GW | Office of Continuing Education in the Health Professions

29th Annual

COMPREHENSIVE REVIEW *for* INFECTIOUS DISEASE BOARD PREPARATION

VOLUME 2

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www.IDBoardReview.com

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Course Overview

About the Course

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

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

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

Educational Objectives

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

GUIDE TO COURSE MATERIALS APP

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

With the App you can:

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

To Access the App via Mobile Device:

1. Search for "eventScribe" in the Apple App Store or Google PlayStore.
2. Install and open the eventScribe app.
3. Search for your event app by entering "**IDBR 2024**."
4. To start using the app, please log in with the email and password emailed to you prior to your arrival.

Please Note:

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

ACCREDITATION, CME & MOC CLAIM INFORMATION - PHYSICIANS

TYPES OF CREDIT

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

1. Attending the Live Course - 43 credits
2. Completing the Online Materials - 75 credits

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

LIVE COURSE

Accreditation

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

CME Credit for Physicians

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

Claiming MOC Points

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

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

Deadline for Claiming MOC Points

ABIM Board Certified physicians need to claim MOC points for this course **by December 31, 2024** in order **for the MOC points to count toward any MOC requirements that are due by the end of 2024.**

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

OVERVIEW AND INSTRUCTIONS FOR CLAIMING CME CREDIT AND MOC POINTS

LIVE MATERIALS

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

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

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

ONLINE MATERIALS

Credit

The George Washington University School of Medicine and Health Sciences designates this enduring material for a maximum of 75 *AMA PRA Category 1 Credit(s)™.* Physicians should claim only the credit commensurate with the extent of their participation in the activity.

MOC Points

Successful completion of this CME activity enables the participant to earn up to 75 MOC points in the American Board of Internal Medicine's (ABIM) Maintenance of Certification (MOC) program.

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

Claiming Credit and MOC

Participants can earn up to 75 hours of CME credit and MOC points by completing the below online activities associated with the course.

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

Deadlines for Claiming MOC Points

ABIM Board Certified physicians need to claim MOC points for this course **by December 31, 2024** in order **for the MOC points to count toward any MOC requirements that are due by the end of 2024.**

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

OVERVIEW OF ONLINE MATERIALS AND INSTRUCTIONS FOR CLAIMING CREDIT AND MOC

Online-Only Lectures	**CME Hours: 9**	**MOC Points: 9**
• These lectures feature topics that were not covered in the live course.		
Board Prep Questions	**CME Hours: 56**	**MOC Points: 56**
• There are four (4) sets of 100 board prep questions. • There is one (1) set of 100 photo opportunity questions. • There is one (1) set of 30 questions on HIV. • You will see the correct answer and rationale after submitting each question. • You can only go in the forward direction when answering questions. • You cannot go backwards, but you can retake each set of questions as many times as you like.		
Online Primers and Study Guides	**CME Hours: 10**	**MOC Points: 10**
• There are eight (7) study guides and primers that present core material for you to review. • This PDF reviews information that summarizes important topics in photos, tables and short summaries.		

GUIDE TO ONLINE MATERIALS ACCESS

Initial Notification

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

Current Access

Instructions for accessing the Online Materials

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

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

Important Links

Please note that you must be logged in to access.

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

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

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

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

FACULTY LISTING

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

FACULTY DISCLOSURES AND RESOLUTIONS

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

FACULTY (SPEAKERS)

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

PLANNERS

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

Both planners also resolved financial disclosures

STAFF

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

The following faculty members (speakers) disclosed commercial relationships:

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

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

Agenda Day 1: Saturday, August 17, 2024

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

Agenda Day 2: Sunday, August 18, 2024

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

Agenda Day 3: Monday, August 19, 2024

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

Agenda Day 4: Tuesday, August 20, 2024

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

Agenda Day 5: Wednesday, August 21, 2024

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

Online Materials

Online Only Lectures

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

Primers and Study Guides

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

Board Review Question Sets

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

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Agenda Day 4: Tuesday, August 20, 2024

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

QP4

Daily Question Preview 4

Dr. Roy Gulick (Moderator)

QP4 – Question Preview: Day 4

Moderator: Roy Gulick, MD

Daily Question Preview: Day 4

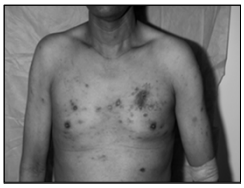
Moderator: Roy Gulick, MD

7/1/2024

PREVIEW QUESTION 2024

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

He has had low grade fevers for several months.



1 of 3

PREVIEW QUESTION 2024

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

A) HHV-6

B) CMV

C) Cryptococcus neoformans

D) Bartonella

E) Rhodococcus

2 of 3

PREVIEW QUESTION 2024

4.2 **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 68 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 2024

4.3 **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) dolutegravir/rilpivirine

C) tenofovir alafenamide/emtricitabine/rilpivirine

D) dolutegravir/lamivudine

E) tenofovir alafenamide/emtricitabine/bictegravir

1 of 2

PREVIEW QUESTION 2024

4.4

- **34 yo MSM receiving CAB IM q 2 months for pre-exposure prophylaxis for last 6 months**
- **Asymptomatic**
- **HIV Ag/Ab test negative**
- **Routine screening: HIV RNA 6.1 c/ml**

1 of 3

QP4 – Question Preview: Day 4

Moderator: Roy Gulick, MD

PREVIEW QUESTION

4.4 **Which of the following ARV resistance mutations is most likely in this setting?**

A) S147G

B) N155H

C) Y143R

D) E92Q

E) K65R

2 of 3

PREVIEW QUESTION

4.5 **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

1 of 2

PREVIEW QUESTION

4.6 **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

1 of 2

PREVIEW QUESTION

4.7 **38yo female with 1 day of sore throat and fever.**

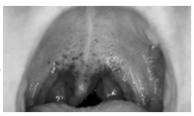
Childhood history of anaphylaxis to penicillin.

Physical exam:

T=102.3

HEENT-tonsillar erythema & petechiae

Neck-Tender bilateral anterior LAN



Labs:

Rapid strep antigen test negative

1 of 3

PREVIEW QUESTION

4.7 **What is the most appropriate antimicrobial treatment?**

A) Cephalexin

B) None

C) Doxycycline

D) Clindamycin

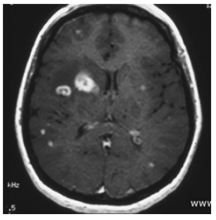
E) Levofloxacin

2 of 3

PREVIEW QUESTION

4.8

- **50 yo M with HIV (CD4 40, HIV RNA 600,000 not on antiretroviral therapy) presents with fever, headache**
- **Northeast US, no travel; no animal or TB exposures**
- **MRI: ring enhancing lesions; no midline shift**
- **Serum toxoplasma IgG + CSF: no WBC, normal protein, toxoplasma (toxo) PCR pending**



1 of 3

QP4 – Question Preview: Day 4

Moderator: Roy Gulick, MD

PREVIEW QUESTION

4.8 You recommend:

A) Brain biopsy

B) Meningeal biopsy

C) Initiate anti-toxo therapy; if no response in 2 weeks, brain biopsy

D) Vancomycin, cefepime, metronidazole

2 of 3

PREVIEW QUESTION

4.9 50-yo woman with HIV (CD4 20, HIV RNA 500,000) presents with fever and headache. Not on antiretroviral therapy (ART). Diagnosed with cryptococcal meningitis.

Started on induction therapy (liposomal amphotericin plus 5FC).

When should she be started on ART?

A) Start ART at the same time as anti-fungal therapy

B) About 4 weeks after starting anti-fungal therapy

C) 6 months after starting anti-fungal therapy

D) After completing a full course of maintenance anti-fungal therapy

1 of 2

PREVIEW QUESTION

4.10 A 39-year-old woman is admitted for 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.

T=104.2ºF.

Tender cervical LAN appreciated.

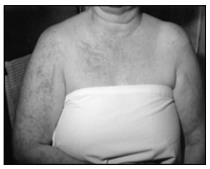
Spleen tip is palpable.

Both knees are swollen & painful.

1 of 4

PREVIEW QUESTION

4.10 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.

2 of 4

PREVIEW QUESTION

4.10 The most likely diagnosis is?

A) Lymphoma

B) Adult Still's Disease

C) Acute Rheumatic Fever

D) Cryoglobulinemia

E) Kikuchi Disease

3 of 4

PREVIEW QUESTION

4.11 A 24-year-old man was referred by the ED for evaluation of ulcers of the mouth and penis. He was born 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.

1 of 4

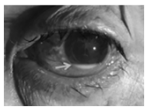
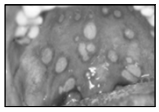
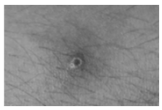
QP4 – Question Preview: Day 4

Moderator: Roy Gulick, MD

PREVIEW QUESTION

4.11

- Left eye is inflamed and there is a hypopyon.
- Numerous painful 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.

2 of 4

PREVIEW QUESTION

4.11 The most likely diagnosis is?

A. Syphilis
B. Behçet's disease
C. Herpes simplex virus infection
D. Sarcoidosis
E. Cytomegalovirus infection

3 of 4

PREVIEW QUESTION

4.12

- 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

1 of 3

PREVIEW QUESTION

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

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

2 of 3

PREVIEW QUESTION

4.13

- 50-year-old man presents with a several day history of fever, headache, and personality change with progression to confusion
- On exam, temperature is 101°F; he is disoriented and unable to follow commands
- CT scan of the head without contrast is negative
- CSF analysis reveals a WBC of 80/mm^3 (95% lymphs), glucose 70 mg/dL (serum 100 mg/dL), protein 120 mg/dL; Gram stain is negative

1 of 4

PREVIEW QUESTION

4.13

- Acyclovir is initiated
- MRI with gadolinium reveals enhancement in the left temporal lobe
- Results of initial cerebrospinal fluid (CSF) polymerase chain reaction (PCR) for HSV-1 and HSV-2 return negative
- After 3 days, the patient is now oriented to name and follows simple commands

2 of 4

QP4 – Question Preview: Day 4

Moderator: Roy Gulick, MD

PREVIEW QUESTION

4.13 What is the next step in the management of this patient?

A) Perform a brain biopsy of the left temporal lobe
B) Obtain new CSF for HSV PCR testing
C) Send serum for HSV IgG antibodies
D) Repeat brain MRI
E) Discontinue acyclovir

3 of 4

PREVIEW QUESTION

4.14 What's the strongest risk factor for progression of COVID-19 to severe disease?

A) Older age
B) Diabetes, heart disease, or other comorbidities
C) Race/ethnicity
D) Vaccine status
E) Being infected with an omicron variant

