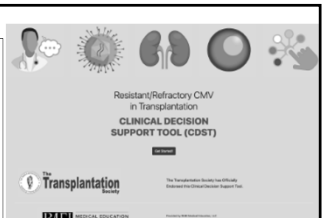
What to do with very low viral load cases? (<500-1000 IU/ml plasma or whole blood)

- *Treatment not always indicated*
- *With very low viral loads, I think about:*
  - *Risk factors for severe viral infection (D+R- versus R+)*
  - *Net state of immunosuppression*
  - *Absolute lymphocyte count*
  - *Likelihood of major disease flare with waiting*
  - *Ability to reliably repeat testing*
- *Important to understand issues with diagnostics at very low results*
- ***Retesting in a week** is key so you know which infection trend*
- *Approaches vary widely among clinicians; need to formalize guidance*



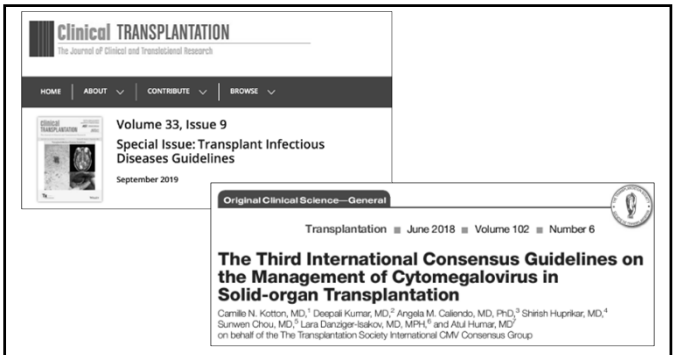
Resistant CMV Management: Guidelines





www.CDSTforCMV.com
Leads to
https://via.juxlyapps.com/pathway/archemedx/cmvsot-cdst/index.html#/disease-selection

Kotton CN, et al. *Transplantation*. 2018;102(6):900-931.



https://onlinelibrary.wiley.com/toc/13990012/2019/33/9

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The Dreaded Pulmonary Nodule

For the boards (and clinical medicine), consider the prophylaxis and what's not covered

Let the prophylaxis and epidemiology drive your differential diagnosis

Who gets fungal infections?

- Post-solid organ transplant: Incidence of invasive fungal infections in the first year has been reported to be 3%[1]
  - Candidiasis (sterile space), esp liver transplant*[surgery]
  - Cryptococcal disease
    - Among most common causes of meningitis
  - Invasive aspergillosis in 1-15%[2]
    - Accounts for significant % of deaths in first year
    - Mortality dropping in recent times, however
  - Mucormycosis less common, higher mortality
- Stem cell transplant: similar, longer risk if graft-vs-host disease
- Non-transplant immunocompromised hosts: less frequent/"net state of immunosuppression"

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1 Shoham S, Marr K. Invasive fungal infections in solid organ transplant recipients. Future Microbio 2012; 7(5): 639-655
2 Singh N, Husain S, Aspergillosis in Solid Organ Transplantation, AJT, 2013

Diagnostics

- Culture
  - Fungal stain and culture
  - Notify lab not to mince specimen if suspicion of mucormycosis
  - Fungal isolators (blood) very rarely +
    - *Candida* will grow in routine cultures
    - *Histoplasma* better; lysis centrifugation isolators is best
- Pathology: Morphology
  - Septate (*Aspergillus*) vs non-septate (*Mucor/Zygomycetes*) hyphae
  - Grocott-Gomori's (or Gömöri) methenamine silver stain
  - Periodic acid-Schiff (PAS)

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Diagnostics: Fungal Markers

Diagnostic Assay	Specimen	Comments
Cryptococcal antigen	Blood, CSF	High sensitivity/specificity
1,3 beta – D - glucan	Blood	Primarily for yeast; Low sensitivity/moderate specificity *Excellent for Pneumocystis*
Galactomannan	Blood, BAL, other body fluids	Primarily for Aspergillus; Low sensitivity/high specificity on blood, higher sensitivity on body fluids
Aspergillus PCR	Blood, BAL, other body fluids	

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Clinical Vignette

- 54 yo woman with history of primary systemic AL amyloidosis, complicated by cardiac amyloidosis, treated cytoxan/bortezomib/dexamethasone initially, followed by lenalidomide/dexamethasone
- Orthotopic cardiac transplant Feb 2016
- Autologous stem cell transplant, Day 0=7/11/16.
- CMV DNA VL on Day 0 was 29,800 IU/ml.
- Neutropenic sepsis with a blood culture on Day 5 with *Strep salivarius*.
- Ongoing fevers, new 2 cm pulmonary nodule by CT on Day 18

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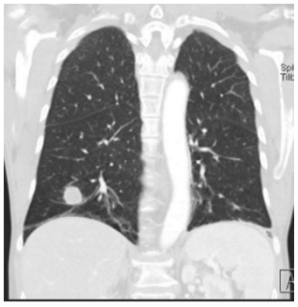
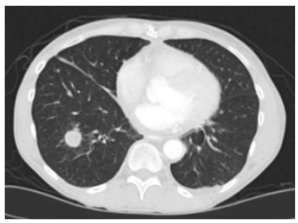

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After ordering bronchoscopy, next best step?

- Start voriconazole
- Start posaconazole or isavuconazole
- Start amphotericin B product
- Start echinocandin (caspofungin/micafungin/anidulafungin)
- Combination therapy

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- Combination therapy

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- "She has had a dry cough but denies any sputum production, chest pain, SOB or headache. She has felt very well, and was quite determined to be discharged in the next few days."
- Voriconazole started
- She was underwent bronchoscopy, radial EBUS, washings, brushings and transbronchial biopsy → **nonseptate hyphae seen**
- **Diagnosis: likely Zygomycetes**
- She was switched from voriconazole to dual antifungal therapy with loading of isavuconazole and Ambisome.
- Repeat CT scan performed 2 days later showed significant increase in size of the nodule with new satellite lesions. She proceeded to RLL resection that evening by the cardiothoracic surgeons.

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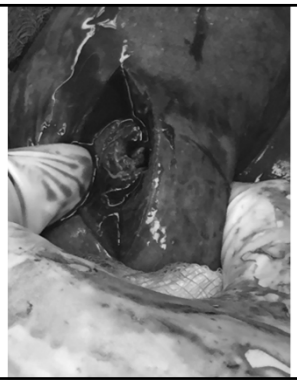

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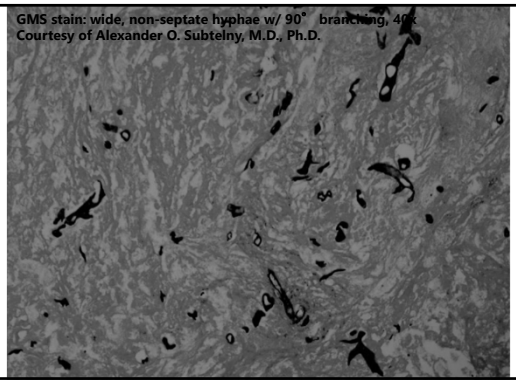

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Very Rare RHIZOPUS SPECIES

SUSCEPTIBILITY Performed at UNIVERSITY OF TEXAS HEALTH SCIENCE CENTER, Dept of Pathology, San Antonio, TX

MIC DILUTION METHOD

No CLSI interpretive guidelines available

Amphotericin B	MIC=1
Isavuconazole	MIC=1
Miconazole	MIC=2
Posaconazole	MIC=0.5

In view of this, Ambisome was stopped on POD #9 and isavuconazole converted to 372mg daily for months/indefinite, plan is for radiographic resolution, immune reconstitution (heart transplant immunosuppression is for life).

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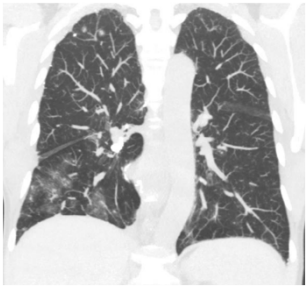

A year after transplant, she presented with disseminated zoster, new patchy infiltrates. Responded well to IV acyclovir.

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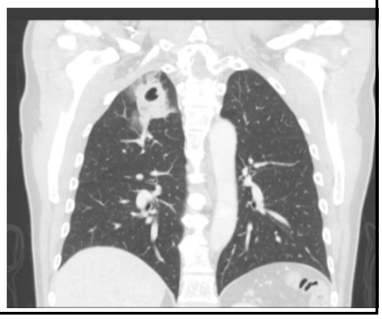
What's This?

- Man in 50s diagnosed with multiple myeloma in 2011 → autologous stem cell transplant in March 2019.
- Due to disease progression in June 2020, he was treated with daratumumab and pomalidomide. He received radiation therapy to the thoracic and cervical spine.
- He consented to participate in a clinical trial protocol and underwent CAR infusion in January 2021. On fluconazole and acyclovir prophylaxis.
- Routine screening PET 4 months later "new thick walled multiloculated cavitary lesion in the right upper lobe with surrounding groundglass and clustered nodularity is concerning for infection, including bacterial as well as atypical and fungal infections in an immunocompromised patient". No symptoms at all



Epidemiology (ID fellow note)

- Living situation - lives with wife, 3 kids
- Outdoor exposures - rare, walks outside with dog in rode, has stopped dirt biking/hiking with thrombocytopenia
- Occupational exposures - Denies, works as a contractor for DoD, currently working at home
- Hobbies - mostly spending time at home right now
- Travel - Frequent travel pre-pandemic for work, has been to Australia, multiple countries in Asia and Europe, never to Africa or South America
- TB – no history of TB or known TB exposures; homeless or incarcerated? Denies
- Animals - Dog
- Food - raw or unpasteurized foods? Denies
- Dental work - None recent, does have a wisdom tooth pressing on a facial nerve
- Smoking - Denies
- Alcohol - Denies
- Recreational drugs - Denies
- Sex and prior STIs- Denies

What would you do next?

A. Start voriconazole, loading dose then maintenance based on weight
B. Start "vancopime" (cefepime plus vancomycin)
C. Start azithromycin
D. A-C (all of the above)
E. Bronchoscopy

Pseudomonas!

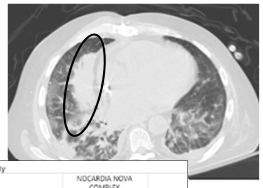
All other studies negative:

- BAL mycobacterial, fungal stains/cultures
- Cryptococcal antigen (blood)
- 1,3 beta D glucan (blood)
- Galactomannan (BAL and blood)
- Pathology: Bronchial epithelium with rare scattered neutrophils. Alveolated lung with fibroinflammatory changes and chronic inflammation. There is no evidence of malignancy. No microorganisms are seen on Brown-Hopps, GMS, Steiner, PAS-D, FITE, and AFB stains. Immunohistochemical stains for CMV, HSV, VZV, and adenovirus are negative. Trichrome and elastic stains were examined. The histologic findings are compatible with acute infection.

04/19/2021 1657	04/29/2021 1323	Wound culture/smear [818905205] (Abnormal) Other from Biopsy RUL LUNG TBBX	
Susceptibility			
		Pseudomonas aeruginosa MIC METHOD	
Amikacin		<=2	Susceptible
Cefepime		2	Susceptible
Ceftazidime		2	Susceptible
Ciprofloxacin		<=0.25	Susceptible
Levofloxacin		1	Susceptible
Meropenem		<=0.25	Susceptible
Piperacillin-tazobactam		<=4	Susceptible
Tobramycin		<=1	Susceptible

Pneumonia

- 45yo s/p heart transplant 3 months earlier on posaconazole, atovaquone prophylaxis (not on TMP-SMX due to renal failure)
- New pneumonia, right middle lobe
- What is the cause?



Susceptibility

	NOCARDIA NOVA COMPLEX MIC METHOD	
Comment	SEE NOTES	Note[1]
Amikacin		Susceptible
Amoxicillin + Clavulanate		Resistant
Ceftriaxone		Susceptible
Ciprofloxacin		Resistant
Clarithromycin		Susceptible
Doxycycline		Intermediate
Imipenem		Susceptible
Linezolid		Susceptible
Minocycline		Susceptible
Moxifloxacin		Resistant
Tobramycin		Resistant
Trimethoprim/sulfamethoxazole		Susceptible

[1] SUSCEPTIBILITY TESTING Performed at the University of Texas Health Center at Tyler, Tyler TX

Let's Switch to Parasites

Clinical Vignette

64yo man from Dominican Republic with end-stage liver disease, chronic abdominal pain, listed for liver transplant

- Eosinophilia (up to 70%) x 6 months
- Recurrent enteric Gram negative rod bacteremias
- Fluffy pulmonary infiltrates
- What does he have?

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Test Results

Strongyloides Antibody by ELISA: 100.00

INTERPRETATION: POSITIVE

All reactions of <=1.7 units/ml should be considered NEGATIVE.

All reactions >1.7 units/ml should be considered POSITIVE, indicative of infection with *Strongyloides stercoralis* at some indeterminate time.

Sensitivity of the test is 93% and specificity is 98%.

Centers for Disease Control testing

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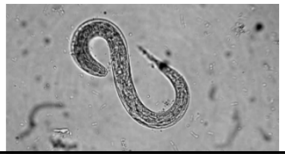
Strongyloides

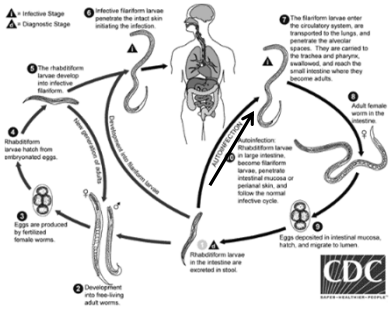
- Nematode "roundworm"
- 100-200 million people worldwide are infected
- Autoinfection*
- >50% mortality immunocompromised patients with disseminated disease



The countries highlighted in **yellow** have sporadic endemicity, on the range of 1-3%. Those that are **orange** are endemic, while those that are **red** are generally hyperendemic, with the highest frequency of *Strongyloides* infection.

http://web.stanford.edu/group/parasites/ParaSites2006/Strongylodiasis/epidemiology.html

Strongyloides stercoralis lifecycle



http://www.cdc.gov/dpdx/strongyloidiasis/

Diagnostics stewardship

MASSACHUSETTS GENERAL HOSPITAL TRANSPLANT CENTER

Consider best methods to achieve most likely diagnosis; Hickam's dictum* vs Occam's razor

The initial work up can be protocol driven

- **We have syndromic evaluations in the emergency room**

Molecular diagnostics are superior but require us to be specific in our requests

- **Multiplex (i.e. Biofire) helps**

Non-invasive fungal diagnostics have been disappointing

- **1,3 beta D glucan, galactomannan (still love cryptococcal antigen!)**
- **serum *Mucorales* polymerase chain reaction is emerging**

New technologies (i.e. cell free DNA testing) are emerging/interesting

The sooner we achieve a diagnosis, the sooner we can stop broad-spectrum antimicrobials & better outcomes for the patient

* Hickam's dictum is usually stated as "patients can have as many diseases as they damn (or darn) well please". This aphorism has been attributed to John Hickam (1914-1970) an American physician, who was Chair of the Department of Medicine at the University of Indiana

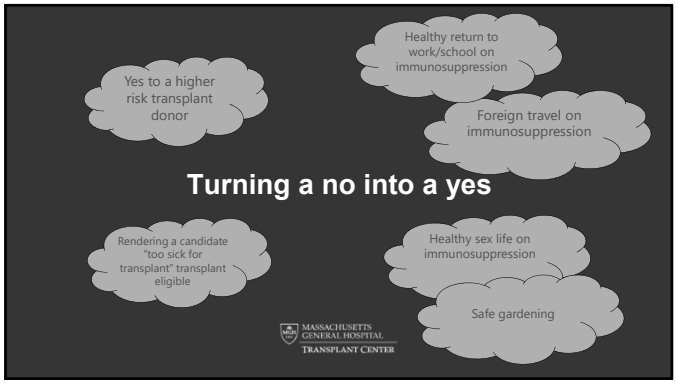
HARVARD MEDICAL SCHOOL TEACHING HOSPITAL

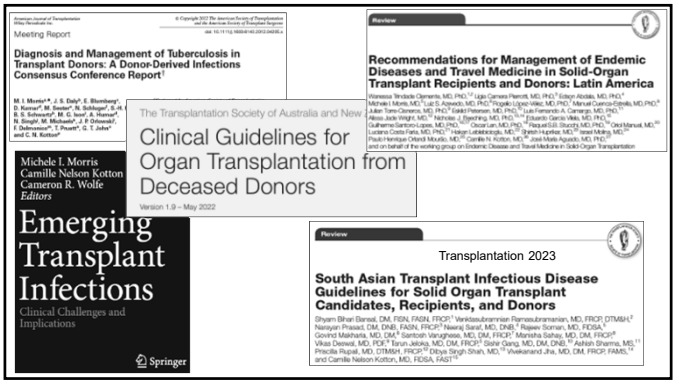
Rapid Diagnosis of Disseminated Tuberculosis Using Cell-Free DNA Sequencing in a Kidney Transplant Recipient, Transplantation 2023
Anna Apostolopoulou & Camille Nelson Kotton

- Middle aged kidney transplant recipient presented with fevers
- Extensive workup done
- "**On hospital day 13, while she remained febrile and without a definitive diagnosis, we sent a quantitative cfDNA test (Karius, Inc., Redwood City, CA). On HD 15, the Karius cfDNA test returned positive for M tuberculosis.**
- Subsequently, the mycobacterial blood, urine, and bronchoalveolar lavage cultures grew M tuberculosis on hospital days 17, 17, and 21, respectively). Bone cultures grew M tuberculosis 34 days after biopsy (after discharged from the hospital)."

Drug Interactions: Transplant & Antimicrobials

- Azoles
  - Voriconazole, posaconazole > fluconazole
  - Isavuconazole – much less interaction
  - Increase tacrolimus (or cyclosporine, rapamycin)
- Rifamycins
  - Rifabutin < rifampin (=rifampicin)
  - Decrease tacrolimus (or cyclosporine, rapamycin)
  - Increase prednisone
- QT prolongation
  - Combination effect
  - May be present with liver disease
- Recommended: Use of on-line drug interaction calculator





Cardinal Rules 2023: Immunosuppression and Infection

1. Immunosuppression and infections not always straightforward
2. Be prepared to be surprised – think broadly
3. Prepare patient before immunosuppression – role for ID specialists
4. Prophylaxis & vaccines alter the risk equation
   Primary and secondary prevention
5. Consider the source of infection: donor, recipient, blood products, geographic, more antibiotic resistance

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Questions? ckotton@mgh.Harvard.edu

@KottonNelson (Twitter)

MASSACHUSETTS GENERAL HOSPITAL
TRANSPLANT CENTER

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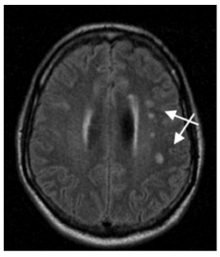
Meningoencephalitis after OLT

- 45yo man moved back home to Boston, cirrhosis/end stage liver disease
- 6 weeks after liver transplant, fevers, headache, seizure
- CSF glucose <20, protein 180, WBC 250 lymph predominant
- Started mycobacterial, fungal coverage



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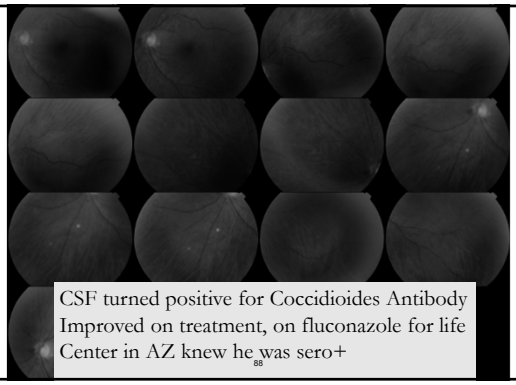

CSF turned positive for Coccidioides Antibody
Improved on treatment, on fluconazole for life
Center in AZ knew he was sero+

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Lip Lesion in a Solid Organ Transplant Recipient

Nicole Theodoropoulos and Michael Angarone

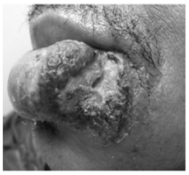


Figure 1. Photograph of lower lip ulcerated lesion at initial presentation.

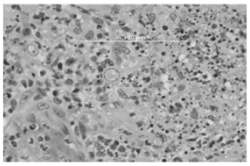


Figure 2. Histopathology of section through lip lesion tissue (hematoxylin-eosin, high-power magnification).

Clinical Infectious Diseases 2012;54(5):1332

COVID-19 and Immunocompromised Hosts

CORRESPONDENCE

Infectious medicine virology

Severe clinical relapse in an immunocompromised host with persistent SARS-CoV-2 infection

Philipp A. Reuken · Andreas Stallmach · Mathias W. Pletz · Christian Brandt · Sabine Hahnfeld · Bettina Löffler · Sabine Baumgart · Thomas Kamradt · Michael

Best treatments?
Role of immunomodulatory therapies?
Best management of immunosuppression?
Optimizing vaccination strategies?

The NEW ENGLAND JOURNAL of MEDICINE

CORRESPONDENCE

Persistence and Evolution of SARS-CoV-2 in an Immunocompromised Host

Clinical Infectious Diseases

MAJOR ARTICLE

IDSA hivma

Coronavirus Disease 2019 in Solid Organ Transplant: A Multicenter Cohort Study

Olivia S. Kates, Kassem Safa, Mayur S. Ramesh, Rachel Friedman-Moraco, Sameep Sehgal, Erika D. Lease, Cynthia E. Fisher, and Ajit P. Limaye, for the UW COVID-19 SOT Study Team

Donor-Derived Infections

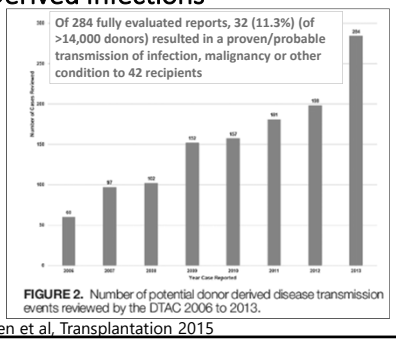


FIGURE 2. Number of potential donor derived disease transmission events reviewed by the DTAC 2006 to 2013.

Green et al, Transplantation 2015

TABLE 2.
Summary of bacteria-associated PDDTE reports to the OPTN Ad Hoc disease transmission advisory committee in 2013

Organism	No. donors reported	No. proven/ probable donors	No. recipients with proven/probable transmission	No. related deaths
Other bacteria	29	4	4	0
Mycobacterium	19	0	0	0
E. coli	3	1	1	0
Enterobaser cl	3	1	1	0
Enterococcus	4	1	1	0
MRSA	10	2	3	1
Streptococcus	5	0	0	0
Staphylococcus	22	1	1	0
Klebsiella	4	1	1	0
Total	99	11	12	1

TABLE 4.
Summary of fungus, parasite, and nonmalignancy/ noninfection–associated PDDTE reports to the OPTN Ad Hoc disease transmission advisory committee in 2013

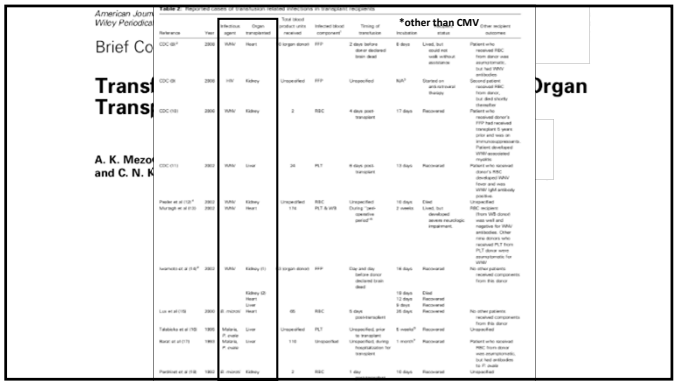
Organism	No. donors reported	No. proven/ probable donors	No. recipients with proven/ probable transmission	No. related deaths
Strongyloides/*T. cruzi*	5	1	1	1
Coccidioides	4	0	0	0
Aspergillus	3	2	2	1
Candida	10	1	1	0
Cryptococcus	6	0	0	0
Histoplasmosis	5	0	0	0
Other fungus	9	1	1	0
Nonmalignancy/ noninfection	16	3	4	1
Total	58	8	9	3

TABLE 3.
Summary of virus-associated PDDTE reports to the OPTN Ad Hoc disease transmission advisory committee In 2013

Organism	No. donors reported	No. proven/ probable donors	No. recipients with proven/probable transmission	No. related deaths
HBV	12	2	2	0
HCV	11	0	0	0
Adenovirus	4	1	1	0
Community respiratory virus	6	1	2	0
CMV	6	2	4	0
HSV	2	0	0	0
West Nile Virus	10	1	3	0
Other viral	11	1	1	1
Total	62	8	13	1

HCV, hepatitis C virus; HBV, hepatitis B virus.

Green et al, Transplantation 2015



Testing for HBV Infection

- Testing for HBV infection (consisting of testing for HBV surface antigen, HBV surface antibody, and HBV core IgG antibody) is recommended for the following persons:
  - persons born in countries of high and intermediate HBV endemicity (HBsAg prevalence ≥2%);
  - U.S.-born persons not vaccinated as infants whose parents were born in countries with high HBV endemicity (≥8%);
  - persons needing immunosuppressive therapy, including chemotherapy, immunosuppression related to organ transplantation, and immunosuppression for rheumatologic or gastroenterologic disorders; donors of blood, plasma, organs, tissues, or semen.

Prevention of Hepatitis B Virus Infection in the United States: Recommendations of the Advisory Committee on Immunization Practices, MMWR Jan 2018

HBV Levels of Risk –UpToDate

- **Very high risk** — Patients are at very high risk of reactivation (>20 percent risk of reactivation) if they are **HBsAg positive** and are going to receive anti-CD20 therapy (ie, rituximab, ofatumumab, obinutuzumab) or undergo hematopoietic cell transplantation.
- **High risk** — Patients are considered at high risk for reactivation (11 to 20 percent risk of reactivation) if they are **HBsAg positive** and are going to receive high-dose glucocorticoids (eg, ≥20 mg/day for at least four weeks) or the anti-CD52 agent, alemtuzumab.

Antiviral therapy ⬆

- **Moderate risk** — **HBsAg-positive** individuals are at moderate risk of reactivation (1 to 10 percent) if they are going to receive any of the following: cytotoxic chemotherapy **without** glucocorticoids; anti-TNF therapy; or anti-rejection therapy for solid organ transplants.
- Patients who are HBsAg negative and **anti-HBc positive** are at moderate risk for reactivation if they are going to receive anti-CD20 therapy or undergo hematopoietic cell transplantation.

- **Low risk** — **HBsAg-positive** individuals are at low risk (<1 percent) for reactivation if they receive methotrexate or azathioprine. HBsAg-negative and **anti-HBc-positive** individuals are at low risk if they receive high-dose glucocorticoids (eg, ≥20 mg/day) or the anti-CD52 agent alemtuzumab.
- **Very low risk** — HBV reactivation occurs rarely in HBsAg-negative and **anti-HBc-positive** patients receiving the following: cytotoxic chemotherapy without glucocorticoids, anti-TNF therapy, methotrexate, or azathioprine.

Feb 2021

HBV Prevention Based on Levels of Risk -UpToDate

- "**Moderate to very high risk** – We recommend that antiviral therapy be administered concurrently or prior to initiating immunosuppressive therapy to patients who are at moderate to very high risk of HBV reactivation. In such patients, we prefer preventive therapy, rather than waiting for evidence of reactivation, since studies in this population have demonstrated that antiviral therapy started after the onset of reactivation may not prevent a flare."
  - Entecavir, tenofovir (not lamivudine)
- "**Low risk or very low risk** — Among those at low risk or very low risk of reactivation, we perform frequent monitoring so that HBV reactivation can be detected early in its course and appropriate therapy can be initiated."

Feb 2021

Clinical Vignette

- 70yo man from Syria needs moderate immunosuppression… what do you think?

	10/31/2011 1245	10/6/2011 1130	9/21/2010 1133
HEPATITIS			
HBV Core Ab(s)		**Positive ***	
HBV Core Ab, IgM	**Negative ***		**Negative ***
HBV e Ab	**Positive ***		
HBV e Ag	**Negative ***		
HBV Surface Ab		**<5.0 ***	**<5.0 ***
HBV Surface Ag		**Negative**	**Negative**
HBV DNA (IU/mL)	**see comment ***		
HCV Ab		**Non Reactive**	**Non Reactive**

Clinical Vignette

70yo man originally from Syria needs moderate immunosuppression… what do you think?

	10/31/2011 1245	10/6/2011 1130	9/21/2010 1133
HEPATITIS			
HBV Core Ab(s)		**Positive ***	
HBV Core Ab, IgM	**Negative ***		**Negative ***
HBV e Ab	**Positive ***		
HBV e Ag	**Negative ***		
HBV Surface Ab		**<5.0 ***	**<5.0 ***
HBV Surface Ag		**Negative**	**Negative**
HBV DNA (IU/mL)	**see comment ***		
HCV Ab		**Non Reactive**	**Non Reactive**

Approach to EBV monitoring

- Only routinely indicated in EBV seronegative recipients of a positive donor
- EBV monitoring post-transplant is done to assess risk for PTLD.
- Screening with EBV PCR periodically (every 1-3 months) for 1 year post-transplant
- If viral load is positive, monitor every month, and if >5,000 or if persistent, reduce IS and consult transplant ID.

Effect of immunosuppressive agents on vaccine immunogenicity

	Methotrexate	TNF alpha inhibitors	Anti-CD20 antibodies (eg, rituximab)	CTLA-4 inhibitors (eg, abatacept)	Janus kinase inhibitors (eg, tofacitinib)	Anti-IL-6 antibodies (eg, tocilizumab)
Pneumococcal vaccine	Decrease	Minimal effect	Substantial decrease	Decrease	Decrease	Minimal effect
Seasonal influenza vaccine	Probable decrease	Minimal effect	Substantial decrease	Decrease	Minimal effect	Minimal effect
Hepatitis B virus vaccine	Unknown	Decrease	Unknown	Unknown	Unknown	Unknown

For most patients with autoimmune inflammatory rheumatic disease using conventional synthetic disease-modifying antirheumatic drugs, most biologics, or glucocorticoids, vaccinations are expected to confer adequate protection, although the immune response to some vaccines may be blunted. The degree to which the immune response may be altered by these medications varies based on the specific immunosuppressive drug regimen, vaccines used, and other patient-specific factors. The effect of immunosuppressive agents on the immune responses to vaccines other than those listed above has not been well studied. Refer to the UpToDate text for additional detail.

TNF: tumor necrosis factor; CTLA: cytotoxic T lymphocyte antigen; IL: interleukin.

Data from:
1. Subesinghe S, Bechman K, Rutherford AI, et al. A systematic review and meta-analysis of antirheumatic drugs and vaccine immunogenicity in rheumatoid arthritis. J Rheumatol 2018; 45:733.
2. Friedman MA, Winthrop K. Vaccinations for rheumatoid arthritis. Curr Opin Rheumatol 2014; 26:330.

From **Immunizations in autoimmune inflammatory rheumatic disease in adults**
Authors:Camille N Kotton, MD, Kevin L Winthrop, MD, MPH

Vaccines: Timing

- Give early with chronic disease – optimizes immunogenicity
  - i.e. early renal disease, cirrhosis
- Don't give during intense immunosuppression – or consider repeating
  - Some data on lightening immunosuppression to optimize response – weigh risks/benefits of disease flare
- Aim to give ~2 weeks before next dose of rituximab
- Accelerate series when needed
  - i.e. Hepatitis B
- Live viral vaccines – need to suspend immunosuppression x 1 month, give vaccine, wait another month, restart immunosuppression
  - Not possible for many – disease flare risk too high
  - MMR, varicella

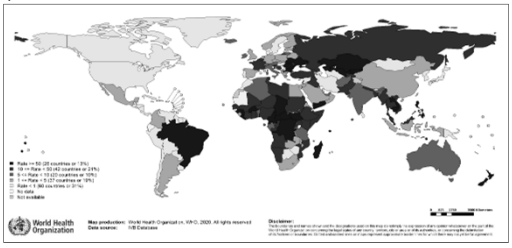
SHINGLES VACCINES

- Shingrix is currently the only shingles vaccine available in the USA
  - recombinant protein (not live!), strong adjuvant
- Minimal data on use after organ transplant; no CDC rec's
  - Check with your local transplant program
- "For patients actively receiving moderate- to high-dose immunosuppressive medications, neither the recombinant vaccine nor the live vaccine is recommended. (Kotton & Winthrop, Immunizations in Autoimmune Inflammatory Rheumatic Disease in Adults (UpToDate))
  - RZV is not strictly contraindicated, but its efficacy and safety have not been thoroughly evaluated. A single observational study evaluating >400 patents with inflammatory diseases using moderately immunosuppressive therapies who received RZV found that the risk of autoimmune disease flare was not increased with RZV use; three cases of Zoster were reported in the first year following vaccination"

Measles Incidence Rate per Million (12M period)

Top 10**		
Country	Cases	Rate/1M
Brazil	29135	137.18
DR Congo	25538	294.46
Philippines	9016	83.4
Nigeria	8294	41.27
India***	7009	5.12
Kazakhstan	6514	350.35
Bangladesh	6473	38.51
Uzbekistan	5201	158.53
Central African Republic	4914	1018.3
Madagascar	3465	126.48

Other countries with high incidence rates***		
Country	Cases	Rate
New Zealand	1910	398.55
Tonga	34	308.98
Seychelles	28	292.57
Samoa	47	236.29
Liberia	793	159.31
Chad	2505	158.4



- Notes: Based on data received 2020-08 and covering the period between 2019-07 and 2020-06

https://www.who.int/immunization/monitoring_surveillance/burden/vpd/surveillance_type/active/measles_monthlydata/en/

Measles/Mumps/Rubella (MMR) Vaccine

- Screen for evidence of protection (via infection or vaccine):
  - Document infection, receipt of 2 doses of vaccine, or check serology*
  - Most born pre-1957 are positive (natural disease), those born 1957-1980 at higher risk
- Imperative to give pre-transplant & > 1 month before immunosuppression; Immunocompromised hosts **should not receive the live viral measles/MMR** vaccine
  - Could potentially cause vaccine-related disease (i.e. encephalitis)
  - Family members should get vaccine if needed (protects family against disease)
- For non-immune immunocompromised hosts with true/high risk measles exposure, consider post-exposure prophylaxis (ASAP, but w/in 3-6 days):
  - Gamma globulin (~8 IM injxns, 0.5 mL/kg (max 15 mL); IVIG adequate protection (400 mg/kg)
  - No antiviral therapy available

"People with severely compromised immune systems who are exposed to measles should receive IVIG regardless of immunologic or vaccination status because they might not be protected by MMR vaccine." (CDC, https://www.cdc.gov/measles/hcp/index.html)

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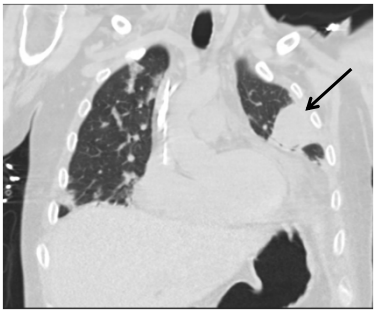
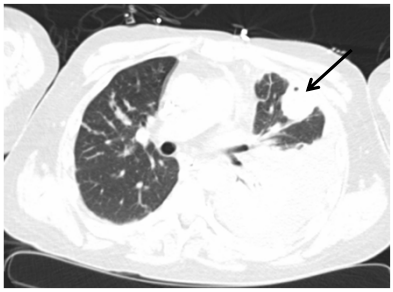
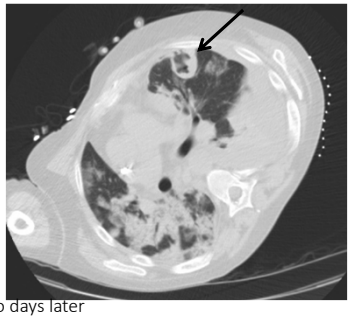
Clinical Vignette

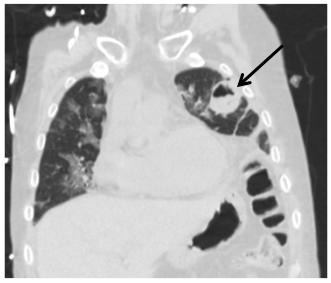
- 36yo male, Type I diabetes, 3 months after kidney/pancreas transplant (on prednisone 5 mg/day, mycophenolate mofetil (Cellcept) 1000mg twice a day, tacrolimus 4 mg twice a day)
- Transferred with three days of worsening left sided abdominal and flank pain
- Chest CT findings concerning for necrotizing pneumonia/cavitating lesion.
- On valganciclovir and TMP/SMX prophylaxis
- Exam: jaundiced, cachectic, dull breath sounds at left base, crackles both lungs







Two days later



Diagnostics

- Fungal markers all negative (blood)
  - 1,3 beta D glucan
  - Galactomannan antigen
  - Cryptococcal antigen
- Thoracentisis → exudate, chest tube placed
- Bronchoscopy, biopsy

What is the diagnosis?

A. *Aspergillus*
B. Mucormycosis
C. Necrotizing Gram negative
D. Mycobacterial (M. kansasii, etc)
E. *Nocardia*

Culture Data

LEFT EFFUSION/PLEURAL FLUID (and BAL)

Gram Stain –abundant polys, moderate red blood cells, few mononuclear cells, **no organisms seen**

Fluid Culture - **NOCARDIA NOVA COMPLEX, subspecies *veterana***

MIC DILUTION METHOD

Amikacin	Susceptible
Amoxicillin/Clavulanate	Susceptible **
Ceftriaxone	Intermediate
Ciprofloxacin	Resistant
Clarithromycin	**Susceptible**
Doxycycline	Resistant
Imipenem	**Susceptible**
Linezolid	Susceptible
Minocycline	Intermediate
Moxifloxacin	Resistant
Tobramycin	Resistant
Trimethoprim/Sulfa	**Susceptible**

Treatment

- Brain CT negative for metastatic infection
- Imipenem + azithromycin until radiographic improvement**
- Markedly improved in first few days (?chest tube placement)
- Doing well at 6 months, double treatment stopped
- Will need long term secondary prophylaxis with TMP/SMX

OL3

Acute Hepatitis

Dr. David Thomas

Online Only Lectures - Acute Hepatitis

Speaker: David Thomas, MD

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

Acute Hepatitis

David L. Thomas, MD
Stanhope Bayne Jones Professor of Medicine
Johns Hopkins University
Chief of Infectious Diseases
Johns Hopkins School of Medicine

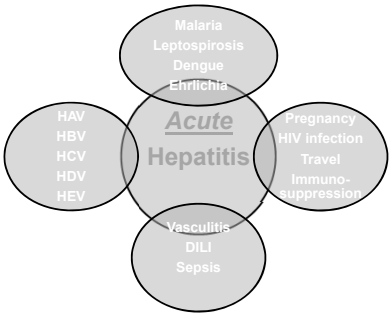
6/15/2023

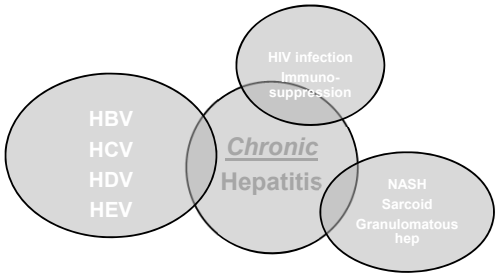
IDBR INFECTIOUS DISEASE BOARD REVIEW LIVE/VIRTUAL AUGUST 19-23 2023

Disclosures of Financial Relationships with Relevant Commercial Interests

Data and Safety Monitoring Board: Merck

Advisory Board: Merck, Evrys, and Excision Bio





18 year-old with jaundice

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

Courtesy E Prochaska, MD

18 year-old with jaundice, con't

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

Courtesy E Prochaska, MD

18 year old with jaundice

The cause of his illness is:

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

Courtesy E Prochaska, MD

18 year old with jaundice

The cause of his illness is:

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

Courtesy E Prochaska, MD

Leptospirosis

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

Leptospirosis

2. Bilirubin fold change > ALT

Leptospirosis

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

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

Leptospirosis

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

Acute Hepatitis in Uganda

- **42 year old female has malaise and RUQ pain; she just returned from 2 months working at an IDP camp in north Uganda. She endorses tick and other 'bug' bites and swam in the Nile. 1st HAV vaccine 2 days before departure. Prior HBV vaccine series.**
- **Exam shows no fever, vitals are normal. RUQ tender. Mild icteric. ALT 1245 IU/ml; Hb 13.4 g/dl; TB 3.2 mg/dl; WBC 3.2k nl differential.**

Acute hepatitis in Uganda

Which test result is most likely positive?

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

Acute hepatitis in Uganda

Which test result is most likely positive?

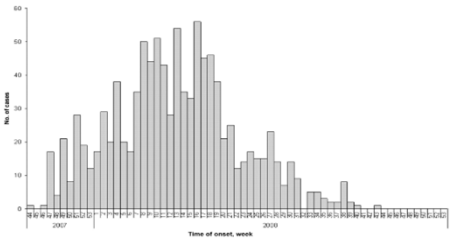
A. Ebola PCR
B. IgM anti-HEV
C. IgM anti-HAV
D. Schistosomiasis antigen in urine
E. 16S RNA for Rickettsial organism

1. Vaccination works vs immune globulin to prevent hepatitis A *up to 14d after* exposure

End Points	Per-Protocol Population		Modified Intention-to-Treat Population†	
	Vaccine Group (N=568)	Immune Globulin Group (N=522)	Vaccine Group (N=740)	Immune Globulin Group (N=674)
	number (percent)			
Clinical				
Primary				
Any symptom plus IgM-positive and ALT ≥ twice ULN	25 (4.4)	17 (3.3)	26 (3.5)	18 (2.7)
Secondary				
Any symptom plus IgM-positive and ALT ≥ twice ULN or HAV RNA–positive on PCR‡	29 (5.1)	19 (3.6)	30 (4.1)	20 (3.0)
Jaundice plus IgM-positive and ALT ≥ twice ULN or HAV RNA–positive on PCR	18 (3.2)	12 (2.3)	19 (2.6)	12 (1.8)

Victor NEJM 2007

2. There are HEV outbreaks, eg. North-Ugandan IDP Camp



Teshale CID 2010; Al-Shimari BMC Public Health 2023

3. Hepatitis E: Epidemiologic Clues

- **Outbreaks – contaminated water in Asia/Africa**
- **Sporadic - undercooked meat (BOAR, deer, etc)**
- **Overseas travel typical**
- **USA: endemic rare, genotype 3, IgG serology positive far more than can be explained by cases - can be hard to interpret**

4. Hepatitis E: Clinical Clues

- –Fatalities in pregnant women
- –Can be chronic in transplant (rarely in HIV)
- –GBS and neurologic manifestations (vs other hep viruses); pancreatitis
- –Diagnosis: RNA PCR; IgM anti-HEV
- –Treatment: ribavirin for chronic
- –Vaccine: not USA (not boards)

Acute Hepatitis at ID Week

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

Acute hepatitis at ID week

Fellow worried about?

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

Acute hepatitis at ID week

Fellow worried about?

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

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

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

Corey M. Peak,[1,2,3] Sarah S. Stous,[2] Jessica M. Healy,[4] Megan G. Hofmeister,[5] Yulin Liu,[5] Sumathi Ramachandran,[5] Monique A. Foster,[5] Annie Kao,[4] and Eric C. McDonald[6]

[1]Epidemic Intelligence Service, Centers for Disease Control and Prevention, Atlanta, Georgia; [2]County of San Diego Health and Human Services Agency; and [3]Division of Global Migration and Quarantine, Centers for Disease Control and Prevention, San Diego, California; and Divisions of [4]Foodborne, Waterborne, and Environmental Diseases, and [5]Viral Hepatitis, Centers for Disease Control and Prevention, Atlanta, Georgia

Morbidity and Mortality Weekly Report (*MMWR*)

CDC • MMWR

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

Weekly / September 22, 2017 / 66(37);999–1000

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

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

State	Case Count
Arkansas	3
California	3
Maryland	12
New York	5
North Carolina	4
Oregon	3
Virginia	109
West Virginia	2
Wisconsin	3
Grand Total	143

Case Count as of December 15, 2016

tropical CAFE

Outbreak of hepatitis A in Hawaii linked to raw scallops

Outbreak

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

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

2. Hepatitis A: Key Clinical Clues

- There are outbreaks all over the world
- The most common cause of acute hepatitis in USA
- Clinical syndrome
  - –fulminant on HCV
  - –relapsing: symptoms/jaundice recur <12 mo

3. Vaccination to Prevent Hepatitis A

- *Pre-exposure:* vaccinate
  - HOW: Inactivated vaccines USA (HAVRIX,VAQTA)(TWINRIX)
  - WHOM: HCV or HBV positive persons/chronic liver disease/homeless/MSM/PWID/Travelers/HIV pos/adoptee exposure
  - All children 1-18 yrs receive hepatitis A vaccine (since 2006)
- *Post-exposure:* vaccinate (and possibly IG)
  - Unless > 40 years or immunosuppressed then IG is 'preferred'
  - Close exposure (sex or IDU partner) not casual (eg office worker)

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

Acute Viral Hepatitis B Clues

- Most linked to sex, drugs, nosocomial
  - –Nosocomial (fingerstick devices, etc)
  - –Most transmissible (HBV>HCV>HIV)
- Clinical
  - –Acute immune complex disease possible
  - –Diagnose: IgM anti-core, HBsAg and HBV DNA
  - –New infection vs reactivation (both can be IgM pos)

More on HBV

- See lecture on chronic hepatitis for prevention, HIV coinfection, and treatment

Acute Viral Hepatitis Delta will be with HBV

- HDV
  - –HBV coinfection
    - Fulminant with acute HBV
  - –HBV superinfection
    - Acute hepatitis in someone with chronic HBV
  - –Test for HDV RNA (antibodies for routine screen)

Acute Viral Hepatitis C clues

- HCV
  - –IDU link (hepatitis in Appalachia)
  - –HIV pos MSM
  - –Acute RNA pos but AB neg or pos
  - –60-80% persist: more in men, HIV pos, African ancestry, INFL4 gene intact

Cox CID 2005

Hepatitis in a pilot

- 70 y/o pilot presents with 1 week of fever, diarrhea and sweats, then "collapses"
- Tooth extraction 1 month before, E. Shore of Maryland and extensive travel, chelation "treatment"
- T 38.1, 135/70, 85, 18, 97% on 2L; few small nodes, petechial rash on legs, neuro- WNL

Pilot Case History, con't

- Hct 33%, WBC 1.4 K (81% P 10% L), Plt 15,000
- Creat 2.8
- AST 495, ALT 159, Alk Phos 47, alb 2.6, TBR 0.8
- CPK 8477
- CXR: infiltrate LLL

Hepatitis in a pilot

What agent caused this illness?

A. Leptospira icterohaemorrhagiae
B. Hepatitis A
C. EBV
D. Ehrlichia chaffeensis
E. Hepatitis G (GB virus C)

Hepatitis in a pilot

What agent caused this illness?