1 of 2

PREVIEW QUESTION

4.15 What's the treatment of choice for COVID-19 with hypoxia?

A) Nirmatrelvir-ritonavir
B) Remdesivir
C) Dexamethasone
D) A and B
E) B and C

1 of 2

34

Clinical Manifestations of Human Retroviral Diseases and Slow Viruses

Dr. Frank Maldarelli

34 – Clinical Manifestations of Human Retroviral Diseases and Slow Viruses

Speaker: Frank Maldarelli, MD

IDBR INFECTIOUS DISEASE BOARD REVIEW AUGUST 17-21, 2024

Clinical Manifestations of Human Retroviral Diseases and Slow Viruses

Frank Maldarelli, MD
Bethesda, MD

7/1/2024

IDBR INFECTIOUS DISEASE BOARD REVIEW AUGUST 17-21, 2024

Disclosures of Financial Relationships with Relevant Commercial Interests

- **None**

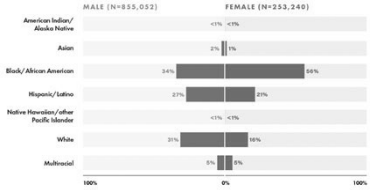
Adults and Children Estimated to be Living with HIV 2022

>75% access to antiretroviral therapy
HIV incidence: 1.3 million new infections/year
HIV prevalence: 39 million persons living with HIV

UNAIDS

Current US Epidemic

Prevalence: 1.1 Million



75% Male
70% Persons of Color

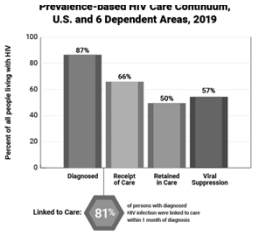
Male to Male Sexual Contact (MMSC): 68%
Heterosexual Contact 22%
IDU 10%

Diagnoses: 31,800 in 2022

CDC, 2022

2030 US HIV Public Health Goals: Treatment Cascade

95 % Diagnosed
95% Undergoing Antiretroviral Therapy
95% Viral RNA Suppressed



>50% Diagnoses are <35
>50% Living with HIV are >50 years

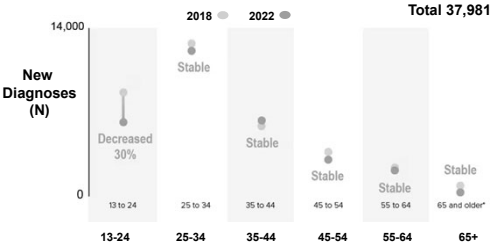
CDC

2030 US HIV Public Health Goals: Transmission

90% Reduction in Incidence by 2030

Trends in HIV Incidence

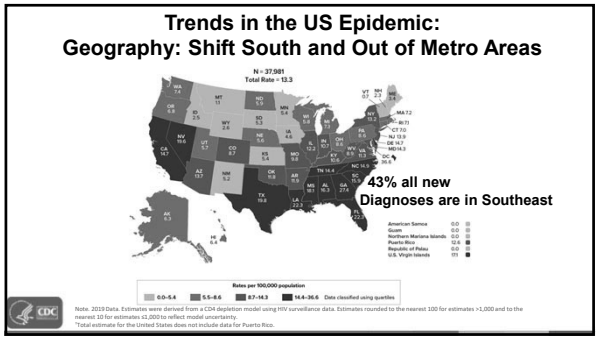
Total 37,981 Diagnoses

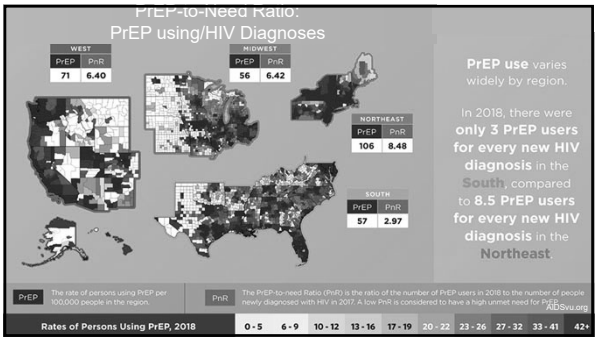


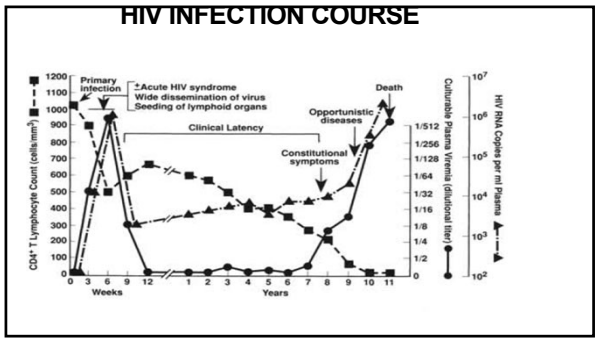
CDC

34 – Clinical Manifestations of Human Retroviral Diseases and Slow Viruses

Speaker: Frank Maldarelli, MD





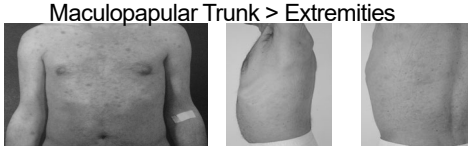


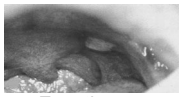
Acute HIV Syndrome

Sign/symptom	Percent Reporting NEJM Review	Kenyan sex workers	HIVNET
Fever	>80-90	53	55
Fatigue	>70-90	26	56
Rash	>40-80	9	16
Headache	32-70	44	33
Lymphadenopathy	40-70	7	35
Pharyngitis	50-70	15	43
Myalgia or arthralgia	50-70	24	39
Nausea, vomiting or diarrhea	30-60	18	12-27
Night sweats	50	nd	nd
Aseptic meningitis	24	nd	nd
Oral ulcers	10-20	nd	6
Genital ulcers	5-15	3	nd
Thrombocytopenia	45	nd	nd
Leukopenia	40	nd	nd
Elevated LFTs	2	nd	nd
Too ill to work	nd	44	58

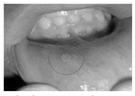
Primary HIV-1 Infection Syndrome

Maculopapular Trunk > Extremities





Enanthem



Aphthous ulcer

HIV Presentation: 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.

34 – Clinical Manifestations of Human Retroviral Diseases and Slow Viruses

Speaker: Frank Maldarelli, MD

HIV Presentation: Question #1 (Cont.)

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 Presentation Question #2

A 30 year old individual who is completely adherent with long-acting cabotegravir as PrEP presents in January to your ED with low grade fever, fatigue, and mild myalgias. 4th generation HIV testing is non-reactive, rapid Flu A testing is negative. The ER physician asks whether this patient may have breakthrough HIV infection in the setting of PrEP, and whether further evaluation for HIV infection should be arranged.

A. **The patient does not have breakthrough infections, because 4th generation assays are always reactive in the setting of breakthrough infection.**
B. **The patient does not have breakthrough infections, because breakthrough infections are always asymptomatic.**
C. **The patient may have breakthrough HIV infection, and further evaluation for HIV infection should be arranged.**
D. **The patient does not have breakthrough infections because breakthrough infections have never been reported with individuals completely adherent with long acting cabotegravir.**

Long Acting Early Viral Inhibition (LEVI) Syndrome

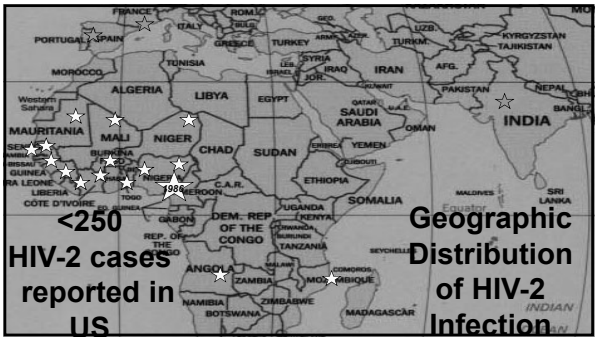
- **True breakthrough infection**
- **Smoldering presentation- symptoms may be present**
- **Serologic testing: seroconversion, seroreversion, "serowaffling" may persist for months**
- **Drug resistance to integrase inhibitor can emerge**

HIV Clinical Presentation: Question #3

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**



34 – Clinical Manifestations of Human Retroviral Diseases and Slow Viruses

Speaker: Frank Maldarelli, MD

HIV-1 and HIV-2

Characteristic	HIV-2	HIV-1
Epidemiology		
Geography	West /Central Africa	Worldwide
Local Distribution	Urban=rural	Urban>rural
Age-Specific Prevalence	Stable or Decreasing	Increasing
Pathogenesis		
Average age at diagnosis	45-55	20-34
Maternal-fetal (without RX)	0-4%	20-35%
Kaposi Sarcoma	Less common (10X)	More common
Therapy	NRTI, PI, INSTI, Corec	NRTI, PI, NNRTI
Diagnosis	**NOT** NNRTI, Fusion,(Capsid)	INSTI, Corec, Fusion
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 #4

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:

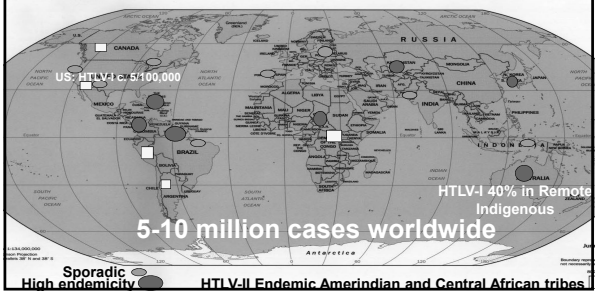
A. **The patient has HIV and B cell lymphoma**
B. **The patient has HIV infection and the elevated CD4 count is due to steroids used in the treatment of the *Pneumocystis* pneumonia**
C. **The patient has HTLV-1 infection only the HIV test is a false positive**
D. **The patient has both HIV infection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

Question #5

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

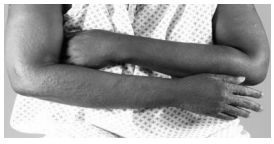


HTLV-I Transmission, Pathogenesis, Diagnostics

- **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 #6

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**

34 – Clinical Manifestations of Human Retroviral Diseases and Slow Viruses

Speaker: Frank Maldarelli, MD

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 #7

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 #7 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**

34 – Clinical Manifestations of Human Retroviral Diseases and Slow Viruses

Speaker: Frank Maldarelli, MD

Question #8

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.