A. Leptospira icterohaemorrhagiae
B. Hepatitis A
C. EBV
D. Ehrlichia chaffeensis
E. Hepatitis G (GB virus C)

Hepatitis with bacterial infections

1. Think Rickettsia/Ehrlichia with exposure, low PMN, modest ALT, and especially low platelets

Hepatitis with bacterial infections

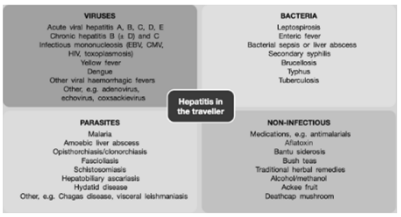
2. Coxiella burnetti and spirochetes (syphilis and lepto) also in ddx with liver, lung, renal, skin, CNS disease but tend to be cholestatic vs Rickettsia/Ehrlichia

Hepatitis with bacterial infections

3. Hepatitis F or G are always WRONG answers

Hepatitis with travel to developing country

There is a broad differential



Jones Medicine 2017

Hepatitis with travel

Especially remember dengue (below), Chickungunya, or Zika

Ref.	Patients	Raised AST	Raised ALT	AST > ALT	Hyper-bilirubinemia	> 10 fold rise (AST, ALT)
Kuo et al[37]	270	93.30%	82.20%	+	7.20%	11.1%, 7.4%
Souza et al[39]	1585	63.40%	45%	+	-	3.4%, 1.8%
Itha et al[41]	45	96%	96%	Equal	30%	-
Wong et al[40]	127	90.60%	71.70%	+ in 75.6%	13.4%	10.2%, 9.5%
Parkash et al[33]	699	95%	86%	+	-	15%
Trung et al[36]	644	97%	97%	+	1.7%	-
Lee et al[14]	690	86%	46%	-	-	1%
Karoli et al[34]	138	92%		+	48%	-
Saha et al[35]	1226				16.9%	

Samanta World J Cases 2015

Hepatitis in Pregnancy

- **25yo G1P1 34 wks gestation with 1wk fever, chills, abd pain. 1 wk earlier cephalexin for GpB Strep.**
- **T 102; other vitals and exam as expected**
- **Plt 143K; Hb 8.6; WBC 6.4K 20% bands; glucose, creat and INR WNL; ALT 279; AST 643; TB 0.8.**
- **Hosp day 4:PLT 83K; PT 16; PTT 44; AST 2,240; ALT 980; BR nl; Fibrinogen NL;**

Allen OB GYN 2005

Hepatitis in pregnancy

What is the best diagnosis?

A. HELLP
B. Acute fatty liver of pregnancy
C. Atypical DRESS from cefelexin
D. HSV infection
E. HEV

Hepatitis in pregnancy

What is the best diagnosis?

A. HELLP
B. Acute fatty liver of pregnancy
C. HAV infection
D. HSV infection
E. HEV

Allen OB GYN 2005

Hepatitis in pregnancy

1. Rule out HSV

~50% have muco-cutaneous lesions

High mortality without acyclovir

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

ACOG 2016

Hepatitis in pregnancy

2. HELLP

- **HTN and can occur post partum**
- **Fibrinogen high vs. sepsis and AFLP**

3. AFLP – severe and low glucose, inc INR, low fibrinogen (Swansea criteria)

Fulminant hepatitis

- **65 year old man with hx of jaundice. 2 weeks before finished amoxacillin/clavulanate acid for sinusitis. Hx of HTN on HCTZ and rosuvastatin. ETOH: 2 drinks per day.**
- **TB24; ALT 162 U/L; AST 97 U/L ALK P 235 U/L. IgM anti-HAV neg; IgM anti-HBc neg; HCV RNA neg. RUQ US neg.**

Fulminant Hepatitis

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

A. toxicity from amox/clav
B. alcohol
C. porphyria flare
D. leptospirosis
E. statin

Fulminant Hepatitis

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

A. toxicity from amox/clav
B. alcohol
C. porphyria flare
D. leptospirosis
E. statin

Drug related liver toxicity

Amoxicillin/clavulanate is most common

- **Cholestatic or mixed**
- **Often AFTER stopping**
- **1/2500 Rx**
- **DRB1*1501**
- **clavulanate>amoxicillin**

Rank	Agent	Year of FDA Approval	No. (%)†	Major Phenotypes
1	Amoxicillin-clavulanate	1984	91 (10.1)	Cholestatic or mixed hepatitis
2	Isoniazid	1952	48 (5.3)	Acute hepatocellular hepatitis
3	Nitrofurantoin	1953	42 (4.7)	Acute or chronic hepatocellular hepatitis
4	TMP-SMZ	1973	31 (3.4)	Mixed hepatitis
5	Minocycline	1971	28 (3.1)	Acute or chronic hepatocellular hepatitis
6	Cefazolin	1973	20 (2.2)	Cholestatic hepatitis
7	Azithromycin	1991	18 (2.0)	Hepatocellular, mixed, or cholestatic hepatitis
8	Ciprofloxacin	1987	16 (1.8)	Hepatocellular, mixed, or cholestatic hepatitis
9	Levofloxacin	1996	13 (1.4)	Hepatocellular, mixed, or cholestatic hepatitis
10	Diclofenac	1988	12 (1.3)	Acute or chronic hepatocellular hepatitis
11	Phenytoin	1946	12 (1.3)	Hepatocellular or mixed hepatitis
12	Methyldopa	1962	11 (1.2)	Hepatocellular or mixed hepatitis
13	Azathioprine	1968	10 (1.1)	Cholestatic hepatitis

http://livertox.nlm.nih.gov; Hoofnagle NEJM 2019

Acute Hepatitis Summary

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

Thanks and good luck on the test!

Questions:

Dave Thomas
–dthomas@jhmi.edu

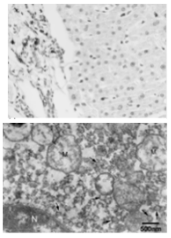
BREAK
SLIDES BEYOND THIS ARE FOR THE PRESENTER'S RECORDS; NOT TO BE DISTRIBUTED OR SHOWN

Hepatitis in 2020: SARS-CoV-2

Table 2. **Laboratory and radiographic findings of patients with COVID-**

	All patients (N = 788)
Leukocytes, $\times 10^9$/L	4.8 (3.8-6.0)
Neutrophils, $\times 10^9$/L	3.0 (2.2-4.0)
Lymphocytes $\times 10^9$/L	1.2 (0.9-1.6)
$\geq 0.8 \times 10^9$/L	654 (83.0)
$<0.8 \times 10^9$/L	134 (17.0)
Platelets, $\times 10^9$/L	181 (147-221)
$\geq 100 \times 10^9$/L	761 (96.6)
$<100 \times 10^9$/L	27 (3.4)
Hemoglobin, g/L	138.0 (127.0-151.0)
International normalized ratio	1.02 (0.97-1.09)
Albumin, g/L	41.4 (38.3-43.8)
Alanine aminotransferase, U/L	21.1 (15.0-33.0)
Aspartate aminotransferase, U/L	25.0 (19.6-33.0)

Hao Am J Gastro 2020



Wang J Hepatol 2020

Case 6. Hepatitis in Pregnancy

- **24yo 33 wks gestation with nausea and vomiting and RUQ pain. Taking acetaminophen 1gm q6; has dog and bird; recent visit to mom in NC.**
- **T 37.2; BP 158/110;2/6 SEM; RUQ tender; no rash.**
- **Plt 103K; Hct 26; WBC 6.6 10%L; PMN 82%; G 85; creat 0.6; ALT 225; AST 559; TB 1.4; CRP 15.8; PT WNL; fibrinogen NL.**

Case 4: Tired and jaundiced

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

Question #4

Which is easiest to justify medically?

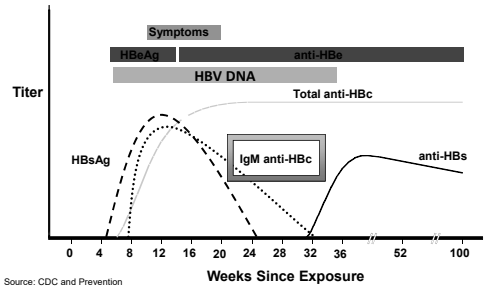
A. Repeat HBsAg and anti-HBs testing for partner
B. HBIG and HBV vaccine for partner
C. HBV vaccine for partner
D. Entecavir 0.5 mg/d for patient
E. TAF for partner

Question #4

Which is easiest to justify medically?

A. Repeat HBsAg and anti-HBs testing for partner
B. HBIG and HBV vaccine for partner
C. HBV vaccine for partner
D. Entecavir 0.5 mg/d for patient
E. TAF for partner

Diagnose acute HBV infection with IgM anti-HBc



2. No treatment indicated for acute HBV (unless fulminant)

3. Prevention by vaccine +/ HBIG

- HBsAg and anti-HBs screening of partners
- Tools: HBIG and/or HBV vaccine (USA)
  - Engerix, Recombivax, Heplisav-B, Pediarix, Twinrix
- Post-exposure:
  - Vaccinated and anti-HBs >10 ever, done*
  - No hx vaccine and/or anti-HBs >10, HBIG and vaccinate

*may be exception for patients with immunosuppression like HIV or dialysis

Schillie MMWR 2018

3. Prevention by vaccine +/ HBIG con't

- Pre-exposure:
  - no vaccine hx – vaccinate
  - Vaccine hx no testing – test for anti-HBs, boost or revaccinate if neg, retest anti-HBs

MMWR 2018

Acute hepatitis in HIV

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

Acute hepatitis in HIV

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

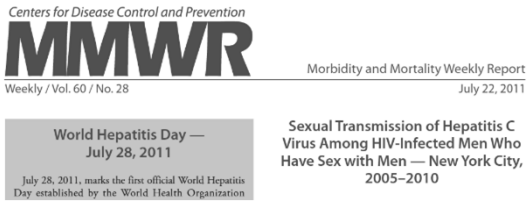
A. toxicity from the RAL
B. acute HCV infection
C. IRIS
D. resistant HBV
E. HDV

Acute hepatitis in HIV

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

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

Recognize acute HCV in HIV POS MSM


Centers for Disease Control and Prevention
MMWR
Morbidity and Mortality Weekly Report
Weekly / Vol. 60 / No. 28
July 22, 2011

World Hepatitis Day — July 28, 2011

July 28, 2011, marks the first official World Hepatitis Day established by the World Health Organization

Sexual Transmission of Hepatitis C Virus Among HIV-Infected Men Who Have Sex with Men — New York City, 2005–2010

OL4

HIV-Associated Opportunistic Infections III

Dr. Henry Masur

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

HIV-Associated Opportunistic Infections III

Henry Masur, MD, FIDSA, MACP
Clinical Professor of Medicine
George Washington University

5/30/2023

IDBR INFECTIOUS DISEASE BOARD REVIEW AUGUST 19-23 2023

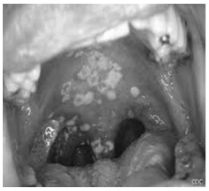
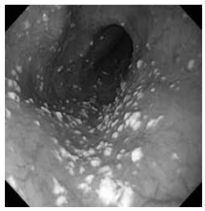
Disclosures of Financial Relationships with Relevant Commercial Interests

- None

Fungal Diseases in HIV-Infected Persons

- **Candidiasis**
- **Cryptococcosis**
- **Histoplasmosis**
- **Coccidiomycosis**
- **Talaromyces**

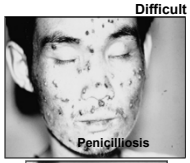
Mucosal Candidiasis

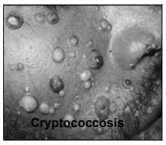



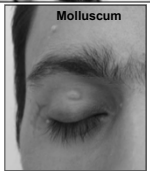

Candida

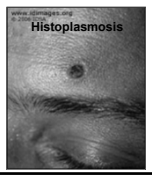
- **Mucosal candidiasis is characteristic**
  - Oral, Esophageal, Rectal, Vaginal
- **Invasive candida is not HIV-related**
  - Candida in blood should raise suspicion of catheter-related bloodstream infection or IV substance use disorder
- **Fluconazole primary prophylaxis or chronic suppression**
  - NOT recommended
    - Initial or recurrent or relapse episode not common esp with ART and easily treatable

Skin Lesions for HIV-Associated Endemic Mycoses Difficult to Distinguish


Penicilliosis


Cryptococcosis


Molluscum


Histoplasmosis

Importance of HIV-Associated Cryptococcosis

- **Prevalence**
  - **Pre ART in United States- 5 – 8% of patients**
  - **More common in Sub-Saharan Africa-**
    - 15% of AIDS-related deaths
  - **Less common in current era in US**
- **High morbidity/mortality**
- **CD4 Count at Onset**
  - **<100 cells/uL in 90% of patients**

HIV-Related Cryptococcal Meningitis

- **Clinical Presentation**
  - **CNS manifestations are usually subacute (median 2 weeks)**
    - **Encephalopathic manifestations such as confusion, lethargy, memory loss may be related to high intracranial pressure**
    - **Classic neck stiffness and photophobia only occur in 25%**
    - **When presents with non CNS manifestation (pneumonia, skin lesions etc)**
      - Meningeal involvement may initially be asymptomatic
      - LP necessary to determine treatment regimen

Crypt IRIS is typically more acute than active infection

Question #1

- **What is the most sensitive test for diagnosing HIV-associated cryptococcal meningitis?**

A. Serum crypt antigen test
B. Serum PCR test for crypt
C. CSF crypt antigen test
D. CSF PCR for cryptococcus

Answer #1

- **What is the most sensitive test for diagnosing HIV-associated cryptococcal meningitis?**

A. Serum crypt antigen test
B. Serum PCR test for crypt
C. CSF crypt antigen test
D. CSF PCR for cryptococcus

Diagnosis of Cryptococcal Disease

- **CSF**
  - Often minimal abnormalities with lymphocyte pleocytosis
  - Opening pressure >20-25cm H20 in 60-80% of patients
- **Crypt Antigen**
  - Highly sensitive in serum and CSF
  - CSF crypt ag can be positive months before symptomatic disease
  - Should be done even if CSF PCR negative is suspicion is high
- **Blood Culture positive**
  - 60% of patients with clinical meningitis
  - Growth in < 7 days

Antigen Tests for Cryptococcal Disease

- **Blood, Serum, Plasma, CSF:**
  - **Antigen**
    - Latex Agglutination or Enzyme Linked Immunoassay (EIA) or Lateral Flow Assay (LFA)
  - **Cryptococcal Lateral Flow Assay (IMMY LFA)**
    - **Dipstick test for whole blood/serum/plasma and CSF**
    - Four-fold higher titers than Latex Aggl or EIA
    - High titers suggest (1:160) or highly suggest (1:640) dissemination

PCR Tests for Cryptococcal Disease C. neoformans and C. gatti

- **PCR for CSF**
  - **Screening test available in multiplex assays**
    - **False positives and false negatives (!!) reported**
    - **Antigen test should be performed if PCR is negative**
  - **PCR may be useful for distinguishing**
    - **IRIS (PCR neg)**
    - **Initial Infection or Relapse (PCR pos)**

Question #2

- **What is the preferred therapy for acute HIV-related cryptococcal meningitis?**

A. Two weeks of Liposomal amphotericin alone followed by Fluconazole
B. Two weeks of Liposomal amphotericin plus Flucytosine followed by Fluconazole
C. Single dose Liposomal amphotericin alone followed by Fluconazole
D. Single dose Liposomal amphotericin followed by two weeks of Flucytosine followed by Fluconazole

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Therapy of Cryptococcal Meningitis

Liposomal Ampho B 3-4 mg/kg qd plus **Flucytosine* 25 mg/kg QID**	→ 2 weeks	Induction
Fluconazole ~~400~~ 800 mg po qd	→ 8 weeks	Consolidation
Fluconazole 200 mg po qd	→ ≥ 52 wks	Maintenance

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***5FC Associated with:**
Earlier sterilization CSF
Fewer relapses
Improved survival

***Flucon 800mg consolidation**
Cidal
Fewer relapses 800 vs 400

** Stop after 12 m total therapy if
CD4 >100- 150 x >3m
Asymptomatic
VL <50 copies

Induction Therapy – New Options for Induction
Not Likely Testable

- **Liposomal ampho B, single dose 10mg/kg IV day 1 only plus**
  - **5FC 25 mg/kg PO four times a day x 14 d with**
  - **Fluconazole 1200 mg/d x 14 d**

- ~~**Amphotericin B deoxycholate 1 mg/kg/d IV x 1 week plus**~~
  - ~~**5FC 25 mg/kg PO q6h x 1 week plus**~~
  - ~~**Fluconazole 1,200 mg/d PO x1week**~~
  - **Ampho deoxycholate is probably the wrong answer for any question on an exam**

Question #3

An HIV infected patient with CD4 count =20 cells/ul has never been on ART, and presented 3 days ago with cryptococcal meningitis.

Induction therapy (but no ART) was started after a diagnostic LP which showed an opening pressure of 30 mmHg and a CT scan which was consistent with meningitis with no signs of hydrocephalus or early herniation.

On day 3, her headache is worse and ultrasound of her eyes reveal increased intracranial pressure.

Which of the following would you initiate if the CNS symptoms persist on day 2:

A. Dexamethasone
B. Acetazolamide
C. Mannitol
D. Lumbar puncture to remove fluid
E. Lumbar puncture for repeat diagnostic studies and MRI to assess for a second, concurrent infectious or neoplastic process

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Management of Cryptococcal Meningitis

- **For flucytosine, therapeutic drug monitoring indicated**
- **Successful induction therapy = substantial clinical improvement and negative CSF culture**
  - Thus LP is necessary after two weeks of induction
  - If not clinically improved, continue induction until culture negative
- **India ink and CSF CrAg frequently positive at Week 2**
  - Not indicative of failure
- **Monitoring of serial crypt ag is often done but**
  - Not likely useful

Monitoring

- **If high opening pressure, those with symptoms and signs of increased ICP require immediate clinical intervention to reduce ICP**
  - Remove volume of CSF that at least halves the opening pressure or normalizes the pressure to <20 cm H2O or
  - Remove of 20 to 25 mL of CSF
  - Among patients with ongoing symptoms, therapeutic lumbar punctures should be repeated daily until symptoms and signs consistently improve and opening pressure normalizes to <20 cm H2O
- **Corticosteroids, mannitol and acetazolamide should not be used**

Clinical Recommendations

- **Irrespective of which regimen is used, patients must be followed carefully in hospital for at least 7 days**
- **Lumbar puncture should be performed at days 7 and 14 to ensure appropriate clinical response and culture sterility**
- **If increased intracranial pressure, daily lumbar punctures should be performed until the pressure is decreased to the normal range**
  - No clear role for acetazolamide or steroids

Elevated CSF Pressure

- **75% of patients have Opening Pressure >20 cm CSF**
  - **Abnormal = >25 cm CSF**
  - **Left lateral decubitus, flat position**
- **Symptoms**
  - **Blurred vision, confusion, obtundation**
- **Management: IF symptomatic and >25cm**
  - **Remove volume to reduce pressure by half or <20cm H20**
  - **Continue LPs daily for symptomatic patients until stable for at least 2 days**
  - **Shunt if regular LPs required for "many" days**
- **Not routinely recommended**
  - **Corticosteroids, Mannitol, Acetazolamide**

Consolidation Therapy

- **At two weeks**
  - Perform LP and repeat CSF culture
  - Success= Substantial clinical improvement AND negative CSF culture
    - Persistent CSF crypt ag is not indicative of failure
  - If patient is not symptomatically improved
    - Continue induction regimen until CSF culture confirmed as negative
    - (or use flucytosine +fluconazole as outpatient)
- **Continue consolidation until**
  - ART started
  - CSF culture negative

Monitoring Therapy for Cryptococcal Meningitis

- **During Therapy**
  - **"Monitoring serum or CSF CrAg titers is of no value in determining initial response to therapy and is not recommended (AII)"**
    - **NIH CDC IDSA Guideline**
  - **Monitor 5FC levels after dose 3 or 5**
  - **Positive CSF culture at 2 weeks indicates need for higher dose fluconazole during consolidation**
  - **Negative serum or CSF Ag is NOT required for termination of therapy**

When To Start ART for Crypt Meningitis

- **4-6 weeks after initiation of antifungal therapy**
  - May have to defer for patients with severe disease
  - When to start for non CNS disease less clear
  - Some experts start ART earlier based on evolving data
- **If IRIS occurs**
  - Continue ART and antifungal rx
  - Reduce ICP if ICP present and patient symptomatic

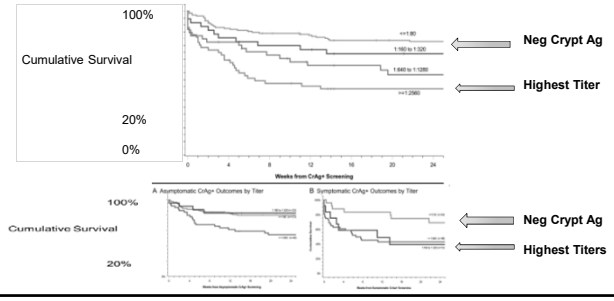
Asymptomatic Cryptococcal Antigenemia

(Pre-emptive Therapy for Crypt Ag +/Low CD4)

- **Recommendation:**
  - **Screen patients with CD4< 100**
    - **Frequency: 2.9% if CD4 <100, 4.3% if CD4 < 50**
    - **Positive serum ag predicts development of active disease**
- **If Positive: Perform LP and Blood Cultures to determine Rx**
  - **If CSF positive or serum LFA is >=640**
    - **Treat like crypt meningitis/disseminated (Ampho/5FC)**
  - **If CSF negative**
    - **Treat with fluconazole 400mg or 800mg x6 months**

IDSA OI Guidelines for Crypt 2021

Association of Serum Crypt Antigen and Survival

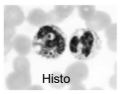


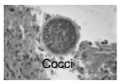
Flucytosine

- **Oral only form available in US**
  - 25mg/kg po q6h
- **Toxicities**
  - Marrow suppression, hepatitis, diarrhea
- **Monitoring**
  - Serum level drawn after 3-5 doses
  - Renal elimination-
    - monitor renal function
  - Maintain 2 hr peak at 30-80ug/ml

Other Fungal Diseases That Are Covered Elsewhere in IDBR

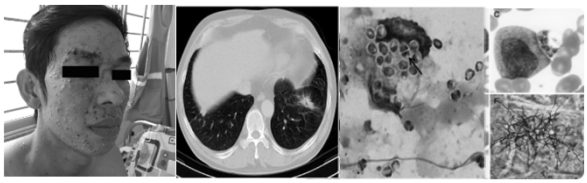
- Look for questions on patients with HIV and ….
  - Histoplasmosis
  - Coccidiomycosis
  - Talaromycosis





Talaromyces – Formerly Penicilliosis marnefii

- Rarely if ever seen in US
- Common in Asia transmitted by bamboo rat or abiotically
- Serum antigen test (research) sensitive and specific
- Treat with Ampho or Itraconazole



Herpesviruses

CMV

Non ARS Question

In an HIV positive patient (CD4 count = 50 cells/uL), a positive CMV PCR test of which of the following specimens would be MOST suggestive that CMV is the cause of end organ disease:

A. Esophageal biopsy to diagnose CMV esophagitis
B. Colonic biopsy to diagnose CMV colitis
C. Bronchoalveolar lavage to diagnose CMV pneumonia
D. Blood to diagnose CMV retinitis
E. CSF to diagnose CMV encephalitis

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CMV Syndromes
CD4<50 and VL Positive In Almost All Cases

- **Retinitis (30% of Patients Before ART)**
- **Colitis**
  - Can lead to perforation
- **Ventriculitis**
  - Rapid cognitive decline with cranial nerve involvement
- Radiculopathy, Myelitis, Mononeuritis Multiplex, Guillain-Barre
- Esophagitis (uncommon)
- Adrenalitis (rare)
- Pneumonia (rare)

Diagnosis of HIV-Related CMV Disease

- **Serology**
  - Disease unlikely if IgG seronegative
  - Rarely done
- **Cytology**
  - Rarely useful
- **Biopsy**
  - Helpful if many inclusions and substantial inflammation
- **PCR**
  - Correlates with CD4 Count
  - "Less than ideal" sensitivity and specificity for clinical disease

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  - Rarely do
- **Cytology**
  - Rarely us
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  - Helpful if
- **PCR**
  - Correlates with CD4 Count
  - "Less than ideal" sensitivity and specificity for clinical disease

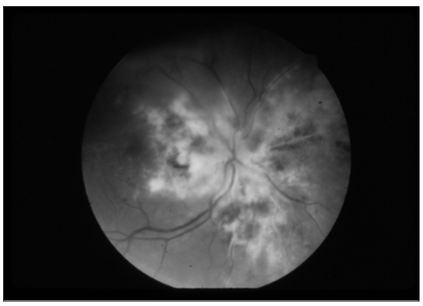
Main Clues to Diagnosis

- **Clinical Presentation**
- **Rule Out Other Causes**
  - **(HSV, VZV, Toxo, Syphilis etc)**

Diagnosis of CMV Retinitis

- **Funduscopic exam**
  - Bilateral in 30% of untreated patients
  - Mustard and Ketchup
  - Necrosis of retina
  - Little vitreal inflammation
- **PCR of blood not useful: 70% sensitive, very non specific**
- **Vitreal taps for diagnosis with PCR rarely necessary**
  - Tap positive in 80% of cases

CMV Retinitis



Therapy for CMV Retinitis
(Ganciclovir intraocular implant no longer available)

- **Immediate sight-threatening lesions**
  - ART
  - IV Ganciclovir or Valganciclovir 900 mg PO (bid x 14–21 days), then qd for at least 3-6 months plus
  - Intravitreal ganciclovir weekly over several weeks until lesion inactivity
    - Injections can be associated with infections or retinal detachment and hemorrhage
- **Small peripheral lesions**
  - ART
  - Oral valganciclovir for at least 3-6 months and immune reconstitution
  - +/- intravitreal ganciclovir

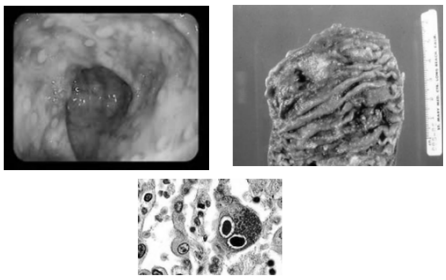
Salvage Therapy for CMV Retinitis
(Hard to Ask on Exam)

- **Systemic Options**
  - **Ganciclovir higher dose**
  - **Foscarnet IV**
  - **Foscarnet IV plus Ganciclovir IV**
  - **Cidofovir IV**
- **Intraocular**
  - **Ganciclovir or Foscarnet**

Treatment of Other CMV Syndromes

- **IV or Oral Ganciclovir or Foscarnet**
- **Duration hard to test**
  - Colitis or Esophagitis
    - 21-42 days or until clinical resolution
  - Ventriculitis
    - Not certain: some would use ganciclovir plus foscarnet

CMV Colitis



Clinical Disease Due to CMV Colitis

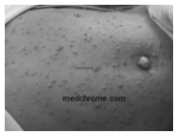
- **Clinical Presentation**
  - **Anorexia, abdominal pain**
  - **Non specific large bowel diarrhea**
    - Mild, moderate, severe
- **Diagnosis**
  - **Colonoscopy with cytology or biopsy**
  - **PCR non specific**
- **Therapy**
  - **Ganciclovir, Valganciclovir, Foscarnet**
  - **Duration: 21-42 days IV vs oral**

Varicella in PWH

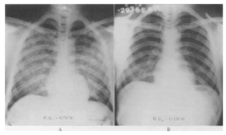
- **Uncommon in US**
- **Important to make the diagnosis by**
  - Exposure
  - Clinical Presentation
  - PCR or DFA of skin lesion

Treatment of Varicella in PWH

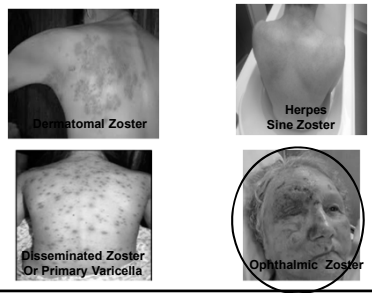
- **Uncomplicated**
  - **Valacyclovir or Famciclovir x 5-7 days**



- **Complicated**
  - **IV Acyclovir x 7-10 Days**



Localized and Disseminated Herpes Zoster



Herpes Zoster

- **Pre ART**
  - 15 fold high incidence of zoster than general population!!
- **Post ART**
  - Still increased risk even on suppressive ART
- **Localized (dermatomal)-common**
  - **Common at all CD4**
    - Frequency inversely proportional to CD4 even if VL<50
    - Recurrence is common with HIV
  - **Unmasking often observed soon after initiation of ART**

Herpes Zoster

- **Disseminated-very rare with HIV**
  - **Almost always CD4<200**

Therapy for Dermatomal Zoster

- **Acyclovir, Famciclovir, Valacyclovir**
  - **Treat within 1 week of rash onset or…. if not fully crusted**
    - (Longer "permissible window" compared to immunologic normal)
      - 48-72 hrs esp if age >50yo
      - Duration 7-10 Days
  - **Steroids NOT recommended to reduce post herpetic neuralgia**

Varicella Post Exposure Prophylaxis

Close Exposure to Varicella or Zoster and Susceptible*

- **Varicella Seronegative HIV Patients**
  - **VariZIG (High titer plasma derived)** **OR**
    - within 96 hrs of exposure ideally but can give up to 10 days
  - **Preemptive Acyclovir** **OR**
    - starting 7-10 days post exposure X 5-7 days
  - **Varicella Vaccination within 5 days of exposure**
    - Only if CD4>200
    - Don't vaccinate within 5 months of varizig or 3 d of ACV

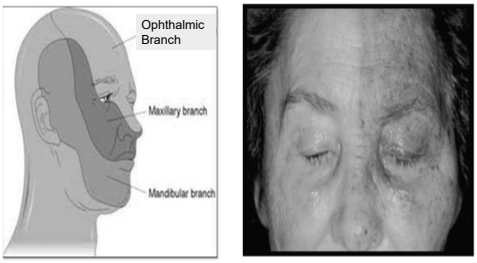
*Susceptible: No known history of Varicella or Shingles and No Vaccine or known to be varicella negative

Prevention of Zoster

- **Recombinant VZV glycoprotein E /adjuvant AS01B (RZV-Shingrix)**
  - Age>18 years
  - Recommended regardless of CD4 count by OI Guideline
    - ACIP is neutral re CD4 count

Three Zoster Syndromes You Should Recognize

Zoster Ophthalmicus
Ophthalmic Branch CN V



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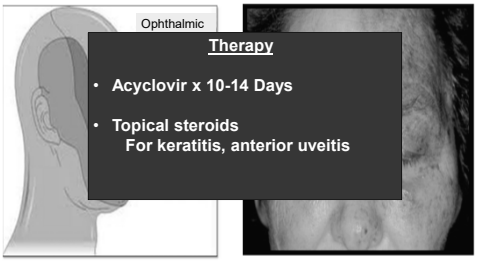


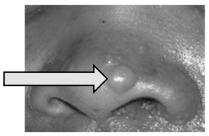
Therapy

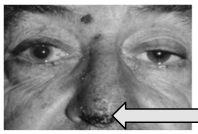
- **Acyclovir x 10-14 Days**
- **Topical steroids**
  For keratitis, anterior uveitis

Complications
HIV-Associated Zoster Ophthalmicus

- **Ocular**
  – 50% of Herpes zoster ophthalmicus
- **VII nerve palsy**
- **CNS**

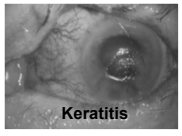
Hutchinson's Sign As Precursor to VZV Eye Disease
(Nasociliary Nerve of Ophthalmic Branch CN V)





Vesicles on the tip of the nose, or vesicles on the side of the nose

Accompanies development of ocular manifestations



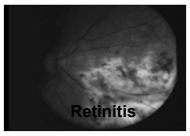


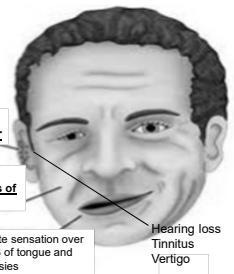
Image C. Stephen Foster, MD, Massachusetts Eye Research and Surgery Institute

Ramsay-Hunt Syndrome-Herpes Zoster Oticus
Geniculate Ganglion of Cranial Nerve VII
External Ear Vesicles and Facial Nerve Paralysis

Ear Pain

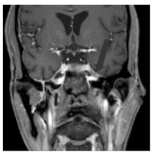
Vesicular rash on external ear

Lower motor neuron paralysis of facial nerve



Loss of taste sensation over anterior 2/3 of tongue and VIII CN palsies

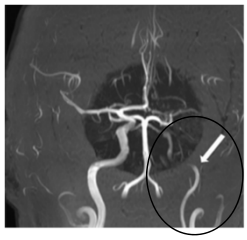
Hearing loss
Tinnitus
Vertigo



Meningeal Compression of Trigeminal Ganglion

Rx: Valacyclovir +/- Prednisone

Herpes Zoster Ophthalmicus
Vascular Inflammation and Occlusion/Stroke



Fugate JE, January 2020, Practical Neurology

Zoster Ophthalmicus-Related Stroke

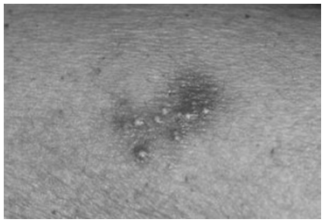
Carotid Intimal Involvement

- **Days or months post zoster (median 4 months)**
- **Occasionally cutaneous lesions absent (33%)**
- **DX-PCR of CSF or VZV antibody production in CSF**
- **Rx acyclovir plus probably steroids**

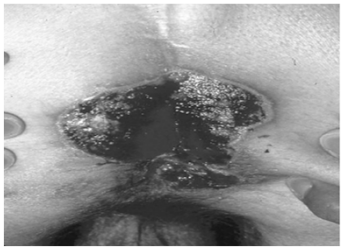
Herpes Simplex

- **Common Manifestations at any CD4**
  - Usual localized cutaneous and genital lesions
- **Dissemination**
  - Extremely uncommon at any CD4 count
- **Occurrences at low CD4**
  - Esophagitis
  - Retinitis
  - Dissemination
  - Chronic, extensive genital ulcers, often ACV resistant
- **Diagnosis**
  - Culture or PCR useful for cutaneous lesion
  - Culture or PCR NOT Useful for mucosal surface-may indicate shedding only

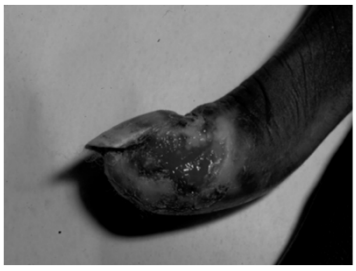
Localized Herpes Simplex



Perirectal HSV
Look for Acyclovir Resistance



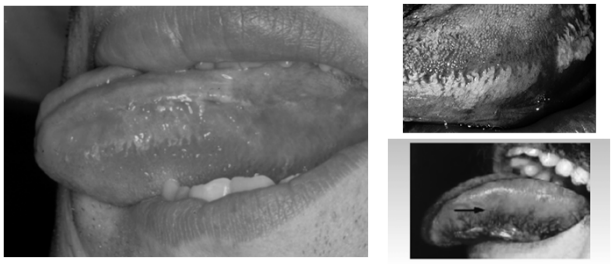
Herpetic Whitlow
Look for Acyclovir Resistance



HIV Diseases Associated with EBV

- **Oral Hairy Leukoplakia**
- **CNS Lymphoma (described later)**
- **Effusion cell lymphoma (described later)**

Oral Hairy Leukoplakia EBV-Associated



Common Bacterial Causes of Diarrhea in PWH

- **Salmonella enterica**
- **Shigella**
- **Campylobacter**
- **Clostridioides**
- **Colitis/Proctitis related to STDs**
  - STDs (LGV, GC, Syphilis)
- **Probably Non Testable (Hard to Diagnose)**
  - Enterohepatic Helicobacter species, non jejuni-non coli Campylobacter
  - CMV, MAC, Kaposi

Salmonella and Shigella in PWH

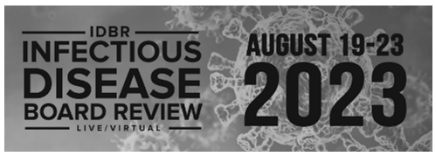
- **Salmonella**
  - **Bacteremia more common in HIV pos (esp low CD4) than HIV neg**
  - **Bacteremia merits HIV test**
  - **Treat all infected patients to reduce likelihood of bacteremia**
  - **Recurrence common**
  - **If recurrence, long term suppression appropriate esp if VL elevated-**
    - **(How long?)**
- **Shigella**
  - **Highly transmissible**
  - **Rarely bacteremic**
  - **Probably treat all diarrhea to reduce shedding, transmission**
  - **Rarely recurs**

Thank You

OL5

HIV-Associated Opportunistic Infections IV

Dr. Henry Masur



HIV-Associated Opportunistic Infections IV

Henry Masur, MD, FIDSA, MACP
Clinical Professor of Medicine
George Washington University

5/30/2023

Disclosures of Financial Relationships with Relevant Commercial Interests

- None

Question #1

Which of the following protozoa can be treated successfully with TMP-SMX?

A. Cyclospora
B. Cryptosporidia
C. Enterocytozoa
D. Encephalitozoa
E. Naegleria

Answer #1

Which of the following protozoa can be treated successfully with TMP-SMX?

A. Cyclospora
B. Cryptosporidia
C. Enterocytozoa
D. Encephalitozoa
E. Naegleria

Intestinal Protozoa of Note in PWH

Cryptosporidium
- *C. parvum:* cows
- *C. hominis:* humans

Cyclospora cayetanensis

Cystoisospora belli

- **All have worldwide distribution**
- **All transmitted by water or food contaminated with oocysts**
- **Organisms invade enterocytes and are mainly small intestine**
- **All cause watery diarrhea that can be prolonged & severe in immunocompromised**

Cryptosporidia

- **Epidemiology**
  - **Small inoculum adequate for transmission**
  - **Shedding persists after sx resolve**
  - **Notorious outbreaks in municipal water supplies (Milwaukee)**
    - **Day care centers, animal contact, water parks, oysters, person to person**

Cryptosporidia

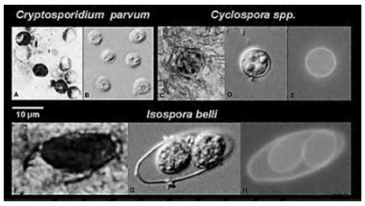
- **Clinical Course**
  - **Immunocompetent**
    - Self limited in 10-14 d (nausea, fever, diarrhea)
    - Occasional entry into biliary or pancreatic
  - **Immunosuppressed (not just HIV!)**
    - Potentially chronic

Cryptosporidia

- **Microbiology**
  - Intracellular protozoan
- **Pathology**
  - Normal hosts
    - small bowel
  - Immunosuppressed
    - small and large bowel

Intestinal Coccidia Characteristics

Pathogen	Size	Stain	Treatment
Cryptosporidium	4 μm	m acid-fast	None
Cyclospora	10 μm	m acid-fast	TMP/SMX
Cystoisospora	20 μm	m acid-fast	TMP/SMX



Microsporidia

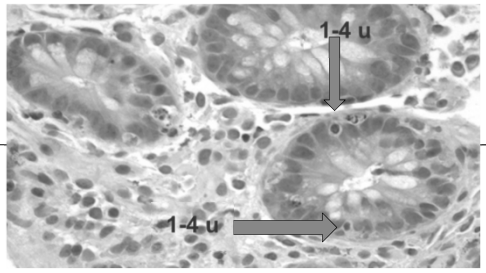
- **Fungus-Not Protozoon**
  - Intracellular
  - Confusing taxonomy
    - Encephalitozoon, Enterocytozoan, Septata….many others
- **Diseases in Immunocompetent Patients**
  - Self limiting diarrhea
  - Keratitis

Microsporidiosis in HIV

- **Enterocytozoa (mostly *E. bieneusi*)**
  - **Diarrhea (CD4 < 50)-90% of cases in US**
    - **sometimes with biliary, pancreatic duct involved**
- **Encephalitozoa (mostly *E. intestinalis*)**
  - **Diarrhea (CD4<50)-10% of cases in US**
    - (*E. intestinalis* was formerly Septata intestinalis)
  - **Disseminated disease with many different species**
    - Encephalitis, myositis, keratoconjuctivitis, cholangitis et al

Microsporidia – Diagnosis

- **Direct Culture**
  - None
- **Microscopy**
  - PCR
  - Stains
    - H + E and many others



Small Bowel Biopsy: Enterocytozoon bieneusi spores
Location: near the luminal surface of enterocyte
(Brown-Hopp, 1000x)

Therapies for Microsporidiosis

Organism	Frequency	Therapy
• Encephalitozoon intestinalis	(10%)	Albendazole
• Entercytozoon bieneusi	(90%)	None (Nitazoxanide)

(Fumagillin-Not Available)

HIV Associated Cholangiopathy

Idiopathic and/or Related to GI Pathogen

- **Biliary obstruction and liver injury in patients with Low CD4**
  - **Presentations**
    - Papillary stenosis
    - Intrahepatic sclerosing cholangitis
    - Bile duct stricture
- **Clinical Manifestations**
  - **Nausea and vomiting**
  - **Severe RUQ pain**
  - **Fever**
  - **Diarrhea and Weight Loss**
  - **Less jaundice than other cholangiopathies**

HIV-Associated Cholangiopathy

- **Associations/Causes**
  - **Cryptosporidia**
  - **Microsporidia**
  - **CMV**
- **Diagnosis and Treatment**
  - **ERCP**
  - **Sphincterectomy**
  - **Treatment of associated pathogens**
  - **ART**

HIV-Associated Neurologic Diseases

- **HIV Associated Encephalopathies**

Question #2

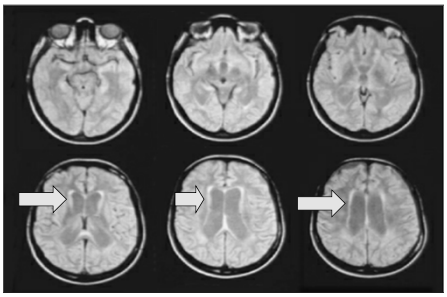
A 32-year-old female with HIV infection VL = 100k, and a CD4 count below 10 cells/mm3 has failed all available ART regimens.

Her mother brings her to clinic because of confusion for 1-2 weeks. She is afebrile, oriented x 1, and slow to respond.

She has nystagmus and CN VI palsy on the right.

The MRI is shown.

MRI Related Encephalitis



Question #2

Which PCR test would support the diagnosis that is most likely in this case?

A. JC
B. EBV
C. CMV
D. HHV6
E. HHV8

Answer #2

Which PCR test would support the diagnosis that is most likely in this case?

A. JC
B. EBV
C. CMV
D. HHV6
E. HHV8

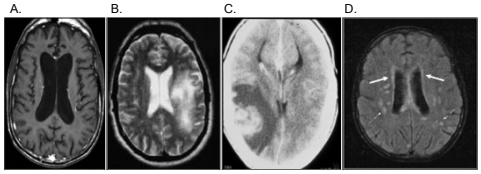
CMV Encephalitis

- **Imaging**
  - **Periventricular Enhancement**
  - **(Micronodular throughout CNS)**
- **Clinical and Laboratory Characteristics**
  - **Low CD4 (<50)**
  - **Rapid onset (days or weeks-unlike HIV)**
  - **Focal CN findings or nystagmus**
  - **CSF pleocytosis sometimes with polys**

Question #3 non ARS

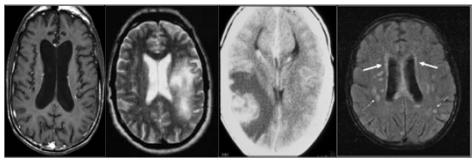
Can you tell what the following lesions are in an HIV infected patient with CD4 <50 cells and dementia of uncertain duration?

A. B. C. D.



Question #3 non ARS

A. HIV Dementia **B. PML** **C. Toxo** **D. CMV**



Question #4

- **A 35-year-old male with long standing HIV, untreated, is brought to the ER for a seizure. His CD4 has been < 20 cells.**
- **The patient admits that he has had a slowly progressive left lower extremity weakness, and his performance at his accounting firm has deteriorated in the past few months.**
- **MRI findings of a right parietal white matter lesion with no atrophy or ventricular dilation.**
- **CSF shows wbc 20 (100% lymphs), protein 60**

Question #4

- **Which of the following CSF PCR tests would be the most useful:**

A. Jakob Creutzfeldt virus
B. HIV
C. EBV
D. BK virus
E. JC virus

Answer #4

- **Which of the following CSF PCR tests would be the most useful:**

A. Jakob Creutzfeldt virus
B. HIV
C. EBV
D. BK virus
E. JC virus

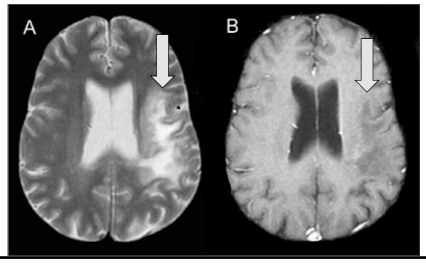
HIV Encephalopathies

Feature	PML	HIVE	CMV
Onset	Subacute	Subacute	**Acute**
CD4	<100	<100	<50
Dementia	+	+	+
Motor deficit	+	+	+/-
Sensory deficit	+	-	-
MRI			
Location	**Asymmetric**	Symm	Symm
Cortical atrophy	-	+	-
Micronodular	-	-	+
Periventricular	-	-	+
CSF PCR	**JC + 70%**	**Not helpful**	**CMV+**

Progressive Multifocal Leukoencephalopathy

A. T2-weighted image = increased signal in the left hemisphere

B. T1-weighted image = decreased attenuation (dark).



Progressive Multifocal Leukoencephalopathy (PML) (JC Virus Encephalitis)

- **Polyomavirus (JC)**
  - **Transmission probably by respiratory route human to human**
    - >80% adults infected by JC by antibody testing
  - **Only known disease is PML**
    - Most cases in patients with well defined immunodeficiency

PML Can Be Associated with Immunosuppressive Diseases Other than HIV

- **Transplants**
- **Cancers**
  - Esp Fludarabine
- **Monoclonal Antibodies**
  - Rituximab
  - Natalizumab
    - (Adhesion molecule inhibitor for Multiple Sclerosis or Crohn's-within 18 months)
- **High Dose Corticosteroids**

Progressive Multifocal Leukoencephalopathy (PML or JC Virus Encephalitis)

- **Disease of White Matter >> Gray Matter**
  - **Slowly progressive**
  - **Non enhancing (80%)**
  - **Multiple focal defects rather than diffuse encephalopathy**
  - **No fever or headache**
  - **Optic nerves and spinal cord usually spared**
  - **Seizures 20%**
    - **(when lesions abut gray matter)**

Progressive Multifocal Leukoencephalopathy

- **CSF:**
  - Cells + protein may be elevated
  - PCR for JC+ in 70-90% of biopsy proven patients
    - Specificity not 100%: interpret with clinical scenario
- **Differential Diagnosis**
  - Multiple Sclerosis
- **Plasma PCR**
  - Correlates with immunosuppression rather than being diagnostic for PML

Progressive Multifocal Leukoencephalopathy

- **Prognosis without ART**
  - **50% die in 2-4 months**
- **Therapy for PML**
  - **ART or reduction in immunosuppression for non HIV**
  - **Check point Inhibitors: nivolumab and pembrolizumab**
  - **Virus specific T cells**
- **Therapy for Inflammatory PML**
  - **IRIS post ART or withdrawal of Natalizumab: Steroids**

HIV and Cancer

Question #5

What virus is associated with HIV-related multicentric Castleman disease?