Question #8

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 #9

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)

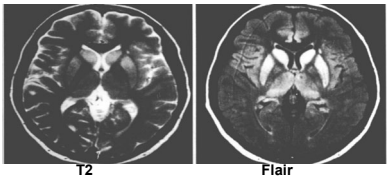
SLOW VIRUSES

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**



T2 Flair

34 – Clinical Manifestations of Human Retroviral Diseases and Slow Viruses

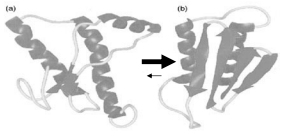
Speaker: Frank Maldarelli, MD

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



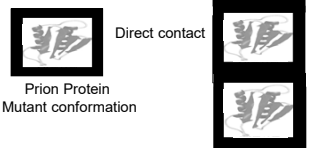
NORMAL ABNORMAL

Transition to abnormal conformation is rare but essentially irreversible

Naturally occurring mutations favor interconversion

Prion Disease Pathogenesis
B. Propagation

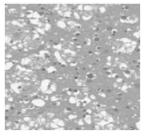
Protein-Protein Contacts recruit normal proteins into abnormal conformation



Prion Protein
Mutant conformation

Direct contact

Prion Protein
Mutant conformation



Disaggregase chaperone proteins may scavenge these proteins with mutant conformation

Spontaneous Creutzfeldt-Jacob Disease (sCJD) Epidemiology

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

Dementia Comparison

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

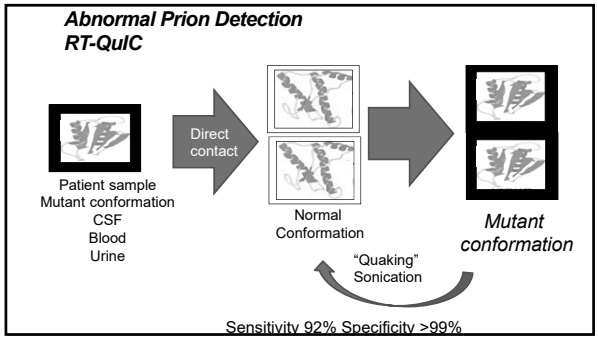
Prion Disease Question #2

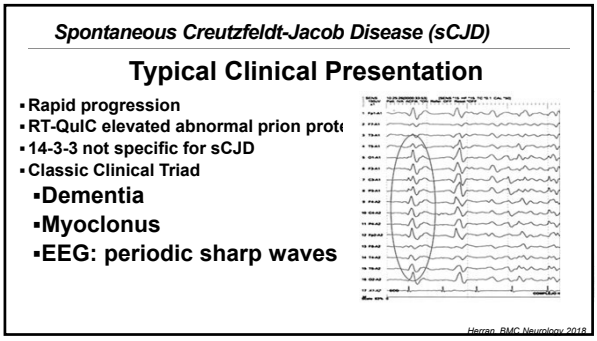
A 68 year old man with dementia progressing over the last 6 months undergoes evaluation. Which of the following CSF results is most consistent with Creutzfeldt Jakob Disease:

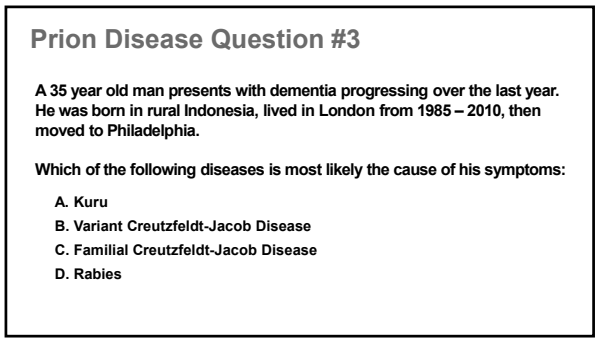
A. **14-3-3 protein: Positive**
B. **RT-QuIC: Positive**
C. **T-tau protein: 3000 pg/ml (normal 0-1150 pg/mL)**
D. **Aβ42: 1250 pg/mL (normal >1026 pg/mL)**

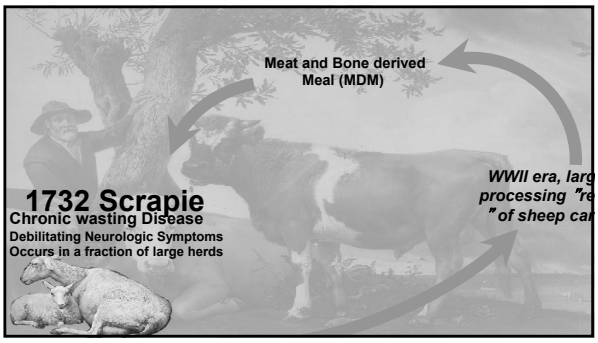
34 – Clinical Manifestations of Human Retroviral Diseases and Slow Viruses

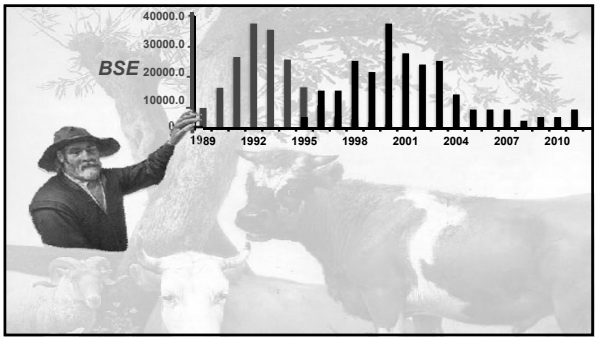
Speaker: Frank Maldarelli, MD











34 – Clinical Manifestations of Human Retroviral Diseases and Slow Viruses

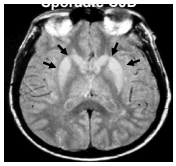
Speaker: Frank Maldarelli, MD

Numbers of vCJD Cases Worldwide

- United Kingdom: 177
- France: 26
- Spain: 5
- **US: 4**
  - **(ALL infections acquired OUTSIDE of US)**
- Ireland: 4
- Netherlands, Italy: 3
- Portugal, Canada, Italy: 2 each
- Saudi Arabia, Japan, Taiwan: 1 each

(https://www.ecdc.europa.eu/en/vcjd/ 2024)

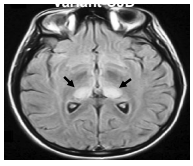
sCJD



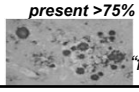
T2 axial proton weighted Putamen and caudate head "Double hockey stick sign"

"Abnormal Prion accumulation"

vCJD



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



"florid plaques"

Prion Diseases Question #4

A 49 year old man recently emigrated from Japan presents with rapidly progressing dementia over the course of months. 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. Alzheimer's disease

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"

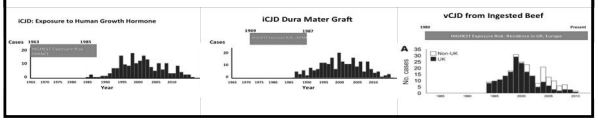
34 – Clinical Manifestations of Human Retroviral Diseases and Slow Viruses

Speaker: Frank Maldarelli, MD

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

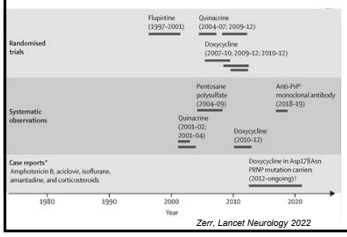
Transmissible Spongiform Encephalopathy

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 121º C, 15 psi 30 min
  - Formic acid for tissue sections
  - Alternatives include hypochlorite (20,000 ppm chlorine) + autoclave
  - REMEMBER: Infectivity is STABLIZED by alcohol, formalin, or glutaraldehyde
- **WHO infection control guidelines**
  - **http://www.who.int/csr/resources/publications/bse/whocdscsraph2003.pdf?ua=1**

Transmissible Spongiform Encephalopathy

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 induction

34 – Clinical Manifestations of Human Retroviral Diseases and Slow Viruses

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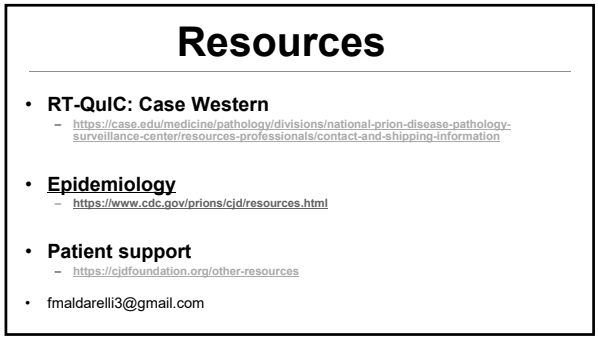
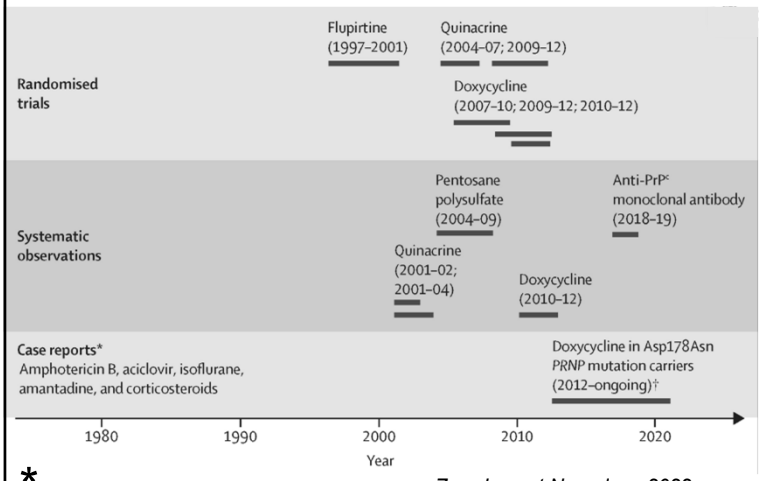


Transmissible Spongiform Encephalopathy

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

35

HIV-Associated Opportunistic Infections I

Dr. Henry Masur

35 – HIV Associated Opportunistic Infections I

Speaker: Henry Masur, MD

IDBR INFECTIOUS DISEASE BOARD REVIEW AUGUST 17-21, 2024

HIV-Associated Opportunistic Infections I

Henry Masur, MD, FIDSA, MACP
Bethesda, Maryland

7/1/2024

IDBR INFECTIOUS DISEASE BOARD REVIEW AUGUST 17-21, 2024

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?

1. Disseminated histoplasmosis
2. Cryptococcal meningitis
3. Coccidiodes meningitis
4. Miliary tuberculosis
5. Disseminated Mycobacterium avium complex

Question #2

PREVIEW QUESTION

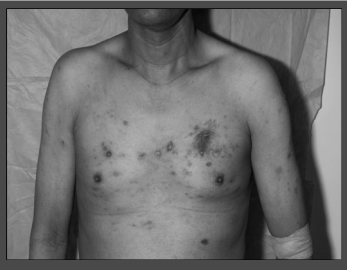
The patient whose photo is shown is HIV positive (CD4=10 cells/uL, VL=2 mil copies) and has noted these lesions developing on his trunk, face and extremities over the past 8 months.

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 #2

PREVIEW QUESTION



Question #2

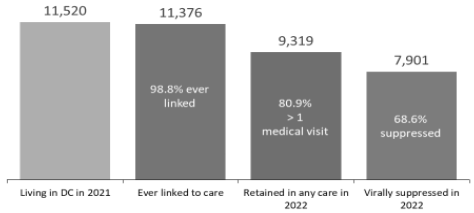
PREVIEW QUESTION

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

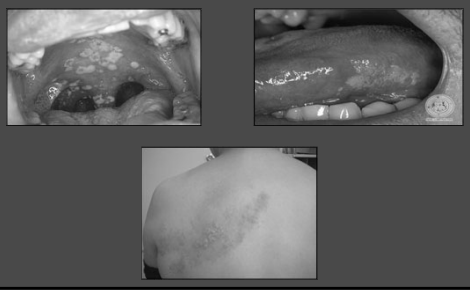
Why Does Anyone in US Develop an HIV Associated Opportunistic Infection in Current Era?