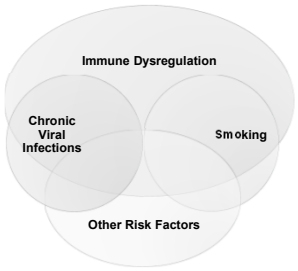
A. CMV
B. HSV
C. HHV 6
D. HHV 7
E. HHV 8

Answer #5

What virus is associated with HIV-related multicentric Castleman disease?

A. CMV
B. HSV
C. HHV 6
D. HHV 7
E. HHV 8

HIV and Cancer



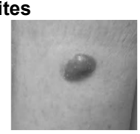
Most Cancers Overrepresented Among Patients with HIV are Related to a Virus

AIDS-Defining	Virus
• Kaposi's Sarcoma	HHV-8
• Non-Hodgkin's Lymphoma	EBV
• Invasive Cervical Carcinoma	HPV
Non-AIDS Defining	
• Multicentric Castleman	HHV-8
• Primary Effusion Cell Lymphoma	HHV-8, EBV
• Anal Cancer	HPV
• Hodgkin's Disease	EBV
• Leiomyosarcoma (pediatric)	EBV
• Squamous Carcinoma (oral)	HPV
• Merkel cell Carcinoma	MCV
• Hepatoma	HBV, HCV

What is Merkel Cell Carcinoma?

Don't Mistake for Benign Lesion

- **Hopefully this is too obscure for the exam**
- **Associated with Merkel cell polyomavirus (MCPyV)**
  - 80% of adults are seropositive
- **Rapidly growing epithelial tumor**
  - Associated with immunosuppression
- **Can metastasize to regional nodes or distant sites**
- **Treatment**
  - Beyond ID boards



Human Herpes Virus 8 (HHV 8)

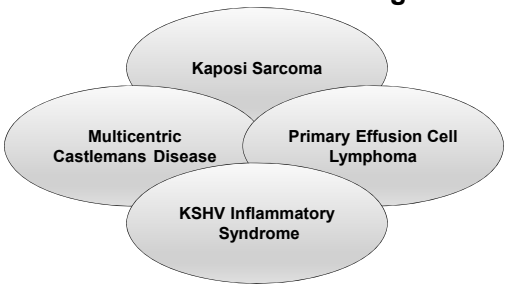
KSHV Associated Diseases (KAD)
Also Reviewed in Herpes Virus Lecture

- **Important**
  - Kaposi sarcoma- (Declining incidence)
  - Castleman disease- (Increasing incidence)
  - Primary Effusion cell lymphoma
  - Kaposi sarcoma inflammatory syndrome
- **Seroprevalence**
  - General population: 2%
  - Men who have sex with men: 13-58%
    - IVDU-no clear association
- **Testing with PCR or Antibody**
  - Not widely done or useful routinely
  - HHV 8 viremia increases risk of KS 8 fold
  - Most PEL are HHV 8 viremic
- **Transmission**
  - Saliva >> sex

Human Herpes Virus 8 (HHV 8)

- **Role of HHV 8 PCR**
  - None clinically
- **Anti HHV 8 Antiviral Therapy**
  - **No role**
    - **Susceptible to Ganciclovir, Foscarnet, Cidofovir**

HHV-8/KSHV-Associated Malignancies

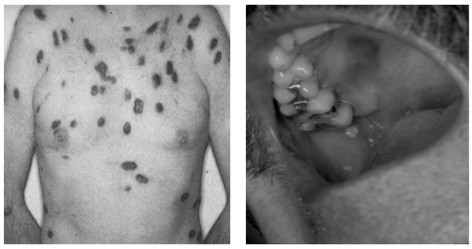


Kaposi Sarcoma

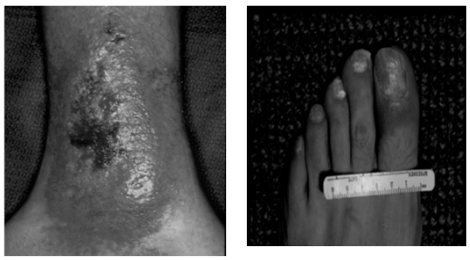
- **Angioproliferative tumor**
- **Four major subtypes**
  - **Classic:**
    - **Indolent** cutaneous **proliferative disease (mainly affecting extremities)**
  - **Endemic**
    - Equatorial and sub-Saharan Africa
  - **Organ transplant associated**
    - After transplant
  - **Epidemic**
    - AIDS-related
    - Commonly presents as unmasking with IRIS when ART started

Yarchoan and Uldrick. NEJM. 2018. 378:1029-1041

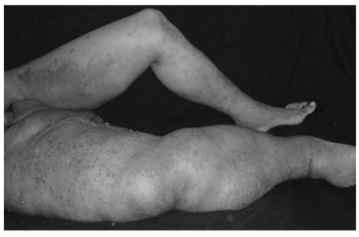
Kaposi Sarcoma



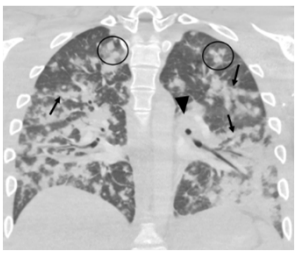
Kaposi Sarcoma



Lymphedema Due to Kaposi Sarcoma



Pulmonary KS



- **Not all have skin lesions**
- **Nodules and alveolar filling**
- **Hemoptysis**
- **Bloody pleural effusion**
- **Endobronchial Lesions**

Clin Infect Dis 2018: 66: 232

Kaposi Sarcoma – Diagnosis

- **Biopsy is standard of care (but not transbronchial or conjunctiva)**
  - Immunohistochemical staining with for HHV-8-encoded latency-associated nuclear antigen (LANA)
  - Polymerase chain reaction (PCR) to identify HHV-8 sequences within tumor tissue

Kaposi Sarcoma Therapy

- **Antiretroviral Therapy**
  - **KS often regresses with ART alone**
  - **Look for IRIS (unmasking or paradoxical worsening)**
- **Antiherpes drugs have minimal efficacy**
- **Chemotherapy**
- **Local excision or radiation**

Kaposi Sarcoma

- **Local Therapies**
  - Intralesional vinblastine
  - Topical cis retinoic acid
  - Radiation therapy
- **Systemic Therapies if no response to ART**
  - Liposomal doxorubicin (doxil)
  - Paclitaxel
  - Pomalidomide
  - (No role for anti-HHV-8 agents such as ganciclovir, foscarnet, cidofovir

Multicentric Castleman Disease

- **B Cell Disorder**
- **Not Only HIV**
  - Occurs with other immunosuppressive disorders
- **Presentation mimics lymphoma, endemic fungi, TB**
  - Occurs at any CD4 count but higher incidence with lowest CD4
  - Fever, weight loss, lymphadenopathy, hepatosplenomegaly
  - Cytopenias, Hypergammaglobulinemia

Castleman Disease : Adenopathy and Splenomegaly

Multicentric Castleman Disease

- **Diagnosis**
  - **Biopsy of lymph node or bone marrow**
  - **HHV-8 levels correlate with disease activity**
    - **Not** diagnostic
- **Therapy**
  - **ART**
  - **Some combination of—(not testable)**
    - Rituximab, Prednisone, Liposomal Doxorubicin, Anti IL6 (sarilumab), AZT + ValGCV

Body Cavity Lymphoma
(Primary Effusion Lymphoma)

- **Uncommon but testable**
  - 4% of AIDS Associated Lymphomas
  - Any CD4 counts
  - HHV-8 plus EBV associated
- **B cell malignancy but no B or T markers**
  - CD45+
- **Presentation**
  - Pleural/pericardial/peritoneal effusion
    - local disease
  - Masses unusual but organ infiltration occurs

Body Cavity Lymphoma
(Primary Effusion Lymphoma)

- **Diagnosis**
  - **Effusion cytology**
    - nuclear HHV8 by immunohistochemistry
- **Therapy and prognosis**
  - **Unclear**

KSHV Inflammatory Cytokine Syndrome

- **Castleman's Disease without positive histology**
- **Mimics Sepsis**
  - Fever, hypotension, hypoxia
  - Pulmonary, GI, CNS manifestations
  - Similar to Castleman's but no adenopathy or splenomegaly
- **Diagnosis of exclusion**
- **Pathogenesis**
  - Elevated levels of IL 6, IL 10 and CRP
  - Elevated levels of HHV-8
- **Treatment**
  - Unclear: Rituximab, anti-IL-6

EBV Associated Lymphomas

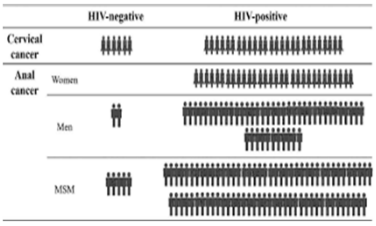
Diffuse Large B Cell Lymphoma in HIV

- **Typically present with**
  - advanced stage and "B symptoms"
- **EBV associated**
- **Outcomes**
  - comparable to non-HIV patients
- **CNS disease frequent**

HHV6 and HHV7 in Patients with HIV
Always the Wrong Answer on Exam for HIV

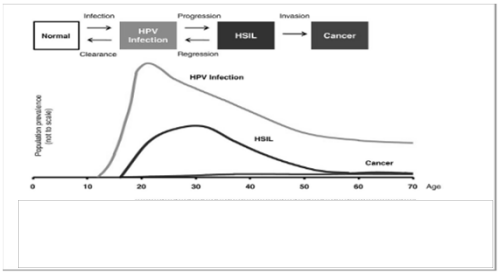
- **HHV6 in Immunocompetent Children**
  - Transmitted by saliva to 70-90% US population
  - Causes Roseola (Sixth Disease), febrile seizures, encephalitis
- **HHV-6 in Patients With HIV Only Rarely important**
  - Several cases of fever, pneumonitis, encephalitis
  - Rx: Foscarnet active against both A and B strains
- **HHV7**
  - Clinical: Uncertain importance if HIV + or neg
  - Rx: Foscarnet, cidofovir >> ACV, GCV

HPV Related Squamous Cell Carcinomas
HIV Related



Oral Squamous Cell Carcinomas Also Over-represented Among PWH

Natural History of HPV-Related Cervical Cancer



HSIL =
High-grade squamous intraepithelial lesion

HPV-Related Tumors

- **Prevention of HPV Infection**
  - Same as non-HIV population
  - Condom for preventing transmission and penile cancer
  - Circumcision
  - 9 valent vaccine to all males and females 9-26 yo regardless of HIV status
- **Prevention of HPV Related Tumors**
  - **Cervical screening for HPV with Pap test for women <30 yo**
    - See Guidelines for testing timeline and strategy—hopefully too detailed for exam
  - **Anal screening recommended with digital exam annually**
    - **See Guidelines re use of high resolution anoscopy, cytology testing, HPV testing**
  - **Oral screening not proven beneficial and not recommended**
  - **Antiretroviral Therapy**
- **Treatment**
  - Hopefully beyond scope of ID boards

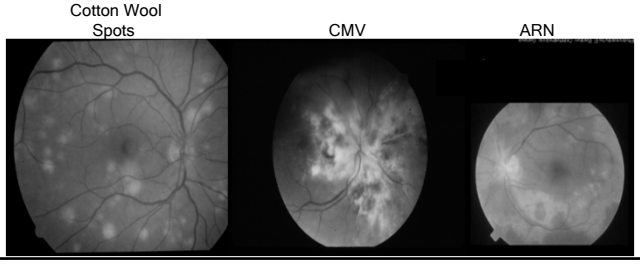
What Else Could Be On The Exam?
Some Topics That Could Be Easy to Make Into Questions

- **Ophthalmology**
  - Retinitis due to pathogens other than CMV
  - Retinal lesions that are not retinitis
- **Hematology**
  - Acute anemia due to Parvovirus
- **Tick bites**

Herpes Zoster Associated Retinitis

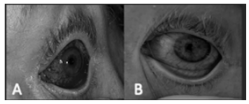
- **Acute Retinal Necrosis: Immunocompetent or HIV/CD4>100**
  - Cutaneous zoster may or may not occur
  - VZV >>HSV, CMV
  - Presents peripherally with pain, floaters
  - WBC in vitreous +/- aqueous
  - Unilateral but can become bilateral if untreated
  - Retinal detachments common
  - Acyclovir followed by long course of valacyclovir +/- intravitreal ganciclovir (14 weeks)
- **Peripheral Outer Retinal Necrosis: HIV/ Immunosuppressed (CD4<50)**
  - Multifocal with little inflammation
    - VZV >>HSV, CMV
    - Often involves optic nerve
    - Associated with retinal detachment, blindness
    - Therapy rarely successful
    - Acyclovir IV plus intravitreal ganciclovir or foscarnet or gcv/foscarnet for long period of time

Will You Be Able to Tell These Apart?

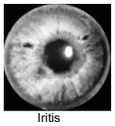


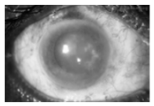
Ocular Syphilis

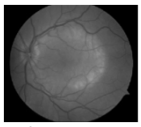
Scleritis, Iritis, Keratitis
Chorioretinitis, and Optic Neuritis

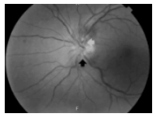


Scleritis


Iritis


Keratitis

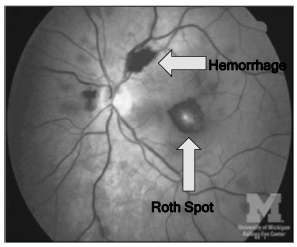

Chorioretinitis


Optic Neuritis

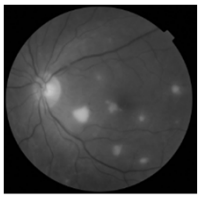
Other Lesions That Might Fool You

- **Retinal disease related to another issue**
  - IV drug use
  - Blood stream infection due to IV catheter

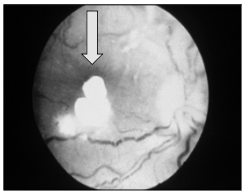
Bacterial Endocarditis
Unrelated to HIV—Related to IVDU or Other Factors



This Might Be Seen In Patient with AIDS But…Related to IVDU or CLABSI
Candida Chorioretinitis and Endophalmitis



Chorioretinitis (early)
Diagnose empirically
No Vitreous Haze
Systemic Rx alone



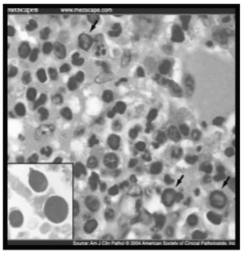
Endophthalmitis (late)
Diagnose with vitreal tap
Central Vitreal Fluff Ball
Vitreal Haze
Rx: Systemic Rx, Intravitreal Ampho, Vitrectomy

Parvovirus Can Cause Severe Anemia in Patients with HIV Infection

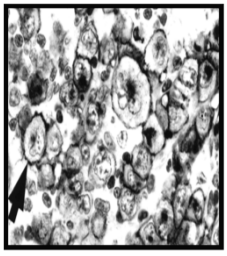
Symptoms	**Weakness over weeks-months**
Hemoglobin	**2.5 - 6.5 g/dl**
Reticulocytes	**Low**
Erythropoietin	**> 500 units (80%)**
Marrow	**Hypocellular**
CD4 Count	**Variable**
B19 Serology	**Variable (40% +)**
B19 PCR	**Positive (Gold Standard)**
	Sensitive but can be positive for months
Therapy: IVIG	**Usually Successful**

Parvovirus in HIV-Infected Patient

Inclusion Bodies



Pronormoblasts



Ticks and HIV with "Septic Shock"

- **Exam question**
  - HIV patient presents with fever and shock or hemolysis
  - Clues: outdoor exposure, geography, peripheral smear
- **Tick borne diseases that are more severe in HIV**
  - *Ehrlichia*
  - Anaplasma
  - Babesia

The End

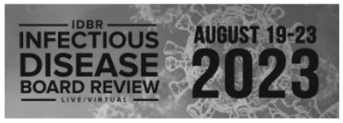
OL6

Other Antibacterial Drugs (Macrolides, TMP, SMX, etc)

Dr. Pranita Tamma

Online Only Lectures – Other Antibacterial Drugs (Macrolides, TMP, SMX, etc)

Speaker: Pranita Tamma, MD



Other Antibacterial Drugs (Macrolides, TMP, SMX, etc)

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

6/15/2023

Disclosures of Financial Relationships with Relevant Commercial Interests

- **None**

Objectives

- Review the spectrum of activity and adverse events for β-lactam antibiotics
- Review the spectrum of activity and adverse events for fluoroquinolones
- Review the spectrum of activity and adverse events for aminoglycosides
- Review the spectrum of activity and adverse events for trimethoprim-sulfamethoxazole, tigecycline, nitrofurantoin, fosfomycin, and metronidazole

β-lactam Agents

Overview

- Gram-positive and gram-negative organisms have a cell wall made of peptidoglycan chains
- *Mycoplasma pneumo*niae, *Chlamydia pneumoniae*, *Legionella pneumophila* do not have a cell wall
- Penicillin binding proteins (PBPs) cross-link peptidoglycans
- β-lactams inhibit cross-linking of peptidoglycans by interfering with PBPs

Resistance to β-Lactam Agents

- Bacteria prevent β-lactam activity by:
  - Changing the shape of PBPs
  - Limiting the availability of porins
  - Upregulating efflux pumps
  - Producing β-lactamase enzymes
- β-lactamase inhibitors prevent the activity of β-lactamase enzymes

Online Only Lectures – Other Antibacterial Drugs (Macrolides, TMP, SMX, etc)

Speaker: Pranita Tamma, MD

Penicillins

Natural Penicillins

- Short half-lives
- Long-acting formulations (procaine, benzathine) administered intramuscularly
- *N. meningitidis* infections *only* if susceptibility confirmed
  - About 10% of *N. meningitidis* isolates resistant to penicillin in the United States

Spectrum of Activity	
Good	*Treponema pallidum*, most Streptococci – including *S. pneumoniae*
Moderate	*Enterococcus faecalis*, *Neisseria meningitidis*

McNamara LA, et al. MMWR Morb Mortal Wkly Rep. 2020;69(24):735.

Aminopenicillins

- Active against some gram-negative organisms
- Increasing prevalence of β-lactamase production in gram-negative organisms
- Not appropriate empiric therapy for gram-negative infections

Spectrum of Activity	
Good	*Streptococci, Enterococcus faecalis, Listeria monocytogenes*
Moderate	*Haemophilus influenzae, enteric gram-negatives (e.g., E. coli)*

Question 1

Compared to ampicillin alone, the combination of ampicillin plus sulbactam, increases the percentage of susceptible isolates for which one of the following bacteria?

A. Staphylococcus aureus
B. Pseudomonas aeruginosa
C. Haemophilus influenzae
D. Stenotrophomonas maltophilia

Question 1

Compared to ampicillin alone, the combination of ampicillin plus sulbactam, increases the percentage of susceptible isolates for which one of the following bacteria?

A. Staphylococcus aureus
B. Pseudomonas aeruginosa
C. Haemophilus influenzae
D. Stenotrophomonas maltophilia

β-lactam-β-lactamase Inhibitors: Ampicillin-sulbactam & Amoxicillin-clavulanate

- MSSA, intestinal anaerobes, and some gram-negative organisms
- Sulbactam active against *Acinetobacter baumannii*
- Unlikely effective against ESBL enzymes
- Higher doses of amoxicillin-clavulanate associated with more diarrhea

Spectrum of Activity	
Good	MSSA, *Streptococci, Enterococci,* many anaerobes, gram-negatives, *Haemophilus influenzae, Acinetobacter baumannii* (ampicillin-sulbactam only)
Moderate	Enteric gram-negatives (e.g., *E. coli*)

Online Only Lectures – Other Antibacterial Drugs (Macrolides, TMP, SMX, etc)

Speaker: Pranita Tamma, MD

β-lactam-β-lactamase Inhibitor: Piperacillin-Tazobactam

- Gram-negatives including *Pseudomonas aeruginosa,* MSSA, and intestinal anaerobes
- Unlikely effective against ESBL enzymes
- Poor CNS penetration

Spectrum of Activity	
Good	MSSA, *Streptococci, Enterococci,* many anaerobes, gram-negatives, *Pseudomonas aeruginosa*
Moderate	Enteric gram-negatives (e.g., *E. coli*)

Cephalosporins

(Cross-allergenicity between penicillin and cephalosporins ~5%)

Question 2

Which one of the following antibiotics generally provides "coverage" against *Pseudomonas aeruginosa*?

A. Cefazolin
B. Ceftaroline
C. Ceftazidime-avibactam
D. Cefuroxime

Question 2

Which one of the following antibiotics generally provides "coverage" against *Pseudomonas aeruginosa*?

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First-Generation Cephalosporins

- Cefazolin (IV), cephalexin (PO), and cefadroxil (PO)
- Surgical prophylaxis
- Skin and soft tissue infections
- Uncomplicated cystitis
- Poor CNS penetration

Spectrum of Activity	
Good	MSSA, *Streptococci*
Moderate	Some enteric gram-negatives (e.g., *E. coli*)

Second-Generation Cephalosporins

- Cefoxitin (IV) and cefotetan (IV)
  - Surgical prophylaxis
  - *Bacteroides* spp. (resistance increasing)
  - Cefotetan inhibits vitamin K production and causes disulfiram-like reaction
- Cefuroxime (IV/PO)
  - Community-acquired pneumonia
- Poor CNS penetration

Spectrum of Activity	
Good	Some gram-negative enterics, *Haemophilus influenzae*
Moderate	Streptococci, staphylococci, intestinal anaerobes

Online Only Lectures – Other Antibacterial Drugs (Macrolides, TMP, SMX, etc)

Speaker: Pranita Tamma, MD

Third-Generation Cephalosporins

- Not preferred for MSSA
- Ceftazidime has Pseudomonal activity
- Ceftriaxone and ceftazidime effective for CNS infections
- Ceftriaxone preferred for gonococcal infections; resistance is a concern
- Cefixime not preferred for gonorrhea

Spectrum of Activity	
Good	Streptococci, gram-negatives, *Pseudomomas* (ceftazidime only), *Neisseria gonorrhoeae* (ceftriaxone only), *Borrelia burgdorferi* (ceftriaxone only)
Moderate	MSSA (ceftriaxone only)

Workowski KA, MMWR Recomm Rep. 2021;70(4):1

Fourth-Generation Cephalosporins

- Cefepime has broad gram-positive and gram-negative activity
- Effective for CNS infections
- Unlikely effective against ESBL enzymes

Spectrum of Activity	
Good	MSSA, streptococci, *P. aeruginosa*, enteric gram-negatives

Newest Cephalosporins

Antibiotic	KPCs	NDMs	OXA-48-like	Carbapenem-resistant *P. aeruginosa*	Carbapenem-resistant *A. baumannii*	*Stenotrophomonas*
Ceftolozane-tazobactam						
Ceftazidime-avibactam						
Cefiderocol						

Question 3

A 34-year-old women is admitted with *E. coli* pyelonephritis. She describes a history of lip swelling, shortness of breath, and hypotension while receiving an infusion of ampicillin 2 years ago. The *E. coli* isolate is susceptible to all of the following β-lactam agents. Which one of the following is a reasonable treatment option?

A. Piperacillin-tazobactam
B. Aztreonam
C. Ceftolozane-tazobactam
D. Ceftriaxone

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B. Aztreonam
C. Ceftolozane-tazobactam
D. Ceftriaxone

Monobactams

(No cross-allergenicity with penicillins or carbapenems)

Online Only Lectures – Other Antibacterial Drugs (Macrolides, TMP, SMX, etc)

Speaker: Pranita Tamma, MD

Aztreonam

- Gram-negative coverage
- CNS infections
- Safe with severe penicillin allergies
- Ceftazidime, cefiderocol, and aztreonam share an identical side chain

Spectrum of Activity	
Good	*P. aeruginosa*, most gram-negatives, *Acinetobacter* spp.