HIV Care Continuum, Washington DC
2023 Annual Report



https://dchealth.dc.gov/service/hiv-reports-and-publications

Clinical Indicators of Immunosuppression



Cardinal AIDS-Defining Illnesses

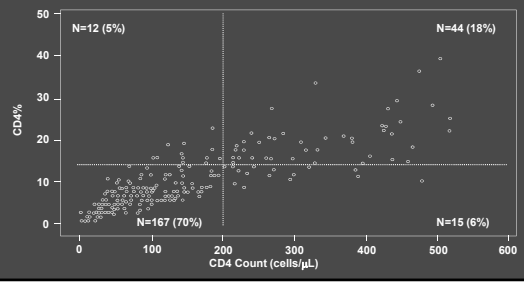
- **Pneumocystis pneumonia**
- **Cryptococcus**
- **Toxoplasma encephalitis**
- **CMV Retinitis**
- **Disseminated Mycobacterium avium complex/Tuberculosis**
- **Chronic cryptosporidiosis/microsporidiosis**
- **Kaposi Sarcoma**

Susceptibility to Opportunistic Infections Patients with HIV

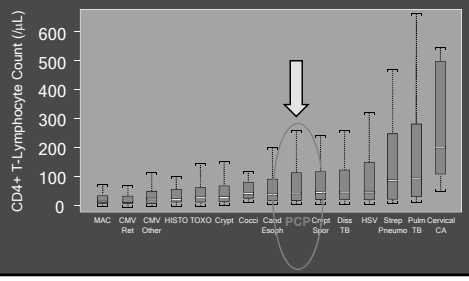
- **CD4 Count**
  - Current count is most important
  - Prior nadir count is much less important
- **Viral Load**
  - Independent risk factor for OIs

At What CD4 Counts Do Opportunistic Infections Occur?

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



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

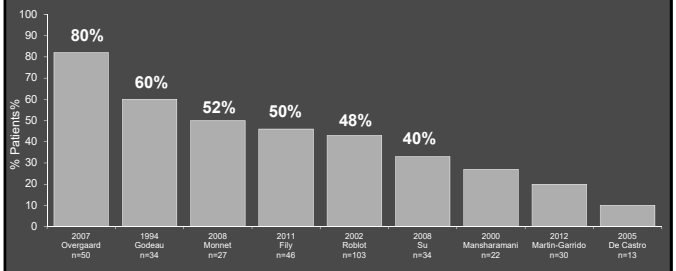


Warning for Utility of CD4 Counts in Non HIV

•

CD4 Count Are Not A Sensitive Indicator of PCP

% Non HIV Patients With PCP When CD4>200



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

What is the Most Effective Intervention to Prevent Opportunistic Infections and Neoplasms?

What is the Most Effective Intervention to Prevent Opportunistic Infections and Neoplasms?

Antiretroviral Therapy

CD4 Count

Viral Load

When to Start ART Following Opportunistic Infection

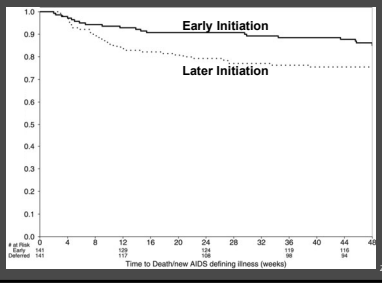
When to Start ART Following Opportunistic Infection

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

ART Initiation Following HIV Related Opportunistic Infections

Early Initiation (<2 weeks) Favors Survival

Survival Without Additional OI



Zolopa PLoS One 2009;4:e5575

When to Start ART : Exceptions to Two Week "Rule"

- **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

*For TB meningitis: potentially longer

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 except patients whose VL cant be suppressed and have CD4 less than 50**
  - *****
- **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<150/200 and would not use histo serology in decision (not reliable)**

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*

Discontinue Prophylaxis/Chronic Maintenance

Many of "Rules" About Primary and Secondary Prophylaxis Are Based on Studies from the 1980-2000 Time Period

- **For Exam: These Recommendations Are Current Guideline**
- **Are they still relevant for patient who durably suppressed by ART?**

Primary Coccidiomycosis Prophylaxis 2024 OI Guideline

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

Primary Prophylaxis
- **Do not administer in endemic area if serology negative**
- **Within the endemic area, administer if…..**
  - 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

Recommended Immunization Schedule for Adults and Adolescents with HIV

Vaccine	All People with HIV	Where Varies by Age	Where Varies by CD4 Cell Count (cells/mm³)	
			<200	≥200
Hepatitis A	Two to three doses (varies by formulation)			
Hepatitis B	Two to four doses (varies by formulation and indication)			
Human papillomavirus (HPV)		Three doses for ages 18–26*		
Influenza	One dose annually			
Measles, mumps, rubella (MMR)			Contraindicated	Two doses if born after 1956 with no history of vaccination or positive antibody titer
Meningococcal A,C,W,Y conjugate (MenACWY)	Two doses, booster every 5 years			
Meningococcal B (MenB)	Two to three doses (varies by formulation)			
Mpox (MVA-BN, attenuated)	Two doses			
Mpox (ACAM2000, live replicating)	Contraindicated			
Pneumococcal conjugate (PCV15 or PCV20)	One dose			
Pneumococcal polysaccharide (PPSV23)	One dose (if conjugate vaccine was PCV-10)			
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	Two doses
Zoster recombinant (RZV)		Two 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

https://clinicalinfo.hiv.gov/en/guidelines/adult-and-adolescent-opportunistic-infection

Recommended Immunization Schedule for Adults and Adolescents with HIV

This is All Oversimplified, But for the Exam

- **Avoid live vaccines at CD4 counts < 200 or Uncontrolled Viral Replication**
  - **MMR, Varicella, Yellow Fever, Oral typhoid, *Intranasal Influenza**
  - **Mpox Jynneos live vaccine is safe because it is non replicating**
- **Administer**
  - **HAV, HBV, Meningococcus ACWY, Pneumococcus, COVID**
    - **All higher incidence or more severe in HIV than non HIV**
  - **RZV (Shingrix) age >18 years**
  - **Pneumococcus, when in doubt use PCV 20**
    - **(or PCV 15 plus 23 valent polysaccharide)**
- **Administer Mpox if possibly exposed or likely to be exposed**
- **Assess Post vaccine titers for HBV (and HAV if CD4<200)**

Slide 28

https://clinicalinfo.hiv.gov/en/guidelines/adult-and-adolescent-opportunistic-infection

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**
    - **Preferred by some: two dose regimen**
      - **Vaccine conjugated to HepBCpG (Heplisav-B©) IM at 0 and 1 months**
  - **NIH/IDSA perspective re assessing post vaccine titers**
    - **1-2 months post vaccine and then some experts would test annually**
    - **Boost responders when annual level <10mIU/ml**

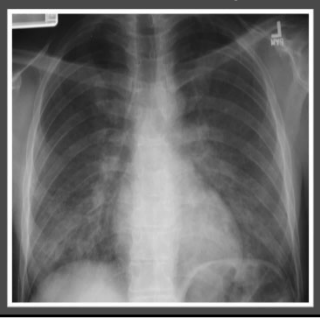
HBV Non-Responders

- **Definition**
  - Anti-HBs <10 international units/mL 1 month after vaccination series
- **Options: Not testable**
  - Switch to another HBV vaccine
  - Double dose of recombinant vaccine (if that was not the initial regimen)
  - Four dose recombinant regimen

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

HIV Associated Pulmonary Disease



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

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

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

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

Approach to Diagnosis and Therapy of Pneumonia in PWH

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

Etiology of HIV Associated Pulmonary Disorders

Common	Less Common	Rare
• Pneumococcus	• Histo/Cocci	• CMV
• Pneumocystis	• Toxoplasma	• MAC
• Tuberculosis	• Lymphoma	• HSV
	• Kaposi sarcoma	• Asperg

Pneumococcal Disease in Persons with HIV Infection

- CD4<200
  - Enhanced Frequency, Severity, Extrapulmonary Complications
- CD4>350
  - Frequency enhanced but NOT severity
- Comorbidities Predisposing to Pneumococci Over-Represented in HIV
  - Opioid Use Disorder, Etoh, Tobacco, Lack of Immunization
  - COPD, CHF, Obesity, MRSA colonization, Liver Disease

Internal Medicine Question

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

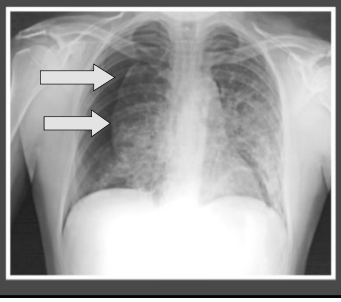
HIV and Covid

- No increased susceptibility
- Probably increased severity
  - May be primarily linked to other co-morbidities
- Drug interactions
  - Integrase inhibitors and Cobicistat and Ritonavir contain regimens likely OK with Paxlovid
  - ART and Remdesivir no interactions

Question #3

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

HIV Patient with Shortness of Breath



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

The most likely INFECTIOUS cause of this pneumothorax is:

A. **Mycobacterium avium complex**
B. **Blastomycosis**
C. **PCP**
D. **CMV**
E. **Aspergillosis**

Pneumocystis Jirovecii (Formerly *P. carinii*)(PCP or PjP)

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

Host Susceptibility to PCP

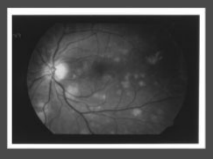
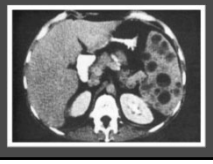
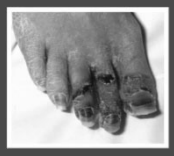
- **CD4 < 200 cells/μL --(90% of cases)**
- **CD4% <14**

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

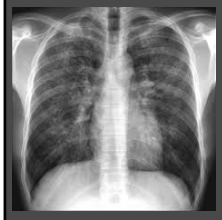
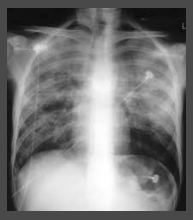
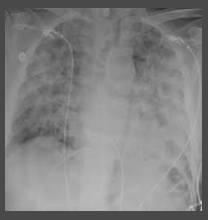
Sign or Symptom	HIV (n=48)	Non-HIV (n=38)
Symptom		
Fever	81%	87%
Cough	81%	71%
Shortness of breath	68%	66%
Duration of symptoms,	28 days	5 days
Temp> 38°C	76%	92%
PaO_2	69 mm Hg	52 mm Hg
A-a gradient	41 mm Hg	59 mm Hg
% with normal ABG	5-20%	