Caruso C, et al. Journal of Asthma and Allergy. 2021;14:31-46.

Carbapenems

(Cross-allergenicity between penicillin and carbapenems <1%)

Question 4

A 42-year-old male recipient of a liver transplant is admitted to the ICU. He is febrile and hypotensive. On laboratory examination he has a leukocytosis with a bandemia, normal renal function, mildly elevated transaminases, and has a low albumin at 2.1 g/dL. He previously grew an ESBL-producing *Klebsiella pneumoniae.* You decide to prescribe a carbapenem as empiric therapy.

Which one of the following carbapenem agents would not be suggested for this patient?

A. Meropenem
B. Ertapenem
C. Imipenem-cilastatin
D. Doripenem

Question 4

A 42-year-old male recipient of a liver transplant is admitted to the ICU. He is febrile and hypotensive. On laboratory examination he has a leukocytosis with a bandemia, normal renal function, mildly elevated transaminases, and has a low albumin at 2.1 g/dL. He previously grew an ESBL-producing *Klebsiella pneumoniae.* You decide to prescribe a carbapenem as empiric therapy.

Which one of the following carbapenem agents would not be suggested for this patient?

A. Meropenem
B. Ertapenem
C. Imipenem-cilastatin
D. Doripenem

Ertapenem

- Highly protein bound; prolonged serum half-life
- Not good for CNS infections
- No activity against *P. aeruginosa*
- Effective for ESBLs

Spectrum of Activity	
Good	Gram-negative enterics including ESBL-producing infections, intestinal anaerobes, MSSA, streptococci

Meropenem & Imipenem-Cilastatin

- Broad gram-positive and gram-negative aerobes and anaerobes
- Effective for invasive ESBL
- Higher propensity than other beta-lactams to induce seizures
- Reduce valproic acid levels
- Imipenem metabolized in kidney to a nephrotoxic product

Spectrum of Activity	
Good	Gram-negative enterics including ESBL-producing infections, *P. aeruginosa, A. baumannii,* intestinal anaerobes, MSSA, streptococci, *E. faecalis* (imipenem > meropenem)

Online Only Lectures – Other Antibacterial Drugs (Macrolides, TMP, SMX, etc)

Speaker: Pranita Tamma, MD

Newest Carbapenems

Agent	KPCs	NDMs	OXA-48-like	Carbapenem-resistant *P. aeruginosa*	Carbapenem-resistant *A. baumannii*	*Stenotrophomonas maltophilia*
Meropenem-vaborbactam						
Imipenem-cilastatin-relebactam						

Fluoroquinolones

- Inhibit topoisomerases
- Calcium, magnesium, iron salts reduce absorption
- Good CNS penetration
- UTI: Ciprofloxacin or levofloxacin. Not moxifloxacin.
- Adverse events
  - *C. difficile* infections
  - QTc prolongation
  - Tendinopathy
  - CNS toxicities (dizziness, confusion, hallucinations)

Spectrum of Activity	
Ciprofloxacin	Gram-negative enterics including *P. aeruginosa*, some atypical bacteria
Levofloxacin	Gram-negative enterics including *P. aeruginosa*, respiratory gram-negatives (e.g., *H. influenzae), S. pneumoniae, Stenotrophomonas maltophilia,* atypical bacteria
Moxifloxacin	Gram-negative enterics (NOT including *P. aeruginosa*, respiratory gram-negatives, *S. pneumoniae*, atypical bacteria, moderate activity against intestinal anaerobes

Aminoglycosides

- Bind to ribosome leading to incorrect protein formation
- Poor distribution in lungs and CNS
- Dosing based on ideal or adjusted body weight
- Nephrotoxicity and ototoxicity
- Neuromuscular blockage
- Resistance = aminoglycoside-modifying enzymes

Spectrum of Activity	
Gentamicin	Gram-negative enteric organisms, combination therapy for serious staphylococcal and enterococcal infections, tularemia, plague
Tobramycin, amikacin	Gram-negative enterics including *P. aeruginosa, Mycobacteria* spp.
Plazomicin	Gram-negative enteric organisms, including *P. aeruginosa*
Streptomycin	Mycobacteria, tularemia, plague, combination therapy for enterococcal infections

Trimethoprim-Sulfamethoxazole (TMP-SMX)

- Inhibits folate synthesis
- Newer data: active against *S. pyogenes*
- Adverse events: hypersensitivity reactions, bone marrow suppression, true and pseudo renal failure, hyperkalemia
- Interactions with warfarin increase prothrombin times
- Use IV formulation with caution in volume-overloaded patients

Spectrum of Activity	
Good	Gram-negative enterics, *S. maltophilia*, MSSA, MRSA, *S. pyogenes*, *Pneumocystis jirovecii*, *Toxoplasma gondii*, *Listeria monocytogenes*

Bowen AC, et al. Open Forum Infect Dis. 2017 Nov 2;4(4):ofx232.

Question 5

Tigecycline is generally active against which of the following organisms?

A. *Morganella morganii*
B. *Providencia rettgeri*
C. *Proteus mirabilis*
D. *Klebsiella aerogenes*

Question 5

Tigecycline is generally active against which of the following organisms?

A. *Morganella morganii*
B. *Providencia rettgeri*
C. *Proteus mirabilis*
D. ***Klebsiella aerogenes***

Online Only Lectures – Other Antibacterial Drugs (Macrolides, TMP, SMX, etc)

Speaker: Pranita Tamma, MD

Tigecycline

- Bind to the bacterial ribosome; prevents protein synthesis
- Enterococci (VRE), staphylococcal (MRSA), *S. pneumoniae*, gram-negatives
- Not active against "MP3": *Morganella* spp., *Providencia* spp. *Proteus* spp., *Pseudomonas* spp.
- Significant nausea and emesis
- Do not administer with calcium, iron, antacids, multivitamins
- Large volumes of distribution; eliminated hepatically
  - Not ideal for UTIs or bloodstream infections

Nitrofurantoin

- Uncomplicated cystitis
- *E. coli* and other enteric gram-negatives (not *P. aeruginosa*)
- Pulmonary toxicities
- Avoid if significant renal dysfunction
- Macrodantin: dosed four times a day
- Macrobid: dosed two times a day

Fosfomycin

- Uncomplicated cystitis
- Inhibits bacterial cell wall synthesis
- Only active against *E. coli* (and *E. faecalis*)
- Only available in United States as a powder

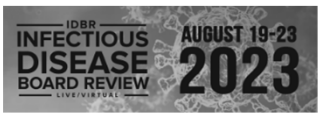
Metronidazole

- Active against anaerobes & protozoa
  - Gram-negatives: *Bacteroides* spp, *Fusobacterium* spp.
  - Gram-positives: *Clostridium* spp. (not preferred for *C. difficile* infections)
  - Protozoa: *Trichomonas vaginalis*, *Entamoeba histolytica*, *Giardia lamblia*
- Adverse events
  - Nausea, vomiting, metallic taste
  - Reversible peripheral neuropathy, confusion, seizures
- Interactions
  - Disulfiram-like reaction with alcohol consumption
  - Potentiation of warfarin because of inhibition of warfarin metabolism

OL7

Viral and Bacterial Meningitis

Dr. Allan Tunkel



Viral and Bacterial Meningitis

Allan R. Tunkel, MD, PhD, MACP
Professor of Medicine and Medical Science
The Warren Alpert Medical School of Brown University

6/15/2023

Disclosures of Financial Relationships with Relevant Commercial Interests

- **None**

CASE #1

- 38-year-old woman presents with a 2-day history of fever, headache and stiff neck; similar episodes have occurred every 3-4 months over several years, with spontaneous abatement after 4-5 days
- She is sexually active only with her husband of 8 years, and has 2 children at home (ages 2 and 5 years)
- On exam, T 99.8ºF and other vital signs are normal; she has evidence of meningismus, but is alert and oriented and with no focal findings
- Laboratory studies are normal
- CSF analysis reveals a WBC of 70/mm^3 (100% lymphs), glucose of 60 mg/dL, and protein of 100 mg/dL; Gram stain negative

QUESTION #1

Which of the following is the most likely etiology of this patient's meningitis?

A. Coxsackie A virus
B. Coxsackie B virus
C. Parvovirus B19
D. Herpes simplex virus type 2
E. Human herpesvirus 6

ANSWER #1

Which of the following is the most likely etiology of this patient's meningitis?

A. Coxsackie A virus
B. Coxsackie B virus
C. Parvovirus B19
D. Herpes simplex virus type 2
E. Human herpesvirus 6

VIRAL MENINGITIS
Major Etiologies

- Enteroviruses
- Mumps virus
- Herpesviruses
- Lymphocytic choriomeningitis virus
- Others
  - Arboviruses
  - Human immunodeficiency virus
  - Adenovirus
  - Parainfluenza virus types 2 and 3

Cerebrospinal Fluid (CSF) Findings in Viral Meningitis

CSF Parameter	Viral
Opening pressure	≤ 250 mm H_2O
WBC count	50-1000/mm^3
WBC differential	Lymphocytes
Glucose	>45 mg/dL
CSF: serum glucose	>0.6
Protein	<200 mg/dL
Gram stain	Negative

Enteroviruses

- Leading cause of "aseptic" meningitis syndrome
- Accounts for 85-95% of cases with identified etiology
- 30,000-75,000 cases annually in US (low estimate)
- Summer/fall seasonality; outbreaks reported
- Fecal-oral spread
- ~100 serotypes; 14 account for 80% of isolates
- CEMA (chronic enteroviral meningoencephalitis in agammaglobulinemia)
- Rituximab

Enteroviruses

- Clinical clues
  - Time of year
  - Outbreak in community
  - Other recognizable enteroviral syndromes
- Specific etiologies
  - Scattered maculopapular rash: echovirus 9
  - Herpangina: coxsackievirus A
  - Pericarditis/pleuritis: coxsackievirus B
  - Rhombencephalitis: enterovirus 71

Enteroviruses

- Symptoms and signs
  - Fever, headache, nuchal rigidity (>50%), photophobia
- Diagnosis
  - Neutrophils may predominate in CSF early (up to 48 hrs)
  - CSF virus isolation (sensitivity 65-75%)
  - Virus isolation from throat or rectum
  - PCR (sensitivity 86-100%; specificity 92-100%)
- Therapy
  - Supportive

Mumps Virus

- Common in unimmunized populations
- Occurs in 10-30% of mumps patients overall
- Peak in children 5-9 years of age; males>females
- Can occur in patients without parotitis; 40-50% have no evidence of salivary gland enlargement
- Symptoms and signs usually follow onset of parotitis (if present) by ~5 days
- Diagnosis
  - Serology
  - CSF RT-PCR
  - CSF culture (sensitivity 30-50%)

Herpes Simplex Virus

- Self-limited syndrome
- Most commonly with primary HSV-2 genital infection
  - 36% of women
  - 13% of men
- Less likely with recurrence of genital herpes
- Recurrent benign lymphocytic meningitis (Mollaret)
  - Most caused by HSV-2
  - Few or at least 10 episodes lasting 2-5 days followed by spontaneous recovery
  - Fever, headache, photophobia, meningismus

Herpes Simplex Virus

13

- Diagnosis
  - Lymphocytic pleocytosis (<500 cells/mm^3); normal glucose, elevated protein
  - CSF PCR
- Therapy
  - Usually self-limited; unclear if antiviral therapy alters course of mild meningitis, but usually recommended
  - Suppressive therapy (valacyclovir) not indicated for recurrent disease; associated with a higher frequency of meningitis after cessation of active drug

Lymphocytic Choriomeningitis Virus

14

- Now rarely reported as an etiologic agent
- Transmitted to humans by contact with rodents (hamsters, rats, mice) or their excreta
- As estimated 5% of house mice in the US are infected; infection more common in winter when mice are indoors
- Risk groups
  - Laboratory workers
  - Pet owners
  - Persons living in impoverished or unhygienic places
  - Rodent breeding factory
- No evidence of human-to-human transmission

CASE #2

15

- 60-year-old man with chronic kidney disease immigrated from Brazil to the US and underwent a cadaveric renal transplant
- Prior to transplant, he had episodes of recurrent epigastric pain. At the time, his WBC was 6,500/mm^3 with 15% eosinophils
- After transplant, he received immunosuppressive therapy

CASE #2

16

- Presented 1 month later with headache, meningismus and altered mental status, and a temperature of T 39^{o}C
- Lumbar puncture had WBC 2500/mm^3 (98% neutrophils), glucose 20 mg/dL, and protein 450 mg/dL
- Placed on empiric antimicrobial therapy with vancomycin, ampicillin, and ceftriaxone
- Cultures of blood and CSF grew *Escherichia coli*

Question #2

17

Which of the following diagnostic tests would most likely establish the pathogenesis of *E. coli* meningitis in this patient?

A. MRI of the head and sinuses
B. Right upper quadrant ultrasound
C. Serial stool examinations
D. Cisternography
E. Colonoscopy

Answer #2

18

Which of the following diagnostic tests would most likely establish the pathogenesis of *E. coli* meningitis in this patient?

A. MRI of the head and sinuses
B. Right upper quadrant ultrasound
C. Serial stool examinations
D. Cisternography
E. Colonoscopy

EPIDEMIOLOGIC FEATURES OF PNEUMOCOCCAL MENINGITIS

19

- Most common etiologic agent in US (58% of cases)
- Mortality of 18-26%
- Associated with other suppurative foci of infection
  - Pneumonia (25%)
  - Otitis media or mastoiditis (30%)
  - Sinusitis (10-15%)
  - Endocarditis (<5%)
  - Head trauma with CSF leak (10%)

EPIDEMIOLOGIC FEATURES OF MENINGOCOCCAL MENINGITIS

20

- Children and young adults; mortality 3-13%
- Serogroups A, B, C, W, and Y
- Serogroup B disease in recent outbreaks
- Predisposition in those with congenital deficiencies in terminal complement components (C5-C8, and perhaps C9) and properdin deficiencies
- Increased risk: MSM, HIV infection, use of complement inhibitors that block C5 (eculizumab, ravulizumab), microbiologists exposed to isolates, travel to epidemic or hyperendemic areas, outbreak-related, college students

EPIDEMIOLOGIC FEATURES OF GROUP B STREPTOCOCCAL MENINGITIS

21

- Important etiologic agent in neonates; mortality 7-27%
- Early-onset septicemia associated with prematurity, premature rupture of membranes, low birth weight
- Late onset meningitis (> 7 days after birth)
- Disease in adults associated with the following:

Diabetes mellitus	Parturient women
Cardiac, hepatic, renal disease	Malignancy
Collagen-vascular disorders	Alcoholism
HIV infection	Corticosteroid use

EPIDEMIOLOGIC FEATURES OF *LISTERIA* MENINGITIS

22

- Rare etiology in US (2-8%); mortality 15-29%
- Outbreaks associated with consumption of contaminated cole slaw, raw vegetables, milk, cheese, processed meats, cantaloupe, diced celery, ice cream, hog head cheese
- Common in neonates
- Low in young, previously healthy persons (4-10%)
- Disease in adults associated with:

Elderly	Alcoholism
Malignancy	Immune suppression
Diabetes mellitus	Hepatic and renal disease
Iron overload	Collagen-vascular disorders
HIV infection	Biologic therapies

EPIDEMIOLOGIC FEATURES OF AEROBIC GRAM-NEGATIVE BACILLARY MENINGITIS

23

- *Klebsiella* species, *Escherichia coli*, *Serratia marcescens*, *Pseudomonas aeruginosa*, *Acinetobacter baumannii*, *Salmonella* species
- Isolated from CSF of patients following head trauma or neurosurgical procedures, and from patients with CSF shunts or drains
- Cause meningitis in neonates, the elderly, immunocompromised patients, and in patients with gram-negative septicemia
- Associated with disseminated strongyloidiasis in the hyperinfection syndrome

EPIDEMIOLOGIC FEATURES OF *HAEMOPHILUS INFLUENZAE* MENINGITIS

24

- Causes 7% of cases in US; mortality 3-7%
- Capsular type b strains were previously in >90% of serious infections; children <6 years of age (peak 6-12 months)
- Concurrent pharyngitis or otitis media in >50% of cases
- Disease in persons >6 years of age associated with:

Sinusitis or otitis media	Pneumonia
Sickle cell disease	Splenectomy
Diabetes mellitus	Immune deficiency
Head trauma with CSF leak	Alcoholism

OTHER BACTERIAL ETIOLOGIES OF MENINGITIS

Bacterial Etiology	Risk Factors
Staphylococcus aureus	Neurosurgery, trauma, diabetes mellitus, alcoholism, hemodialysis, injection drug use, malignancy
Staphylococcus epidermidis	CSF shunts and drains
Diphtheroids (e.g., *Cutibacterium acnes*)	CSF shunts and drains
Anaerobes	Contiguous foci in head and neck
Streptococcus salivarius	Spinal anesthesia, myelogram
Streptococcus suis	Vietnam, eating undercooked pig blood or pig intestine, pig exposure

INCIDENCE OF BACTERIAL MENINGITIS (UNITED STATES)

Organism	Incidence (cases per 100,000)		
	1986	1995	2006-2007
H. influenzae	2.9	0.2	0.08
S. pneumoniae	1.1	1.1	0.81
N. meningitidis	0.9	0.6	0.19
Group B streptococcus	0.4	0.3	0.25
L. monocytogenes	0.2	0.2	0.05

CEREBROSPINAL FLUID FINDINGS IN BACTERIAL VERSUS VIRAL MENINGITIS

CSF Parameter	Bacterial	Viral
Opening pressure	200-500 mm H_2O	≤ 250 mm H_2O
WBC count	1000-5000/mm^3	50-1000/mm^3
WBC differential	Neutrophils	Lymphocytes
Glucose	<40 mg/dL	>45 mg/dL
CSF: serum glucose	≤ 0.4	>0.6
Protein	100-500 mg/dL	<200 mg/dL
Gram stain	(+) in 60-90%	Negative

CASE #3

- A 25-year-old man presents to the hospital with a 2-day history of fever, chills, headache, and mild confusion. He has paroxysmal nocturnal hemoglobinuria, and is currently on therapy with ravulizumab; he also takes oral penicillin V daily. Prior to starting ravulizumab, he received the quadrivalent (ACWY) meningococcal conjugate vaccine and the serogroup B meningococcal vaccine.
- T 40.5°C, P 120, RR 28, BP 90/60 mmHg; obtunded, stiff neck
- WBC 30,000/mm^3 (40% bands), platelets 40,000/mm^3
- Lumbar puncture revealed an opening pressure of 300 mm H_2O, WBC 1500/mm^3 (99% segs), glucose 20 mg/dL, and protein 300 mg/dL

Question #3

Which of the following empiric antimicrobial regimens should be initiated?

A. Penicillin G
B. Ceftriaxone
C. Vancomycin + ampicillin
D. Vancomycin + ceftriaxone

Answer #3

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B. Ceftriaxone
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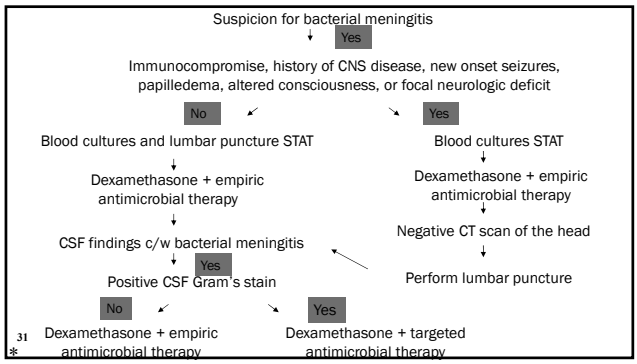
D. Vancomycin + ceftriaxone



EMPIRIC ANTIMICROBIAL THERAPY OF PURULENT MENINGITIS

32

Age	Antimicrobial Therapy
<1 month	Ampicillin + gentamicin + either cefotaxime (if available) or cefepime
1-23 months	Vancomycin + a third-generation cephalosporin[a]
2-50 years	Vancomycin + a third-generation cephalosporin[a,b,c]
Older than 50 years	Vancomycin + ampicillin + a third-generation cephalosporin[a]

[a]ceftriaxone or cefotaxime
[b]some experts would add rifampin if dexamethasone is also given
[c]add ampicillin if Listeria is suspected

EMPIRIC ANTIMICROBIAL THERAPY OF PURULENT MENINGITIS

33

Predisposing Condition	Antimicrobial Therapy
Immunocompromise	Vancomycin + ampicillin + either meropenem or cefepime
Basilar skull fracture	Vancomycin + a third generation cephalosporin[a]
Head trauma or after neurosurgery	Vancomycin + either ceftazidime or cefepime or meropenem
Cerebrospinal fluid shunt or drain	Vancomycin + either ceftazidime or cefepime or meropenem

[a]ceftriaxone or cefotaxime

TARGETED ANTIMICROBIAL THERAPY IN BACTERIAL MENINGITIS

34

Microorganism	Antimicrobial Therapy
S. pneumoniae	Vancomycin + a third-generation cephalosporin[a,b]
N. meningitidis	Third-generation cephalosporin[a]
H. influenzae	Third-generation cephalosporin[a]
L. monocytogenes	Ampicillin or penicillin G[c]

[a]ceftriaxone or cefotaxime
[b]addition of rifampin may be considered, especially if dexamethasone given
[c]addition of an aminoglycoside may be considered

ANTIMICROBIAL THERAPY IN BACTERIAL MENINGITIS

35

Organism	Antimicrobial Therapy
Streptococcus pneumoniae	
PCN MIC ≤0.06 μg/mL	Penicillin G or ampicillin
PCN MIC ≥0.12 μg/mL	
CTX[a] MIC <1.0 μg/mL	Third-generation cephalosporin[a]
CTX[a] MIC ≥1.0 μg/mL	Vancomycin + a third-generation cephalosporin[a,b]

[a]ceftriaxone or cefotaxime
[b]consider addition of rifampin if ceftriaxone MIC ≥4 μg/mL

ANTIMICROBIAL THERAPY IN BACTERIAL MENINGITIS

36

Organism	Antimicrobial Therapy
Neisseria meningitidis	
PCN MIC <0.1 μg/mL	Penicillin G or ampicillin
PCN MIC 0.1-1.0 μg/mL	Third-generation cephalosporin[a]
Haemophilus influenzae	
β-lactamase-negative	Ampicillin
β-lactamase-positive	Third-generation cephalosporin[a]

[a]ceftriaxone or cefotaxime

ANTIMICROBIAL THERAPY IN BACTERIAL MENINGITIS

37

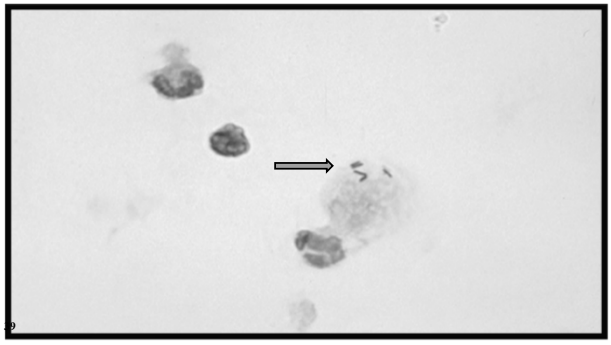
Organism	Antimicrobial Therapy
Pseudomonas aeruginosa	Ceftazidime or cefepime or meropenem
Acinetobacter baumannii	Meropenem or colistin (formulated as colistimethate sodium)[a] or polymyxin B[a]
Streptococcus agalactiae	Ampicillin or penicillin G
Listeria monocytogenes	Ampicillin or penicillin G[b]
Staphylococcus aureus	
MSSA	Nafcillin or oxacillin
MRSA	Vancomycin

[a]might also need to be administered by intraventricular or intrathecal routes
[b]addition of an aminoglycoside should be considered

CASE #4

38

- 60-year-old male with chronic lymphocytic leukemia presented with fever, headache, ataxia, and altered mental status. Recently traveled to an outdoor family picnic in rural Virginia. He is allergic to penicillin (anaphylaxis)
- T 102°F, P 120, RR 24, BP 100/60 mmHg
- He was obtunded and had nuchal rigidity
- WBC was 25,000/mm^3 (30% bands)
- LP revealed a WBC 1500/mm^3 (50 neutrophils, 50% lymphocytes), glucose 30 mg/dL, and protein 200 mg/dL



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Question #4

40

Which of the following antimicrobial regimens should be initiated?