Kovacs et al. Ann Intern Med 1984

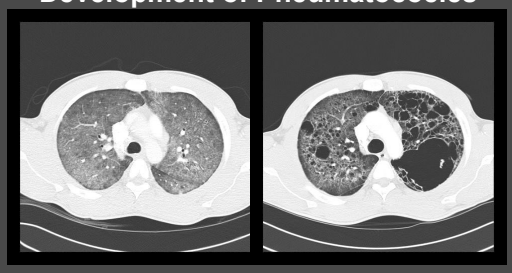
Uncommon Manifestations of PCP

HIV Related PCP

Development of Pneumatocoeles



May 23 June 13

Radiologic Patterns Associated with Documented Pneumocystis Pneumonia

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

Radiologic Patterns Associated with Documented Pneumocystis Pneumonia

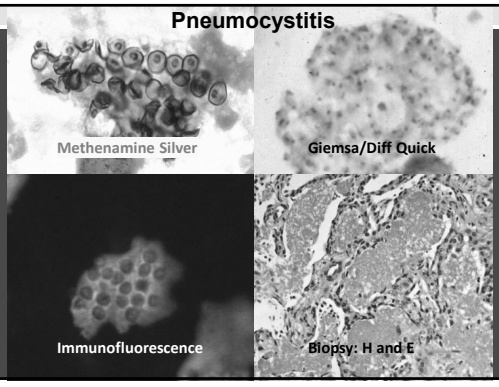
- Other Patterns Recognized
  - (Other concomitant infectious or neoplastic disease processes?)
  - Lobar infiltrates
  - Upper lobe infiltrates
  - Pneumothorax
  - Solitary nodules
  - Cavitating lesions
  - Infiltrates with effusions
  - Asymmetric or unilateral processes
  - Normal chest x-ray

Diagnosis of Pneumocystis Pneumonia

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

1957 ↓ 2024

Pneumocystitis



PCR
Diagnosis of Pneumocystis Bronchoalveolar Lavage or Sputum

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

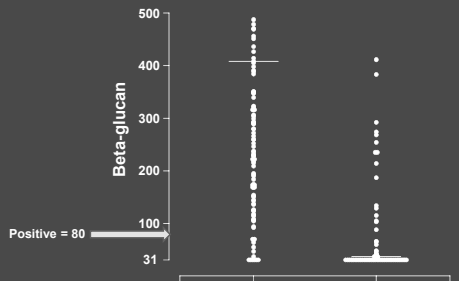
PCR
For Diagnosis of Pneumocystis in Bronchoalveolar Lavage

- High
  - No
- High
  - Po
  - Cy

Negative BAL PCR rules out PCP

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

Don't Use Beta Glucan Test for Diagnosis of PCP!!



Sax PE. *Clin Infect Dis* 2011

DelCorpo. Clini Microb and Infection 2020

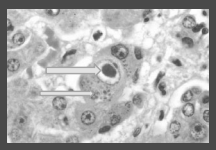
Question #4

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

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 and Lungs



Eosinophilic Intranuclear Inclusion and Basophilic Cytoplasmic Inclusions

CMV almost never causes pneumonia In PWH

CMV in pulmonary secretions or blood is a marker of more severe immunosuppression but not usually the cause of pneumonia…in this population

Question #5

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

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

Pulse oximetry shows an O2 saturation of 85% which does not increase with supplemental oxygen

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

A. **Covid-19**
B. **Pneumocystis pneumonia unmasking**
C. **Fluconazole interaction with another drug**
D. **Dapsone**
E. **Dolutegravir**

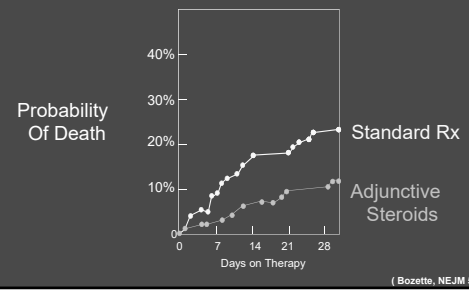
Two Pharmacologic Issues To Watch For

- **Methemoglobinemia (>8-10%)**
  - **Most common antimicrobial causes: dapsone and tafenoquine, primaquine (and occasionally chloroquine, quinolones and sulfa)**
  - **O2 Saturation low compared to pO2 and does not improve with O2 (stays at 85%)**
    - **Cyanosis out of proportion to pulse oximetry**
    - **Specifically detected by co-oximetry but NOT routine pulse oximetry**
  - **Rx Methylene blue**
- **Glucose-6-Phosphate Deficiency**
  - **Genetic**
  - **Hemolysis**
  - **Trigger: Dapsone, quinolones, primaquine/tafenoquine**
    - **Sulfa and trimethoprim probably not important**
    - **Even trigger drugs can be safe to give for life threatening diseases**

Therapy for HIV Related 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)

How to Manage Patients Who Are Failing TMP-SMX

- **Deterioration common first 1-2 days (steroids)**
- **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)**

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- **Pneumothora**
- **Unrecognized**
- **Immune Reco**

Patients Failing TMP-SMX Not Testable!

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

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

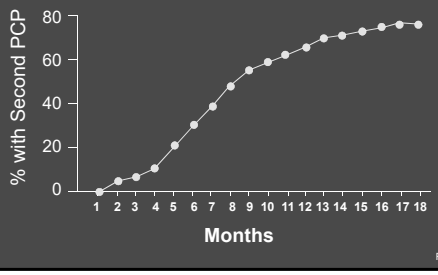
Toxicities of TMP-SMX and Pyrimethamine-Sulfadiazine

Drug	Toxicities
TMP-SMX	↓WBC, ↓Plat, ↑LFT, ↑Creat, ↑Amylase, rash, fever, pruritus, "Sepsis" syndrome-distributive shock Hyperkalemia 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---What Are Risk Factors and Timeline of Risk

- **Long List of Immunosuppressive Diseases and Drugs**
  - Risk Factor is cell mediated immunity (lymphocytes) not neutrophils
  - Severe hypoglobulinemia also risk factor
- **CD4 Count**
  - <200 cells indicates susceptibility
  - >200 cells is not necessarily protective
- **Duration of risk not well established**
  - e.g. Dose of drug, number of weeks after dose
- **Prophylaxis is effective**
  - TMP-SMX is optimal but often stopped arbitrarily or after perceived toxicity, ie cytopenia, renal dysfunction, transaminitis

Primary or Secondary Prophylaxis for Pneumocystis Pneumonia

- **First Choice**
  - TMP-SMX (dose not testable)
- **Other Options**
  - Aerosol pentamidine **OR**
  - Atovaquone **OR**
  - (Monthly IV pentamidine-poor data in adults) **OR**
  - (Dapsone)

36

HIV Diagnosis

Dr. Frank Maldarelli

36 – HIV Diagnosis

Speaker: Frank Maldarelli, MD

HIV Diagnosis

Frank Maldarelli, MD
Bethesda, MD

7/1/2024

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

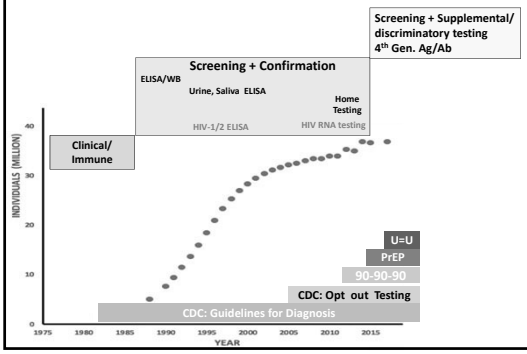
C. This person is infected with an HIV variant that is not detected by the supplemental test

D. This person is not HIV-infected

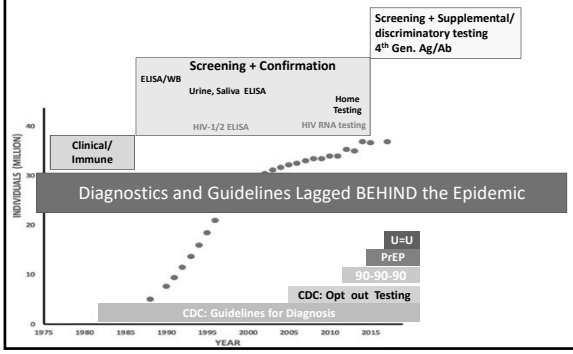
HIV Diagnosis: New Modalities and New Terminology Old Limitations Persist

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

Evolution of the HIV Diagnostic Approach



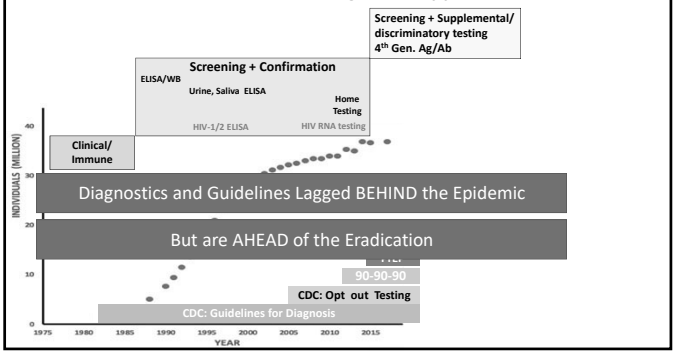
Evolution of the HIV Diagnostic Approach



36 – HIV Diagnosis

Speaker: Frank Maldarelli, MD

Evolution of the HIV Diagnostic Approach



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?

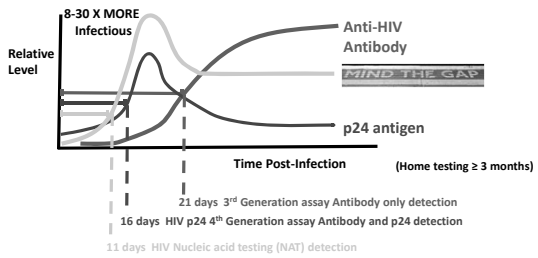
A. She can immediately initiate PrEP with tenofovir-FTC with no additional testing

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



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**

36 – HIV Diagnosis

Speaker: Frank Maldarelli, MD

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 Serologic Testing Pregnancy

- **False positive results with antibody testing are possible in pregnancy**
- **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.

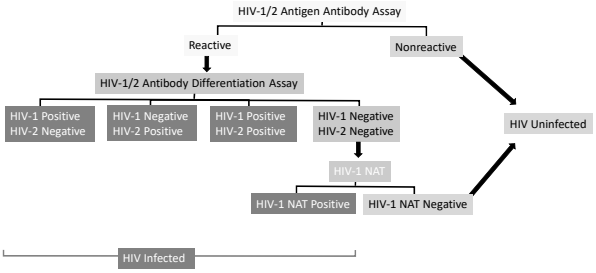
D. The patient is not infected with HIV-1 or -2, all tests are false positive.