A. Vancomycin
B. Trimethoprim-sulfamethoxazole
C. Chloramphenicol
D. Moxifloxacin
E. Daptomycin

Answer #4

41

Which of the following antimicrobial regimens should be initiated?

A. Vancomycin
B. Trimethoprim-sulfamethoxazole
C. Chloramphenicol
D. Moxifloxacin
E. Daptomycin

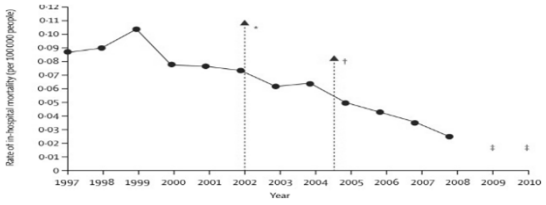
ADJUNCTIVE DEXAMETHASONE IN BACTERIAL MENINGITIS

42

- Attenuates subarachnoid space inflammatory response resulting from antimicrobial-induced lysis
- Recommended for infants and children with *Haemophilus influenzae* type b meningitis and considered for pneumococcal meningitis in childhood, given before or with parenteral antimicrobial therapy
- Recommended in adults with pneumococcal meningitis
- Administer at 0.15 mg/kg IV every 6 hours for 4 days in adults concomitant with or just before first antimicrobial dose

IN-HOSPITAL MORTALITY FOR PNEUMOCOCCAL MENINGITIS

43



Castelblanco et al. Lancet ID 2014;14:813

ADJUNCTIVE DEXAMETHASONE IN LISTERIA MENINGITIS

44

- French nationwide prospective cohort study of 252 patients with neurolisteriosis, 13% of whom received dexamethasone (Lancet Infect Dis 2017;17:510)
  - Increased mortality in those receiving dexamethasone (48% vs. 27%)
- Dutch prospective cohort study of 162 patients with Listeria meningitis, 58% of whom received dexamethasone (eClinicalMedicine 2023;58:101922)
  - Rate of unfavorable outcome higher in those not receiving dexamethasone (72% vs. 46%)
  - Not receiving dexamethasone was associated with an increased risk of death in the multivariable analysis (OR 0.40; CI 0.19-0.84)

45 QUESTIONS

Allan R. Tunkel, MD, PhD, MACP
Email: allan_tunkel@brown.edu

OL8

Chronic Hepatitis

Dr. David Thomas

IDBR INFECTIOUS DISEASE BOARD REVIEW AUGUST 19-23 2023

Acute Hepatitis

David L. Thomas, MD
Stanhope Bayne Jones Professor of Medicine
Johns Hopkins University
Chief of Infectious Diseases
Johns Hopkins School of Medicine

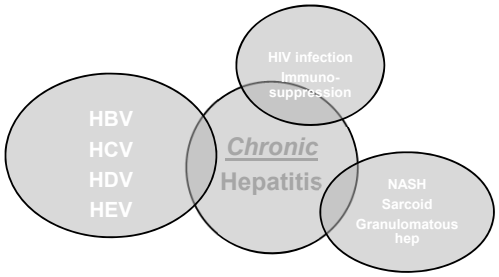
6/15/2023

IDBR INFECTIOUS DISEASE BOARD REVIEW AUGUST 19-23 2023

Disclosures of Financial Relationships with Relevant Commercial Interests

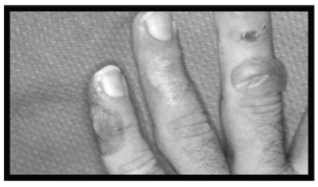
Data and Safety Monitoring Board: Merck

Advisory Board: Merck, Evrys, and Excision Bio



Case: Hepatitis C and a rash

A 44 year old, anti-HCV and HCV RNA positive man feels bad after a recent alcohol binge. He has a chronic rash on arms that is worse and elevated ALT and AST.



OConnor Mayo Clin Proc 1998

Question: HCV with a rash

The most likely dx is:

A. **Cirrhosis due to HCV and alcohol**
B. **Necrolytic acral erythema**
C. **Porphyria cutanea tarda**
D. **Essential mixed cryoglobulinemia**
E. **Yersinia infection**

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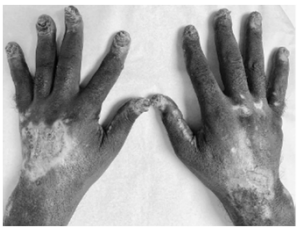
Porphyria Cutanea Tarda Associated with Hepatitis C

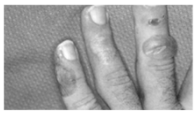
Tejesh S. Patel, M.D., and Evgeniya Teterina Mohammed, M.D.



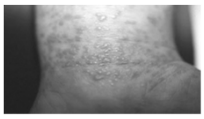
June 10, 2021
N Engl J Med 2021; 384:e86

Compare

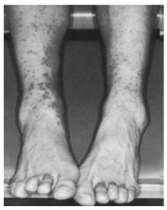
Porphyria cutanea tarda



Lichen planus



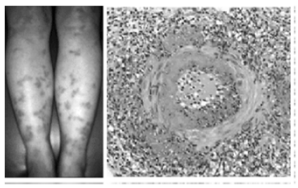
Cryoglobulin vasculitis



blogspot.com; OConnor Mayo Clin Proc 1998

Case: HBV and rash

46 year old woman HBsAg pos, anti-HCV neg



Chen Rheum 2014

Question: HBV with a rash

The most likely dx is:

A. **Necrolytic acral erythema**
B. **Porphyria cutanea tarda**
C. **Essential mixed cryoglobulinemia**
D. **Polyarteritis nodosa**
E. **Secondary syphilis vasculitis**

Question: HBV with a rash

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B. **Porphyria cutanea tarda**
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E. **Secondary syphilis vasculitis**

Question: Who needs an HCV antibody test?

A. **55 year old man with new exposure after HCV treatment**
B. **24 year old pregnant woman with no risk factors**
C. **Former PWID who was HCV negative 1 yr ago**
D. **HIV positive MSM with negative HCV antibody test 5 years ago and no risk factors**

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IDSA/AASLD guidelines

Recommendations for One-Time Hepatitis C Testing

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

RECOMMENDATION The USPSTF recommends screening for HCV infection in adults aged 18 to 79 years. (B recommendation)

JAMA. doi:10.1001/jama.2020.1123
Published online March 2, 2020.

Case: 54 y/o with HCV antibodies and RNA

54 year old man was anti-HCV pos after elevated ALT noted by primary. Brief IDU when 20-21; moderate ETOH; otherwise well.

HCV RNA 4 million IU/L; Genotype 1a; ALT 42 IU/ml; AST 65 IU/ml; TB 1.6 mg/dl; Alb 3.9 mg/dl; Hb – 13.4 mg/dl; creatinine 1.2 mg/dl; HBsAg pos; anti-HBc pos. HIV neg

Question: 54 y/o with HCV antibodies and RNA

Which of the following is the next appropriate step:

A. **Treat with oral regimen for 8-12 weeks**
B. **Check HCV 1a resistance test**
C. **Elastography**
D. **Confirm HCV antibody test**

Question: 54 y/o with HCV antibodies and RNA

Which of the following is the next appropriate step:

A. **Treat with oral regimen for 12 weeks**
B. **Check HCV 1a resistance test**
C. **Elastography**
D. **Confirm HCV antibody test**

HCV NS5 RAS testing is uncommonly recommended

Treatment naive

- **Genotype 1a and elbasvir/grazoprevir**
- **Genotype 3 AND cirrhosis for sofosbuvir/velpatasvir**

Treatment experienced

- **1a and ledipasvir/sofosbuvir 'considered'**
- **Genotype 3 and sofosbuvir/velpatasvir**

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

Wyles, HCVguidelines.org

Staging is needed for chronic HCV

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

Hcvguidelines.org

Of imperfect tests elastography is most sensitive for detection of cirrhosis

Test	% Sens	% Spec	AUROC
Fibrotest[1] >.56	85	74	.86
Fibrotest > .73	56	81	-
FIB4[2], >1.45	87	61	.87
APRI[3], >1.0	51	91	0.73
Elastography 12.5 kPa	89	91	0.95

Singh Gastro 2017; Chou Ann Intern Med 2013; Castera Gastro 2012

$$\text{FIB 4} = \frac{\text{Age (yrs) x AST (U/L)}}{\text{Platelet count } (10^9/\text{L}) \text{ x ALT (U/L)}^{1/2}}$$

847 liver biopsies with chronic HCV

	Liver Biopsy (METAVIR)		
FIB4 Index	F0-F1-F2	F3-F4	Total
<1.45	94.7% (n = 521)	5.3% (n = 29)	550
1.45-3.25	73.0% (n = 168)	27.0% (n = 62)	230
>3.25	17.9% (n = 12)	82.1% (n = 55)	67
Total	82.8% (n = 701)	17.2% (n = 146)	847

Sterling Hepatology 2006; Vallet-Pichard Hepatology 2007

Case con't: 54 year old with HCV

Elastography (17.3 kPa) and Fib-4 (5.5) consistent with cirrhosis. Ultrasound and UGI are ok and you recommend treatment. He wants to know why. Which can you NOT say is true of successful treatment?

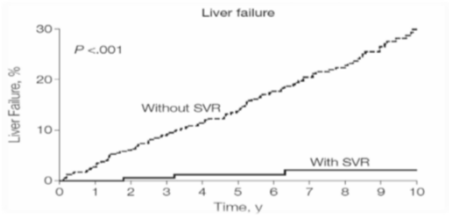
A. reduces risk of reinfection
B. reduces risk of death
C. reduces risk of HCC
D. reduces risk of liver failure

54 year old with HCV

Ultrasound and UGI are ok and you recommend treatment but he wants to know why. Which is NOT true of successful treatment?

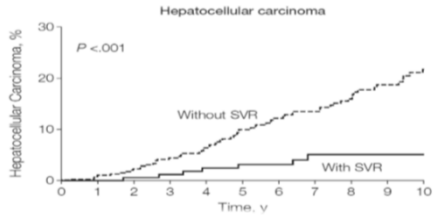
A. reduces risk of reinfection
B. reduces risk of death
C. reduces risk of HCC
D. reduces risk of liver failure

SVR reduces clinical outcomes



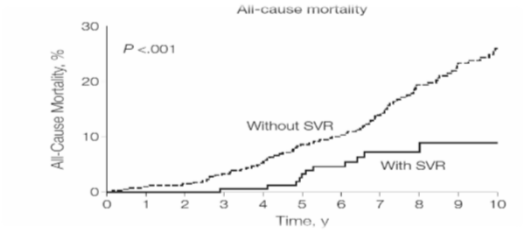
Van der Meer, *JAMA* 2012. Backus, *Clin Gastro* 2011. Imazeki, *Hepatology* 2003. Shiratori, *Ann Intern Med* 2005. Veldt, *Ann Intern Med* 2007. Berenguer, *Hepatology* 2009.

SVR reduces clinical outcomes



Van der Meer, *JAMA* 2012. Backus, *Clin Gastro* 2011. Imazeki, *Hepatology* 2003. Shiratori, *Ann Intern Med* 2005. Veldt, *Ann Intern Med* 2007. Berenguer, *Hepatology* 2009.

SVR reduces clinical outcomes



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AASLD AMERICAN ASSOCIATION FOR THE STUDY OF LIVER DISEASES | HCV Guidance: Recommendations for Testing, Managing, and Treating Hepatitis C | IDSA Infectious Diseases Society of America

Test, Evaluate, Monitor | Treatment-Naive | Treatment-Experienced | Unique & Key Populations

Recommended regimens listed by evidence level and alphabetically for:
Treatment-Naive Genotype 1a Patients With Compensated Cirrhosis[a]

RECOMMENDED	DURATION	RATING
Daily fixed-dose combination of ledipasvir (90 mg)/sofosbuvir (400 mg)	12 weeks	I, A
Daily fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg)	12 weeks	I, A
Daily fixed-dose combination of glecaprevir (300 mg)/pibrentasvir (120 mg)[b]	8 weeks	I, B

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

54 y/o with HCV antibodies, RNA, and cirrhosis

Treatment is given with glecaprevir and pibrentasvir

Treatment week 8: HCV RNA undet; ALT 1279 IU/L; AST 987 IU/L; TB 3.2 mg/dl.

Which test is likely to be most helpful?

A. Glecaprevir level
B. HCV resistance test
C. HCV IRIS T cell marker
D. HBV DNA
E. Liver biopsy with EM

54 y/o with HCV antibodies, RNA, and cirrhosis

Treat with glecaprevir and pibrentasvir. Treatment week 8 HCV RNA undet; ALT 1279 IU/L; AST 987 IU/L; TB 3.2 mg/dl.

Which test is likely to be most helpful?

A. Glecaprevir level
B. HCV resistance test
C. HCV IRIS T cell marker
D. HBV DNA
E. Liver biopsy with EM

FDA U.S. Food and Drug Administration Protecting and Promoting Your Health | Drug Safety Communications

FDA Drug Safety Communication: FDA warns about the risk of hepatitis B reactivating in some patients treated with direct-acting antivirals for hepatitis C

All are tested for HBV

- HBsAg pos: treat per HBV guidelines
- Anti-HBc pos: monitor

Bersoff-Macha Ann Intern Med 2017; Thio and Balagopal CID 2015

Which is NOT a pangenotypic regimen?

A. Glecaprevir and pibrentasvir
B. Sofosbuvir and velpatasvir
C. Sofosbuvir and ledipasvir

Which is NOT a pangenotypic regimen?

A. Glecaprevir and pibrentasvir
B. Sofosbuvir and velpatasvir
C. Sofosbuvir and ledipasvir

Which regimen is approved for ESRD?

A. Glecaprevir and pibrentasvir
B. Sofosbuvir and velpatasvir
C. Sofosbuvir and ledipasvir
D. All of the above

Which regimen is approved for ESRD?

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B. Sofosbuvir and velpatasvir
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D. All of the above

Which regimen is worst with darunavir?

A. Glecaprevir and pibrentasvir
B. Sofosbuvir and velpatasvir
C. Sofosbuvir and ledipasvir

Which regimen is worst with darunavir?

A. Glecaprevir and pibrentasvir
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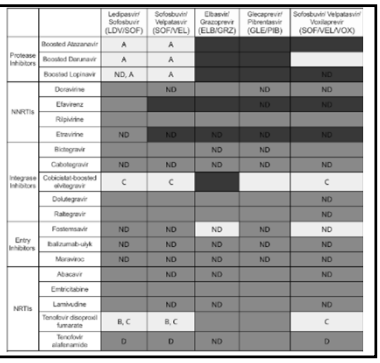
HCV-HIV ART drug interactions



		Ledipasvir/ Sofosbuvir (LDV/SOF)	Sofosbuvir/ Velpatasvir (SOF/VEL)	Elbasvir/ Grazoprevir (ELB/GRZ)	Glecaprevir/ Pibrentasvir (GLE/PIB)	Sofosbuvir/ Velpatasvir/ Voxilaprevir (SOF/VEL/VOX)
Protease Inhibitors	Boosted Atazanavir	A	A			
	Boosted Darunavir	A	A			
	Boosted Lopinavir	ND, A	A			ND
NNRTIs	Doravirine		ND		ND	ND
	Efavirenz				ND	ND
	Rilpivirine					
	Etravirine	ND	ND	ND	ND	ND
Integrase Inhibitors	Bictegravir			ND	ND	
	Cabotegravir	ND	ND	ND	ND	ND
	Cobicistat-boosted elvitegravir	C	C			C
	Dolutegravir					ND
	Raltegravir					ND
Entry Inhibitors	Fostemsavir	ND	ND	ND	ND	ND
	Ibalizumab-uiyk	ND	ND	ND	ND	ND
	Maraviroc	ND	ND	ND	ND	ND
NRTIs	Abacavir		ND	ND		ND
	Emtricitabine					
	Lamivudine		ND	ND		ND
	Tenofovir disoproxil fumarate	B, C	B, C			C
	Tenofovir alafenamide	D	D	ND		D

www.hcvguidelines.com

Slide 37 of 44

HCV treatment summary 2023

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

New 2023 HBV Testing Recs for USA

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

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

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

MMWR March 10, 2023

Case of chronic hepatitis B

31 yr old Asian woman is referred to see you because she had a positive HBsAg test. She is otherwise feeling fine.

HBsAg pos, HBeAg neg, anti-HBe pos, ALT 78 IU/ml, AST 86 IU/ml, TB 0.8, albumin 4.2 g/dl, INR 1.

Which of the following tests is NOT recommended?

A. HIV test
B. HBV resistance
C. HBV genotype
D. Hepatitis Delta testing
E. Quantitative HBV DNA level

Which of the following tests is not recommended?

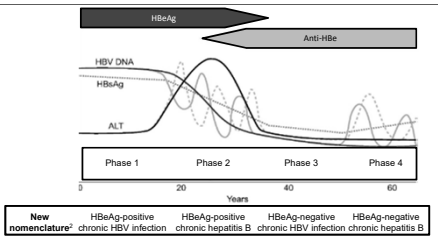
A. HIV test (necessary)
B. HBV resistance (not recommended)
C. HBV genotype (can be useful)
D. Hepatitis Delta testing (recommended)
E. Quantitative HBV DNA level (necessary)

Terrault Hepatology 2018

The essential evaluation of persons with CHB

- **HBeAg, HIV, HBV DNA, delta, genotype**
- **Stage (liver enzymes and/or elastography or biopsy)**
- **Renal status**
- **US to r/o HCC**
  - **Asian: male 40; female 50**
  - **African: 25-30**

Use testing to define disease phase[1]



New nomenclature[2]	HBeAg-positive chronic HBV infection	HBeAg-positive chronic hepatitis B	HBeAg-negative chronic HBV infection	HBeAg-negative chronic hepatitis B

1. Lok A, et al. J Hepatol 2017;67:847–61;
2. EASL CPG HBV. J Hepatol 2017;67:370–98

Use testing to define disease phase

The natural history of chronic HBV infection has been schematically divided into five phases

Chronic HBV infection	HBeAg positive		HBeAg negative		
	Phase 1	Phase 2	Phase 3	Phase 4	Phase 5
	Chronic HBV infection	Chronic hepatitis B	Chronic HBV infection	Chronic hepatitis B	Resolved HBV infection
HBsAg	High	High/ intermediate	Low	Intermediate	Negative
HBeAg	Positive	Positive	Negative	Negative	Negative
HBV DNA	>10^7 IU/mL	10^4–10^7 IU/mL	<2,000 IU/mL*	>2,000 IU/mL	<10 IU/mL‡
ALT	Normal	Elevated	Normal	Elevated†	Normal
Liver disease	None/minimal	Moderate/ severe	None	Moderate/ severe	None§
Old terminology	Immune tolerant	Immune reactive HBeAg positive	Inactive carrier	HBeAg negative chronic hepatitis	HBsAg negative /anti-HBc positive

*HBV DNA levels can be between 2,000 and 20,000 IU/mL in some patients without signs of chronic hepatitis;
†Persistently or intermittently, based on traditional ULN (~40 IU/L). ‡cccDNA can frequently be detected in the liver;
§Residual HCC risk only if cirrhosis has developed before HBsAg loss.
EASL CPG HBV. J Hepatol 2017;67:370–98

Use disease phase to determine whom to treat

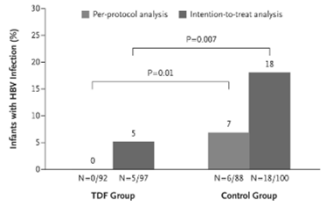
Chronic HBV infection	HBeAg positive		HBeAg negative	
	Phase 1	Phase 2	Phase 3	Phase 4
	Chronic HBV infection	Chronic hepatitis B	Chronic HBV infection	Chronic hepatitis B
HBV DNA	>10^7 IU/mL	10^4–10^7 IU/mL	<2,000 IU/mL*	>2,000 IU/mL
ALT	Normal	Elevated	Normal	Elevated†

Treat with both high DNA and ALT

*HBV DNA levels can be between 2,000 and 20,000 IU/mL in some patients without signs of chronic hepatitis;
†Persistently or intermittently, based on traditional ULN (~40 IU/L). ‡cccDNA can frequently be detected in the liver;
§Residual HCC risk only if cirrhosis has developed before HBsAg loss.
EASL CPG HBV. J Hepatol 2017;67:370–98

Test pregnant women for HBsAg and, if pos, for HBV DNA* and treat if > 200,000 IU/ml

Rec for all pregnant women to have quantitative HBV DNA TEST



*test in 3rd trimester

Terrault Hepatology 2015; Pan NEJM 2016

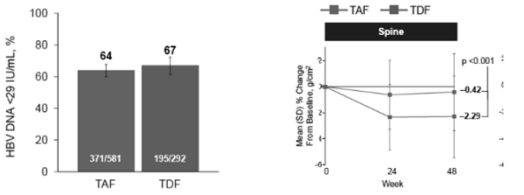
Four preferred treatments for chronic hepatitis B

HBeAg Positive	Peg-IFN*	Entecavir†	Tenofovir Disoproxil Fumarate†	Tenofovir Alafenamide‡
% HBV-DNA suppression	30-42 (<2,000-40,000 IU/mL)	61 (<50-60 IU/mL)	76 (<60 IU/mL)	73 (<29 IU/mL)
(cutoff to define HBV-DNA suppression)§	8-14 (<80 IU/mL)			
% HBeAg loss	32-36	22-25	—	22
% HBeAg seroconversion	29-36	21-22	21	18
% Normalization ALT	34-52	68-81	68	—
% HBsAg loss	2-7	4-5	8	1
	11 (at 3 years posttreatment)			
HBeAg Negative	**Peg-IFN**	**Entecavir**	**Tenofovir Disoproxil Fumarate†**	**Tenofovir Alafenamide‡**
% HBV-DNA suppression	43 (<4,000 IU/mL)	90-91 (<50-60 IU/mL)	93 (<60 IU/mL)	90 (<29 IU/mL)
(cutoff to define HBV-DNA suppression)§	19 (<80 IU/mL)			
% Normalization ALT¶	59	78-88	76	81
% HBsAg loss	4	0-1	0	<1
	6 (at 3 years posttreatment)			

TAF 25 mg with or without FTC

AASLD guidelines, Terrault Hepatology 2018

TAF is as effective and safer than tenofovir DF for chronic hepatitis B



Chan Lancet Gastro 2016

Treatment of HBV changes with renal insufficiency

- **GFR 30-60 mL/min/1.73 m²** : TAF 25 mg preferred
- **GFR <30-10:** TAF 25mg OR entecavir 0.5 mg q 3d
- **GFR <10 no dialysis:** entecavir 0.5 mg
- **Dialysis:** TDF 300mg/wk PD or entecavir 0.5mg/wk or TAF 25mg PD

It is hard to stop HBV treatment

- **If HBeAg conversion noted and no cirrhosis *consider* stopping after 6 months**
- **HBeAg neg when treatment started and all with cirrhosis stay on indefinitely**
- **(Newer practice is to use quantitative HBsAg and stop only when low (eg <100))**

HIV/HBV coinfected need treatment for both

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

What if HBV levels stay detectable?

- **Continue monotherapy, ideally with TAF or TDF**
- **Rising levels (breakthrough)**
  - **Counsel on adherence**
  - **Add second drug or switch esp if initial Rx with ETV**

Hepatitis serology in the oncology suite

You are called about 62 year old Vietnamese scientist who is in oncology suite where he is about to get R-CHOP for Non Hodgkins lymphoma.

Baseline labs: normal AST, ALT, and TBili. Total HAV detectable; anti-HBc pos; HBsAg neg; anti-HCV neg.

What do you recommend?

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

What do you recommend?

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

HBV Reactivation with immunosuppression

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

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

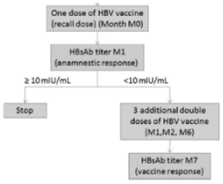
AASLD Terrault Hepatology 2018

Isolated anti-core antibodies usually reflect occult hepatitis B in high-risk groups

- Primary responses to vaccination
- 29 anti-HBc and 40 negative for anti-HBc
  - anamnestic response in anti-HBc pos (24%) vs anti-HBc neg (10%)
  - 50% anti-HBc pos also tested positive for anti-HBe
  - Anti-HBs seroconversion in ~60% both groups

Gandhi JID 2005; Terrault Hepatology 2018; Piroth CID 2018

HBV vaccination recommended in persons with isolated anti-HBc



Gandhi JID 2005; Terrault Hepatology 2018; Piroth CID 2018

HBV Prevention: vaccine and sometimes HBIG

Pre-exposure:

- vaccinate ALL < 60 yrs and get post vaccination titers (<2 months) if exposure likely
- Engerix; Recombivax; Heplisav (2 dose); PreHevbrio; Twinrix

MMWR April 1, 2022 71 (13) 477-483; MMWR / January 12, 2018 / Vol. 67 / No. 1

HBV Prevention: vaccine and sometimes HBIG

Post Exposure:

- vaccinate if not already done or not known to respond
- add HBIG when infection likely
- infants of HBsAg pos mothers get immediate vaccination and HBIG

MMWR April 1, 2022 71 (13) 477-483; MMWR / January 12, 2018 / Vol. 67 / No. 1

A final case of chronic hepatitis in transplant recipient

51 y/o HTN, and ankylosing spondylitis s/p renal transplant presents with elevated liver enzymes. Pred 20/d; MMF 1g bid; etanercept 25mg twice/wk; tacro 4mg bid. Hunts wild boar in Texas

HBsAg neg, anti-HBs pos, anti-HBc neg; anti-HCV neg; HCV RNA neg; CMV IgG neg; EBV neg; VZV neg. ALT 132 IU/ml, AST 65 IU/ml; INR 1. ALT and AST remained elevated; HBV, HCV, HAV, CMV, EBV serologies remain neg.

Barrague Medicine 2017

Which test is most likely abnormal

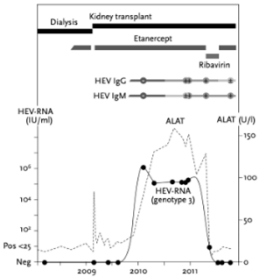
1. HEV PCR
2. HCV IgM
3. Tacrolimus level
4. Adenovirus PCR
5. Delta RNA PCR

Which test is most likely abnormal

1. HEV PCR
2. HCV IgM
3. Tacrolimus level
4. Adenovirus PCR
5. Delta RNA PCR

Chronic HEV in transplant recipient

- Europe (boar)
- Can cause cirrhosis
- Tacrolimus associated
- Ribavirin may be effective



Barrague Medicine 2017

Chronic Hepatitis for the Boards Summary

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

Thanks and good luck on the test!

Questions:

Dave Thomas
–**dthomas@jhmi.edu**

BONUS CASE

OL9

Even More Worms

Dr. Edward Mitre

Online Only Lectures – Even More Worms

Speaker: Edward Mitre, MD

IDBR INFECTIOUS DISEASE BOARD REVIEW AUGUST 19-23 2023

Even More Worms

Edward Mitre, MD
Bethesda, MD

7/25/2023

IDBR INFECTIOUS DISEASE BOARD REVIEW AUGUST 19-23 2023

Disclosures of Financial Relationships with Relevant Commercial Interests

- **None**

Disclaimer: Dr. Mitre is giving this presentation in a personal capacity. The views expressed in this presentation are the sole responsibility of the presenter and do not necessarily reflect the views, opinions, or policies of the Uniformed Services University of the Health Sciences, the Department of Defense, or the United States Government.

Major Helminth Pathogens

TREMATODES

Blood flukes
- *Schistosoma mansoni*
- *Schistosoma japonicum*
- *Schistosoma haematobium*

Liver flukes
- *Fasciola hepatica*
- *Clonorchis sinensis*
- *Opisthorchis viverrini*

Lung flukes
- *Paragonimus westermani*

Intestinal flukes
- *Fasciolopsis buski*
- *Metagonimus yokagawai*

CESTODES

Intestinal tapeworms
- *Taenia solium*
- *Taenia saginata*
- *Diphyllobothrium latum*
- *Hymenolepis nana*

Larval cysts
- *Taenia solium*
- *Echinococcus granulosus*
- *Echinococcus multilocularis*

NEMATODES

Intestinal
- *Ascaris lumbricoides*
- *Ancylostoma duodenale*
- *Necator americanus*
- *Trichuris trichiura*
- *Strongyloides stercoralis*
- *Paracapillaria philippinensis*
- *Enterobius vermicularis*

Tissue Invasive
- *Wuchereria bancrofti*
- *Brugia malayi*
- *Onchocerca volvulus*
- *Loa loa*
- *Trichinella spiralis*
- *Angiostrongylus cantonensis*
- *Anisakis simplex*
- *Toxocara canis/cati*
- *Baylisascaris procyonis*
- *Gnathostoma spinigerum*

Intestinal Flukes

Fasciolopsis buski

("Giant Intestinal Fluke" 2cm w x 8 cm)
- acquisition: eating encysted larval stage on aquatic vegetation
- symptoms: usually asymptomatic
  - can cause diarrhea, fever, abdominal pains, ulceration, and hemorrhage

Dx: eggs in stool

Metagonimus yokagawi

(2.5mm x 0.75mm)
- acquisition: eating larvae in undercooked fish
- symptoms: diarrhea and abdominal pain

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Hymenolepis nana

"Dwarf tapeworm" (4-6 cm long)

Found worldwide → the most common cestode infection of humans

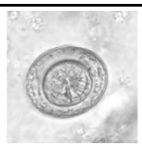
Predator (larval stage): rodents, humans
Prey (tapeworm stage): beetles!

Acquisition: by ingestion of eggs in contaminated food or water
OR by ingestion of infected grain beetle!

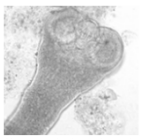
Symptoms: Often asymptomatic
With large parasite burdens, can cause
-loose stools, diarrhea
-crampy abdominal pain
-weakness

Diagnosis: finding eggs or proglottid segments in stool
(note: sometimes confused for pinworms)

Treatment: praziquantel 25 mg/kg x 1, repeat dose in 10 days
(higher than for most tapeworm infections)

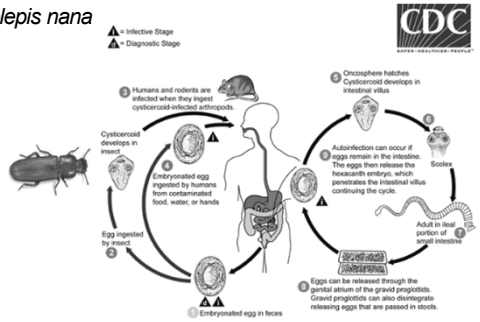


H. nana egg in wet mount (note the hooklets)
CDC DpDx



H. nana scolex in stool sample (note the hooklets and suckers)
CDC DpDx

Hymenolepis nana

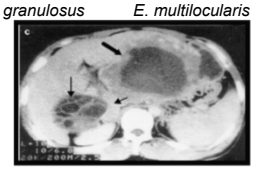


Echinococcus multilocularis

fox/rodent lifecycle

causes an infiltrative, tumor-like growth in liver
- → poorly demarcated
- → has a semi-solid nature (does <u>not</u> form large cysts)

E. granulosus *E. multilocularis*



Lancet 2003 362:1295-304

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- *Hymenolepis nana*

Larval cysts
- *Taenia solium*
- *Echinococcus granulosus*
- *Echinococcus multilocularis*

<u>NEMATODES</u>

Intestinal
- *Ascaris lumbricoides*
- *Ancylostoma duodenale*
- *Necator americanus*
- *Trichuris trichiura*
- *Strongyloides stercoralis*
- *Paracapillaria philippinensis*
- *Enterobius vermicularis*

Tissue Invasive
- *Wuchereria bancrofti*
- *Brugia malayi*
- *Onchocerca volvulus*
- *Loa loa*
- *Trichinella spiralis*
- *Angiostrongylus cantonensis*
- *Anisakis simplex*
- *Toxocara canis/cati*
- *Baylisascaris procyonis*
- *Gnathostoma spinigerum*

Paracapillaria philippinensis

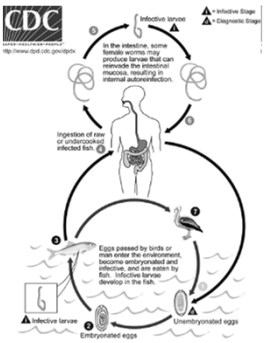
<u>Epidemiology:</u> primarily SE Asia

<u>Risk factor:</u> **eating raw freshwater fish**

<u>Sxs:</u>
often initially asymptomatic

Over time develop:
- borborygmus
- abdominal pain
- watery diarrhea

→ If not treated over weeks to months get large electrolyte losses and dehydration which can lead to death



Paracapillaria philippinensis

<u>Pathogenesis:</u>

Eat infected raw fish

→ larvae released into intestine

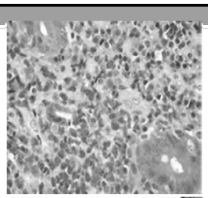
→grow to adults which burrow in mucosa

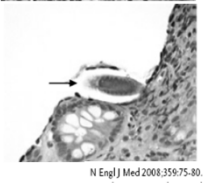
→ female worms lay eggs (oviparous)

→ some female worms are larviparous

→ some larvae burrow into the intestinal lining and develop into adults

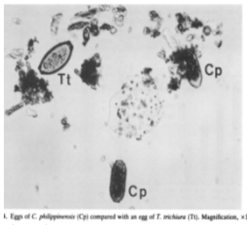
→ over weeks to months the worm burden increases (from a few worms to tens of thousands) and symptoms progress



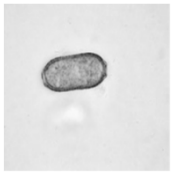


N Engl J Med 2008;359:75-80.

Paracapillaria philippinensis



1. Eggs of *C. philippinensis* (Cp) compared with an egg of *T. trichiura* (Tt). Magnification, ×160.
Cross J, Clin Micr Reviews, 1992

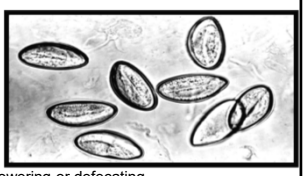


N Engl J Med 2008;359:75-80.

Dx: stool o/p (eggs similar to Trichuris)

Rx: 10 d course albendazole + supportive Rx (IVF, replete electrolytes, etc.)

Enterobius vermicularis (pinworm)



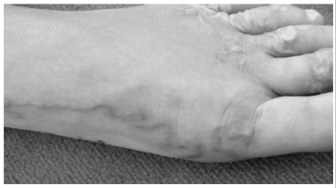
- Found everywhere
- Fecal/oral
- Humans are the only hosts
- peri-anal itching (rare: appendicitis)

Dx: stool o&p exams not very helpful
→ "pinworm paddle test" early am before showering or defecating
→ eggs have one flat side

Rx: pyrantel pamoate, albendazole, or mebendazole single dose
→ treat all members of household
→ retreat everyone in two weeks
→ careful trimming of fingernails, handwashing, washing of bedclothes to rid house of eggs

Question

A 13 year old girl developed a pruritic rash on her foot after moving to rural northeast Florida. Which of the following helminths is the most likely cause of the rash?



Am Fam Physician 2010, 81(2): 203-4.

A. *Enterobius vermicularis*
B. *Ascaris lumbricoides*
C. *Trichuris trichiura*
D. *Toxocara canis*
E. *Anyclostoma caninum*

Cutaneous Larva Migrans

Creeping eruption caused by dog or cat hookworms

Ancylostoma caninum
Ancylostoma braziliense
Uncinaria stenocephala

- Worms migrate laterally
- Unable to penetrate basal membrane of human skin
- Can occur 2-8 weeks after exposure

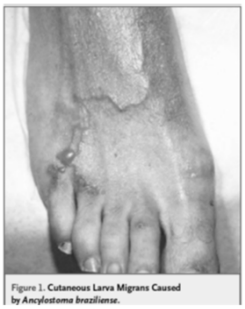


Figure 1. Cutaneous Larva Migrans Caused by *Ancylostoma braziliense*.
N ENGL J MED 351;8 WWW.NEJM.ORG AUGUST 19, 2004

Nodding syndrome

Neurological disease
- *Progressive cognitive dysfunction*
- *Nodding seizures – especially when children start to eat*
- *Growth stunting*

→ associated with Onchocerciasis

Tanzania 1960s
South Sudan 1990s
Northern Uganda 2007

A child in Uganda with nodding syndrome. NPR 2/15/2017

May be due to cross-reactive antibodies, triggered by Onchocerca infection, that recognize leiomodin-1 in the hippocampus

Johnson et al, Science Translational Medicine 2017 v9 issue 377

Onchocerciasis in the U.S.?

The Emergence of Zoonotic *Onchocerca lupi* Infection in the United States – A Case-Series

Clinical Infectious Diseases® 2016;62(6):778–83

- *Onchocerca lupi → an infection of wolves*
- *as with O. volvulus, is transmitted by blackflies*
- *6 human cases reported to date*
- *3 with deep nodules near cervical spinal cord*
- *Southwestern U.S.(Arizona, New Mexico, Texas)*

Question

A 6 yo boy from Indiana who has a pet dog and likes to play in a sandbox presents with fever, hepatosplenomegaly, wheezing, and eosinophilia. He has never travelled outside the continental U.S.

The most likely causative agent acquired in the sandbox is:

A. *Anisakis simplex*
B. *Onchocerca volvulus*
C. *Enterobius vermicularis*
D. *Toxocara canis*
E. *Anyclostoma braziliense*

Toxocariasis (and Baylisascariasis)

Due to dog (*Toxocara canis*), cat (*Toxocara cati*), and raccoon (*Baylisascaris procyonis*) ascarids.

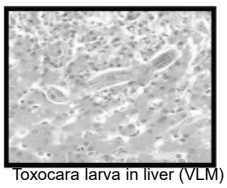
Humans acquire infection by ingestion of animal feces.
In humans → larvae hatch in intestine and migrate to liver, spleen, lungs, brain, and/or eye.

Symptoms

Visceral Larva Migrans (VLM)
usually 2-5 year olds
fever, eosinophilia, hepatomegaly
also wheezing, pneumonia, splenomegaly

Ocular Larva Migrans (OLM)
often in 10-15 year olds
retinal lesions that appear as solid tumors

Baylisascaris often more severe and more likely to cause CNS disease (eosinophilic meningitis)



Toxocara larva in liver (VLM)
CDC DPDx

Toxocariasis

Dx: Clinical picture + Toxocara antibody testing
(serum and intraocular fluid by ELISA testing)

NOTE: Toxocara IgG is only supportive b/c many individuals have + Ab due to prior exposure

Rx: usually self-limited disease.
acute VLM or OLM can be Rx with albendazole and steroids

Gnathostoma spinigerum and hispidum

Undercooked freshwater fish (ceviche!), frogs, birds, reptiles
Asia (esp Thailand), Central/South America, parts of Africa

→ Disease due to migrating immature worms.
→ Often with peripheral eosinophilia

SKIN: migratory, painful subcutaneous swellings (recur every few weeks, can last for years)
creeping eruption/cutaneous larva migrans

TISSUE: visceral larva migrans
eosinophilic meningoencephalitis
radiculomyelitis
ocular disease (anterior and posterior uveitis)

Dx: empiric or by biopsy, no antibody test available in the U.S.

Rx: can be difficult, may require 3 weeks of albendazole

Good Luck!

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OL10

Statistics

Dr. Khalil Ghanem

Statistics

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Division of Infectious Diseases
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7/2/2023

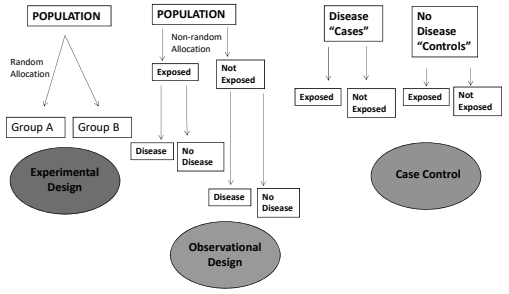
Disclosures of Financial Relationships with Relevant Commercial Interests

- **None**

Overview

- Study designs
- Incidence & Prevalence
- Relative risk, relative odd, & attributable risk
- Confidence intervals
- Number needed to treat
- Sensitivity, specificity, positive predictive value, negative predictive value
- Bias and confounding

Study Designs



Example: Study Designs

- **Choose the most appropriate study design for the following scenarios:**
  - You are trying to determine what caused 35 people to experience fever and severe hemorrhagic complications upon returning from a Caribbean cruise
  - You want to get FDA approval for a novel influenza vaccine
  - You want to determine whether hormonal contraception increases your risk of HIV

Incidence vs. Prevalence

- **Incidence**= *new* infection occurring during a specified period of time in a population at risk for developing the infection
  - A measure of events (a disease that develops in someone who did not have it), thus, a measure of *risk*
- **Prevalence:** number of affected persons present in the population at a given time(i.e. *existing* infections)
- **Prevalence=Incidence X duration of disease**

Example: Incidence vs. Prevalence

- **In a population that includes persons with HIV who exhibit high medication adherence, what would the impact of ART be on HIV incidence and prevalence over a 10 year period?**
  -Incidence= new HIV infections. ART should decrease the risk of transmission of HIV and thereby **decrease** the incidence
  -Prevalence= all existing HIV infections. ART allows people with HIV to live longer so it may **increase** the prevalence of HIV

Estimating Risk

- **Relative Risk (RR)**= Incidence in exposed/ Incidence in nonexposed
  - If the RR=1, there is no association
  - If the RR >1, the risk in exposed > nonexposed
  - If the RR<1, the risk in exposed < nonexposed
- **Hazards Ratio(HR)**: A form of RR; HR is instantaneous while RR is cumulative.
- **Odds**= Probability that disease developed/Probability that it did not develop
- **Odds Ratio:**
  - **Cohort study:** ratio of odds of disease occurring in exposed to the odds of disease occurring in non-exposed
  - **Case Control**: ratio of the odds that the cases were exposed to the odds that the controls were exposed
  - If the OR=1, there is no association between exposure and disease
  - If the OR>1, the exposure is positively related to the disease
  - If the OR<1, the exposure is negatively related to the disease

Example: Estimating Risk

- **In a population of 1000 people, 400 were having condomless sex. Infection-Y occurred in 100 of the 400 who were having condomless sex and in 5 of the 600 who were not.**
- **What is the RR of Y in those having condomless sex?**
- **What are the relative odds (odds ratio) of Y in those having condomless sex?**

- RR: 100/400/5/600= 31.3
- OR: 100/300/5/595=41.3

- The odds ratio is a good estimate of the relative risk when the disease being studied is RARE

Estimating Risk 2

- The **attributable risk** is the proportion of disease incidence that can be attributed to a specific exposure
  AR= Incidence in exposed- Incidence in non-exposed
- This is one of the most important measures when deciding *how* to spend money and resources in public health

Example: Estimating Risk 2

A new deadly fungal infection is described with a mortality rate of 30%.
You are given 1 million dollars to spend on prevention in your state.
-Persons with Exposure A have a RR of 16 for getting infected.
-Persons with Exposure B have a RR of 2 for getting infected.

How will you spend your money?

Example: Estimating Risk 2

- Exposure A is spelunking and Exposure B is gardening
  - **NOW how are you going to spend your money?**
- Even though the relative risk of spelunking is far more than gardening, most of the cases in your state are likely the result of gardening (a lot more people garden).
- The attributable risk of gardening, therefore, is much greater than that of spelunking

Exposure	Incidence	Relative Risk	Attributable Risk
Spelunking	32 per million	**16**	30 per million
No Spelunking	2 per million		
Gardening	640 per million	2	**320 per million**
No Gardening	320 per million		

Confidence Intervals

- Confidence intervals (CI) are used to indicate the reliability of an estimate
  - CI is *directly* related to the standard deviation and *indirectly* related to the sample size (i.e. the larger the sample size, the smaller the CI)
- In simple terms, a 95% CI means: If you were to repeat this experiment many times, 95% of the time, your results will fall within this range.
  - The wider the CI surrounding the point estimate, the more uncertainty there is about the reliability of that point estimate

Example: Confidence Intervals

- Match each scenario to the more likely prevalence point estimate and CI:
  - **Scenario 1**: We test 100 people in the population for HIV.
  - **Scenario 2**: We test 3500 people in the population for HIV

A. The prevalence of HIV is 1.3% (95%CI: 1.1 %-1.5%)
B. The prevalence of HIV is 3.3% (95%CI: 0.3%-7.2%)

Number Needed to Treat (NNT)

- NNT= 1/(Rate in untreated)- (Rate in treated)

Example: NNT

RCT for a new Ebola vaccine: the mortality rate in the experimental group is 20 per 100,000 while the mortality rate in the control group is 85 per 100,000. How many people do we need to vaccinate to prevent one death from Ebola?

NNT= 1/(0.85-0.20)=1.5

1.5 people need to be vaccinated to prevent a single death from Ebola. This would be a GREAT public health intervention in endemic areas.

Sensitivity, Specificity, Positive Predictive Value (PPV), Negative Predictive Value (NPV)

	Disease	No Disease
Positive	True Positive	False positive
Negative	False negative	True negative

Sensitivity= TP/ TP + FN
Specificity= TN/ TN +FP
PPV= TP/ TP + FP
NPV= TN/TN +FN

Sensitivity and specificity are INDEPENDENT of prevalence whereas PPV and NPV are DEPENDENT on prevalence

- **Sensitivity**= the ability of a test to correctly identify those who have a disease
- **Specificity**=the ability of a test to correctly identify those who do not have a disease
- **PPV**= the proportion who test positive and actually have the disease
- **NPV**=the proportion who test negative and actually don't have the disease

Example: Sensitivity Specificity, PPV, NPV

The glycoprotein-G- based antibody tests for the detection of HSV-2 antibodies have a sensitivity of 99% and specificity of 98.5%. We plan to test two populations: (A) 1000 commercial sex workers (B) 1000 nuns confined to a convent.

In which population will the tests have a higher: Sensitivity? Specificity? PPV? NPV?

- Sensitivity and specificity are INDEPENDENT of prevalence of disease. As such, the sensitivity and specificity of these tests will be the same in both populations
- Population A likely has a higher prevalence of HSV-2 compared to population B. As such, the PPV of the test will be higher in population A and the NPV will be higher in population B

Definitions

- **Precision**: How close do the results cluster to ***each other***?
- **Accuracy**: How close do the results cluster to ***the truth***?
- **Bias**: systematic error leading to a decrease in accuracy
  - Bias is reduced by careful study design
- **Confounding**: a distortion in the degree of association between an exposure and an outcome due to a mixing of effects between the exposure and an incidental factor, which is known as the confounder
  - **You must adjust for confounding; otherwise, it will lead to misinterpretation of results**
- **Effect Modification** (i.e. interaction): a variable that differentially (positively and negatively) modifies the observed effect of a risk factor on disease status. Different groups have different risk estimates when effect modification is present
  - **Effect modification is a true phenomenon that should be reported. You do NOT need to adjust for it.**

Example: Definitions

- Drinking coffee is found to be strongly associated with an increased risk of HPV-induced cervical cancer. We later find out that those who drink coffee are much more likely to smoke cigarettes.
- Cigarette smoking is a _____ in the relationship between coffee drinking and cervical cancer

Thank you!