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



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

36 – HIV Diagnosis

Speaker: Frank Maldarelli, MD

Question #6

A 42 year old woman has a reactive 4th generation test for HIV infection. She is 7 months pregnant, and had COVID-19 infection one month ago despite vaccination with Moderna COVID vaccine four months prior to testing. She had a nonreactive 4th generation screen 7 months ago at the beginning of her pregnancy, she denies any HIV exposures. Subsequent qualitative HIV RNA testing is negative. The most likely explanation for these results is:

A. **False positive 4th generation test for HIV infection due to pregnancy**
B. **False positive 4th generation test for HIV infection due to COVID vaccination**
C. **False positive 4th generation test for HIV infection due to COVID infection**
D. **False negative HIV RNA testing in the setting of recent HIV infection**

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
  - COVID infection
  - …

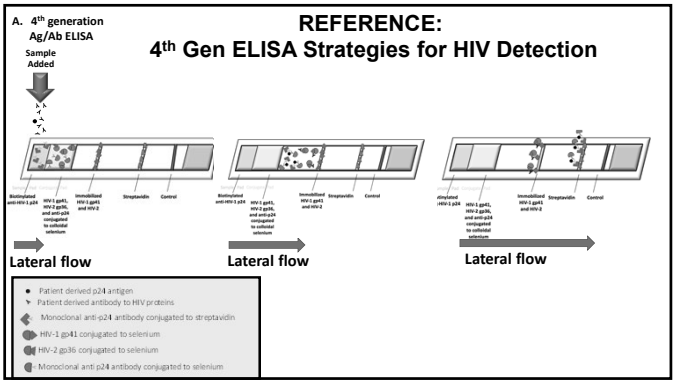
HIV Testing

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

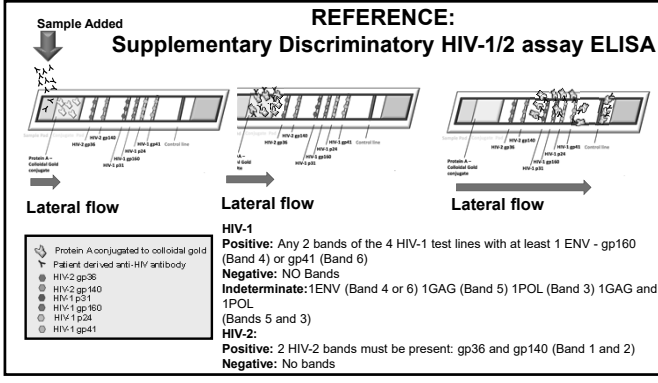
Pearls for Board Exam

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

REFERENCE:
4th Gen ELISA Strategies for HIV Detection



REFERENCE:
Supplementary Discriminatory HIV-1/2 assay ELISA



HIV-1
Positive: Any 2 bands of the 4 HIV-1 test lines with at least 1 ENV - gp160 (Band 4) or gp41 (Band 6)
Negative: NO Bands
Indeterminate:1ENV (Band 4 or 6) 1GAG (Band 5) 1POL (Band 3) 1GAG and 1POL
(Bands 5 and 3)
HIV-2:
Positive: 2 HIV-2 bands must be present: gp36 and gp140 (Band 1 and 2)
Negative: No bands

37

Antiretroviral Therapy

Dr. Roy Gulick

37 – Antiretroviral Therapy

Speaker: Roy Gulick, MD

Antiretroviral Therapy (ART)

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

7/1/2024

- **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

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.

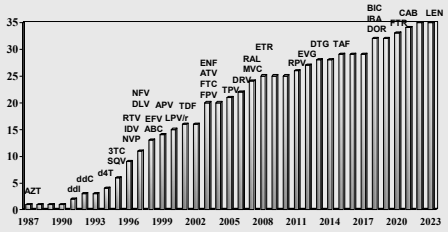
When to Start?: Chronic Infection

	AIDS/ symptoms	Asymptomatic			
		CD4 <200	CD4 200-350	CD4 350-500	CD4 >500
US DHHS 2024 www.clinicalinfo.hiv.gov	recommended				
IAS-USA 2023 Gandhi JAMA 2023;329:63-84	recommended				

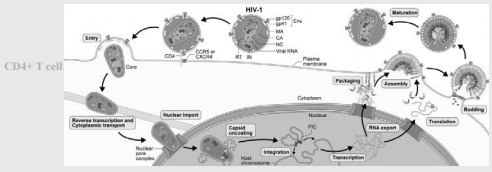
Goal of Antiretroviral Therapy

- 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 - 2024

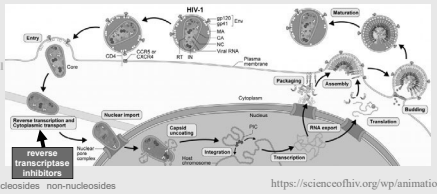


Life Cycle of HIV



https://scienceofhiv.org/wp/animations/

Life Cycle of HIV



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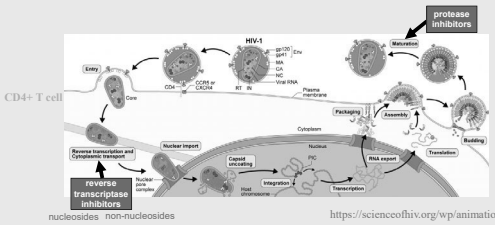
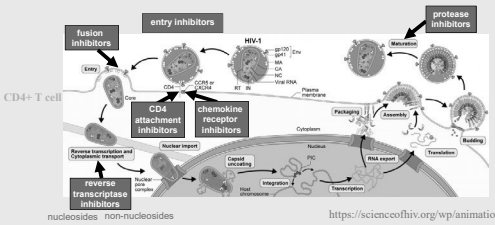
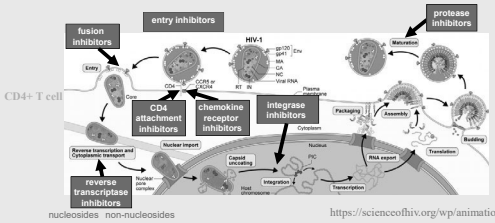
Life Cycle of HIV



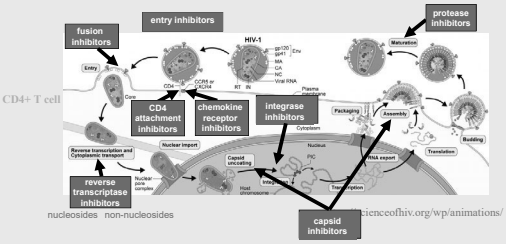
Life Cycle of HIV



Life Cycle of HIV



Life Cycle of HIV



Approved ART: 2024*

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, APV, and FPV discontinued from market

WHAT TO START?

Question #2

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. dolutegravir/rilpivirine
C. tenofovir alafenamide/emtricitabine/rilpivirine
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 2/27/24 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 2/27/24 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 2/27/24 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 2/27/24 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 2/27/24

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 2/27/24

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 2/27/24

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, 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 2/27/24

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

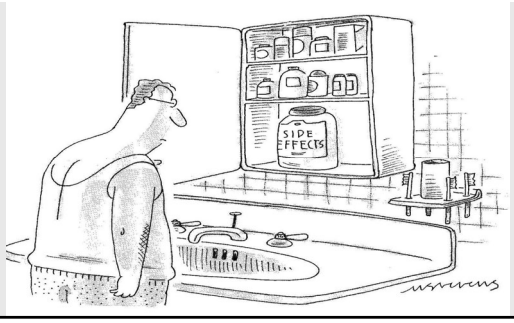
Selected Drug Interactions (2)

- 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 2/27/24



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 by HLA-B*5701 screening
    - stop nevirapine or etravirine for rash with 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)
  - 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/3TC; DTG/RPV; Boosted PI (ATV, DRV) + [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 2/27/24

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

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 68 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 2/27/24

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)
- Do not add a single active drug to a failing regimen
- Goal:

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

DHHS Guidelines 2/27/24

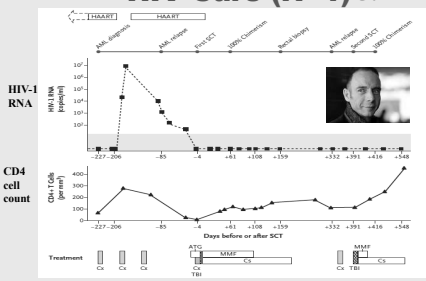
TREATMENT = PREVENTION

Treatment = Prevention

- Pregnant women with HIV *Fowler NEJM 2016;375:1726*
  - 3-drug ART ↓ transmission risk to child to 0.5%
- Men and women with HIV *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 (e.g. TDF/FTC + DTG)
- At-risk men and women without HIV
  Molina NEJM 2015, McCormack Lancet 2016, Landovitz NEJM 2021, Delany-Moretlwe Lancet 2022; Choopanya Lancet 2013
  - PrEP ↓ HIV acquisition by sex >75-85% (TDF/FTC ♂♀; TAF/FTC ♂ only; IM CAB ♂♀)
  - PrEP ↓ HIV acquisition by injection drug use ~50% (TDF/FTC)

CURE

HIV Cure (N=1) 5!



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

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

Cure #4
Dusseldorf
Jensen, et al
Nat Med 2023;29:583-587

Cure #5
City of Hope
Dickter, et al
NEJM 2024;39;669-671

Hutter NEJM 2009;360:692

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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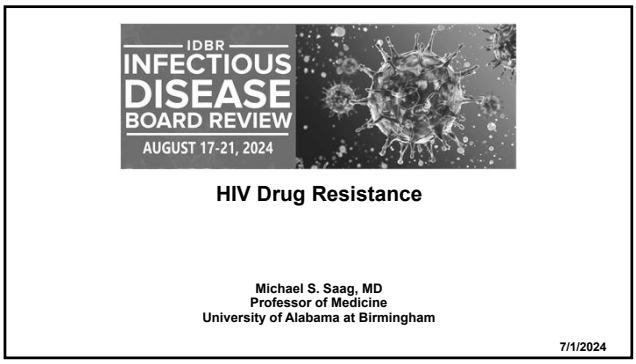
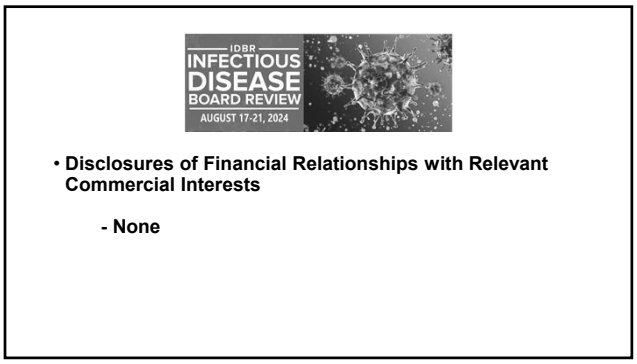
HIV Drug Resistance

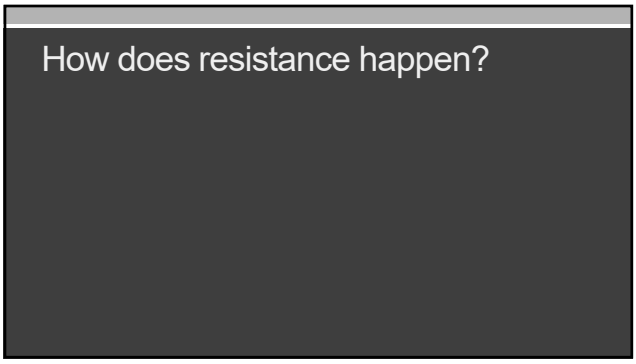
Dr. Michael Saag

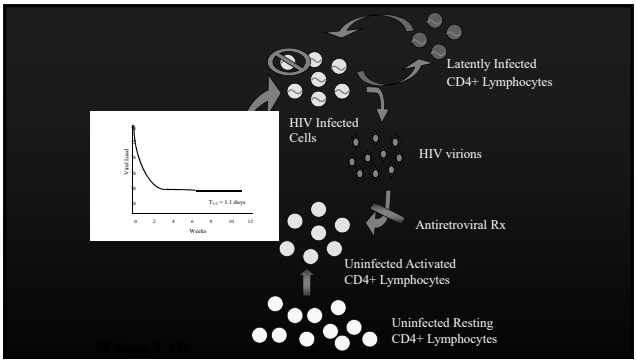
38 – HIV Drug Resistance

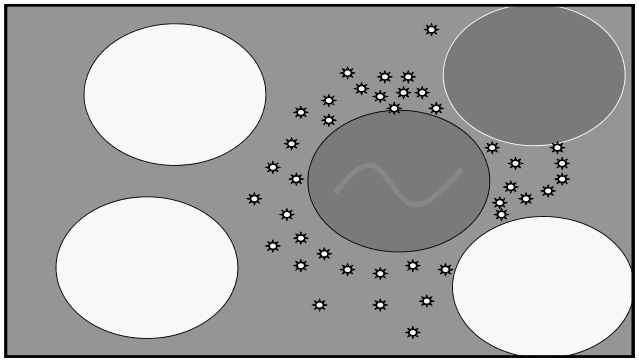
Speaker: Michael Saag, MD

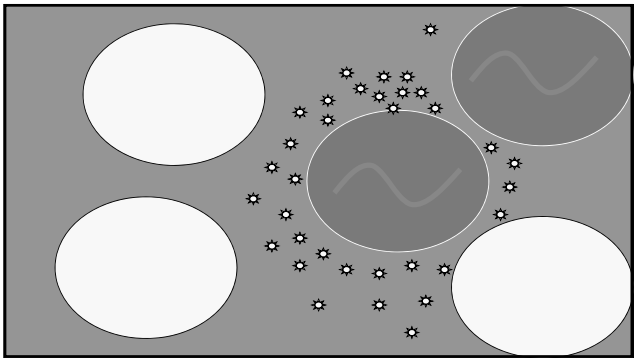


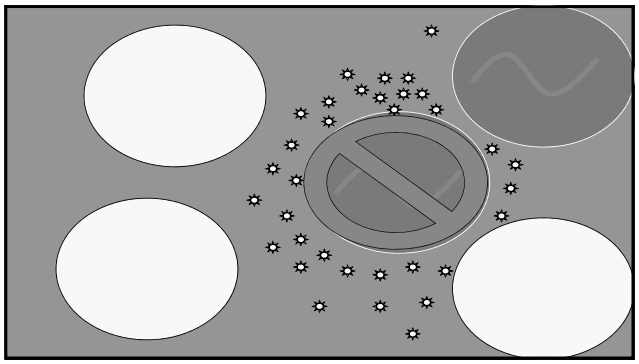


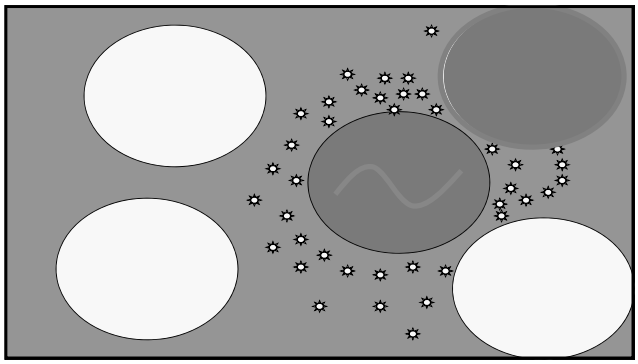


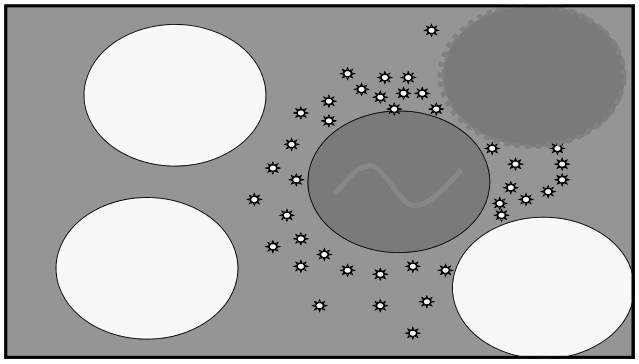


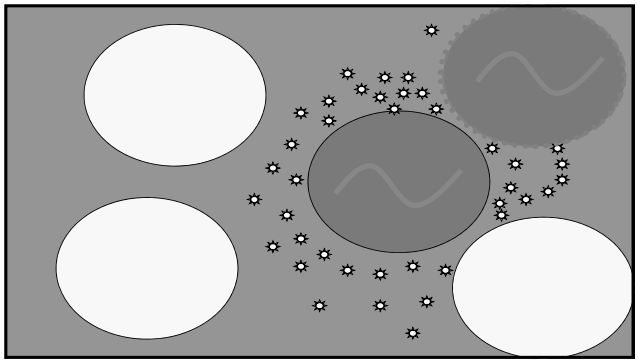












Resistance Testing

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

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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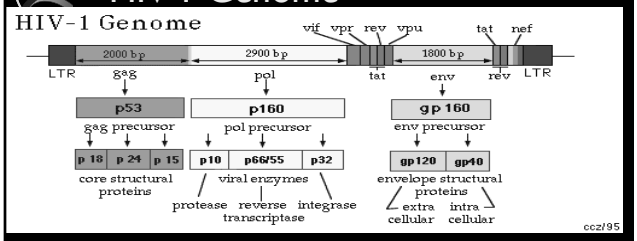
HIV Drug Resistance Testing

- 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
K65R	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)

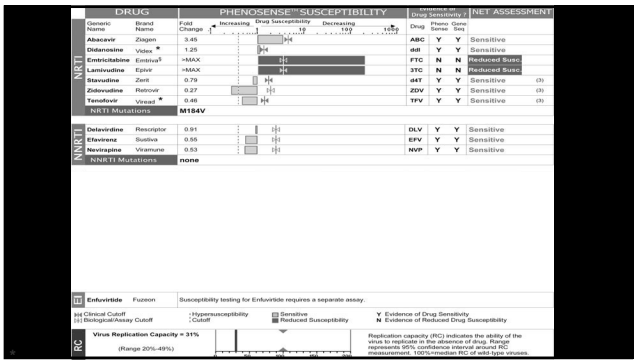
CASE 1

- 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

Question #1

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

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



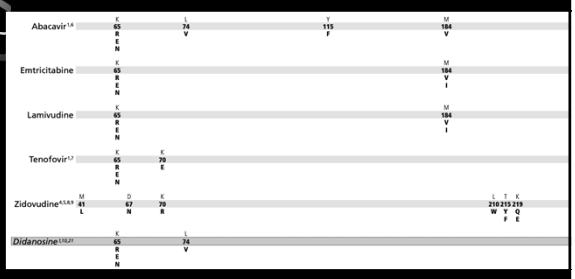
CASE 2

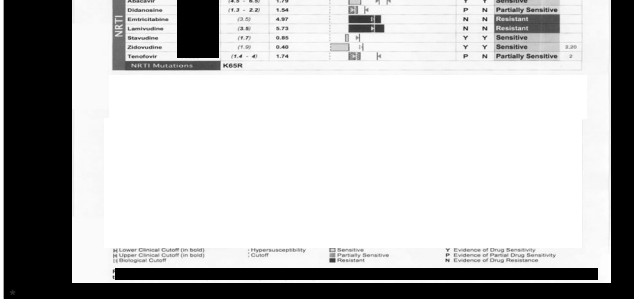
- 34 yo woman diagnosed with HIV 10 years ago
- Initially presented with PJP
- Initial Lab values
  - CD4 82 cells/uL
  - VL 106,000 c/mL
- Started on TDF / FTC / EFV (FDC)
- Did well for a while, then the regimen failed

Question #2

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

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





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

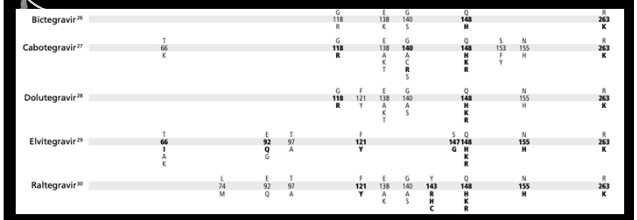
- 34 yo woman diagnosed with HIV three years ago
- Initially presented with PJP
- Initial Lab values
  - CD4 82 cells/uL
  - VL 106,000 c/mL
- She was treated with TDF / FTC / ELV/ Cobi (FDC)
- The regimen failed after 12 months

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



Lenacapavir Resistance Mutations

MUTATIONS IN THE CAPSID GENE ASSOCIATED WITH RESISTANCE TO CAPSID INHIBITORS

	L	M	Q	K	N	A	T
Lenacapavir[31]	56	66	67	70	74	105	107
	I	I	H	N	D	T	N
				S	S		
				R			

Case #4

PREVIEW QUESTION

- 34 yo MSM receiving CAB IM q 2 months for pre-exposure prophylaxis for last 6 months
- Asymptomatic
- HIV Ag/Ab test negative
- Routine screening: HIV RNA 6.1 c/ml

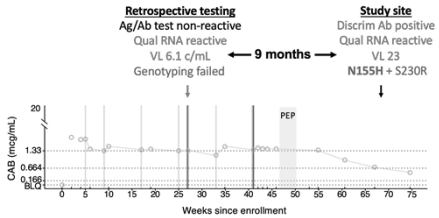
Question #4

PREVIEW QUESTION

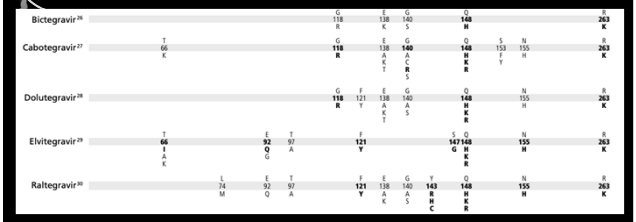
Which of the following ARV resistance mutations is most likely in this setting?

A. S147G
B. N155H
C. Y143R
D. E92Q
E. K65R

Case Study: Confirmation of Infection



InSTI Resistance Mutations



CASE 4

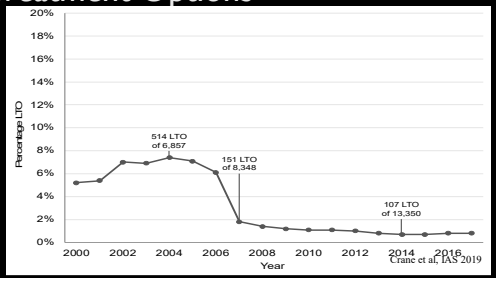
- 34 yo woman diagnosed with HIV 22 years ago
- Initially presented with PJP
- Initial Lab values
  - CD4 82 cells/uL
  - VL 106,000 c/mL
- Has been on multiple regimens over the years

Question #5

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

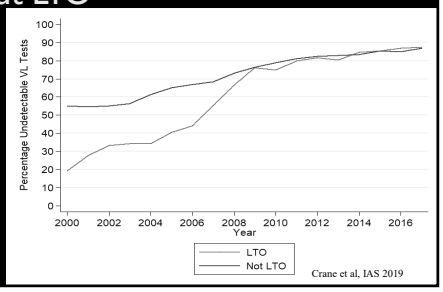
A. < 1 %
B. 1 - 5 %
C. 5 -10%
D. 10 - 20%
E. > 20%

Prevalence of Patients with Limited Treatment Options



Crane et al. IAS 2019

Virologic Success in Those with or without LTO



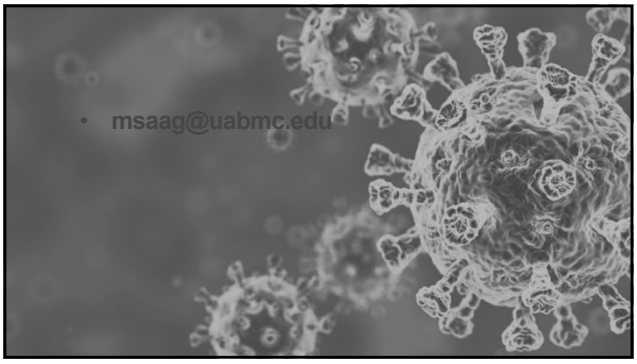
Common Mutations To Memorize

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

Summary

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

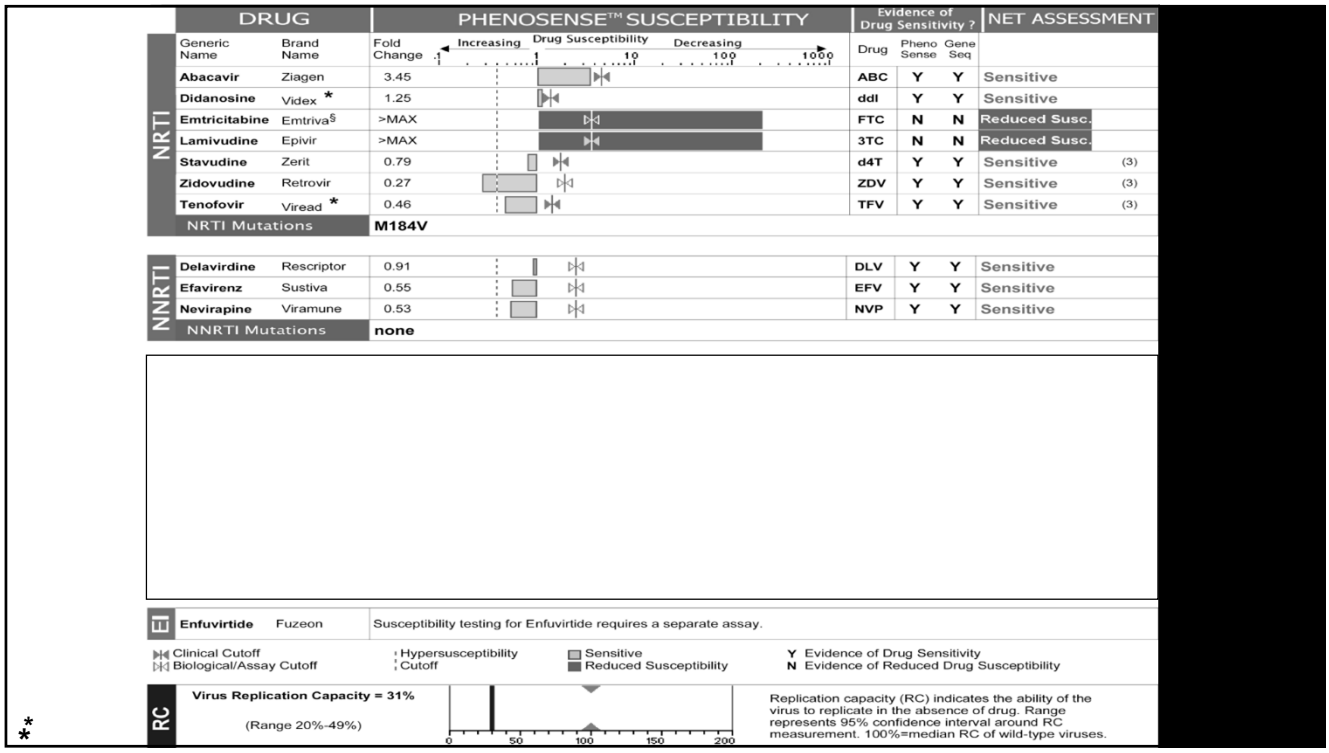
39



38 – HIV Drug Resistance

Speaker: Michael Saag, MD

Enlarged Slide: 22



39

Antiretroviral Therapy for Special Populations

Dr. Roy Gulick

39 – Antiretroviral Therapy for Special Populations

Speaker: Roy Gulick, MD

Antiretroviral Therapy (ART) for Special Populations

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

7/1/2024

- **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

PREVIEW QUESTION

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 2/27/24

Question #2

PREVIEW QUESTION

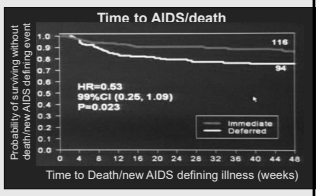
A 52-year-old woman is admitted for progressive SOB, is intubated, undergoes BAL and is found to have PCP. HIV Ab test is positive, CD4 103, HIV RNA 135,000 copies/ml. She is day 4 of IV trimethoprim-sulfa and corticosteroids and still intubated.

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 (e.g. cryptococcus, TB)



Zolopa PLoS One 2009;4:e5575

HIV-TB Co-infection

- Treat active TB the same with or without HIV.
- All PWH with TB should start TB meds immediately.
- In PWH 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 with HIV and TB on ART as early as feasible.
- For TB meningitis, monitor closely.

DHHS Guidelines 2/27/24

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 of the following ART regimens 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** – do not use
    - ↓ **dolutegravir (DTG)** (need to ↑ DTG to 50 mg bid)
    - significantly ↓ **bictegravir (BIC)** – do not use **(**conflicting data)
    - ↓ 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 directly observed therapy (DOT) of TB rx is strongly recommended.

DHHS Guidelines 2/27/24

Question #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

Of the following, which ART regimen would you recommend?

A. abacavir/lamivudine/dolutegravir
B. dolutegravir/lamivudine
C. tenofovir (TAF or TDF) + atazanavir (boosted)
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 2/27/24

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 2/27/24

Question #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.

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
  - Start (or continue if safe/tolerated) standard 3-drug ART as early as possible (while awaiting drug resistance testing):
    - 2-drug regimens can be continued, if virologically suppressed
    - Modify regimen when drug resistance testing results available
  - ART does NOT increase the risk of birth defects
- Near delivery, if HIV RNA >1000 (or unknown), use intravenous zidovudine, and recommend Cesarean section at 38 weeks

DHHS Perinatal Guidelines 1/31/24 <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 1/31/24 <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 (could continue if on):
  - etravirine (not for treatment-naïve pts)
  - nevirapine (toxicity, need for lead-in dosing, low barrier to resistance)

DHHS Perinatal Guidelines 1/31/24 <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 1/31/24 <www.clinicalinfo.hiv.gov>

ART in Pregnancy: INSTI

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

DHHS Perinatal Guidelines 1/31/24 <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 (for EVG or PIs)
  - enfuvirtide (limited data; could continue if on)
  - fostemsavir (limited data; could continue if on)
  - ibalizumab (limited data; could continue if on)
  - lenacapavir (limited data; could continue if on)
  - maraviroc (need tropism testing; limited data, could continue if on)

DHHS Perinatal Guidelines 1/31/24 <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), Bloch, Gandhi, Maldarelli, Masur, Saag, and Tunkel

BR4 –Board Review: Day 4

Moderator: Roy Gulick, MD

Board Review: Day 4

Moderator: Roy Gulick, MD, MPH
Faculty: Drs. Bloch, Gandhi, Maldarelli, Masur, Saag, and Tamma

7/1/2024

BOARD REVIEW DAY 4 2024

#40 **A 30-year-old woman presented with newly diagnosed HIV infection 9 months ago. She was 6 weeks pregnant.**

Initial: HIV RNA 28,000 c/ml

CD4 count 650 cells/ul

She was started on DTG + TAF/ FTC. Viral load became below level of detection and remained so throughout pregnancy and delivery.

A healthy baby girl was delivered 2 days ago.

1 of 3

BOARD REVIEW DAY 4 2024

#40 **Mom is in the US and wants to breastfeed. You tell her?**

A) Yes, she should feel free to breast feed her infant

B) No, it is unsafe to breast feed in any situation

C) No, it's unsafe to breast feed because of her viral load when she presented early in pregnancy

D) Breastfeeding is a possible option: Discuss pros and cons of breastfeeding with her and let her decide

2 of 3

BOARD REVIEW DAY 4 2024

#41 **A 40-year-old apple-grower from Eastern Washington State presented to the Emergency Department with the acute onset of diplopia and exertional dyspnea which started evolving over 12 hours.**

Over a few hours, the muscle weakness extended to all 4 extremities with concomitant decreases in his oxygen saturation.

He required intubation.

1 of 6

BOARD REVIEW DAY 4 2024

#41 **His last meals in the 24 hours prior to the onset of symptoms were breakfast that included eggs, and toast with locally grown peaches and lunch in which he had a venison sandwich with mayonnaise with home canned corn; he had shot, butchered, and frozen the deer meat 6 months previously.**

One day before he developed diplopia and dyspnea, he sprayed 10 acres of his apple trees with a potent insecticide on a windy day.

2 of 6

BOARD REVIEW DAY 4 2024

#41 **His vital signs were normal including a normal temperature with the exception of an oxygen saturation of 89% with a respiratory rate of 20 per minute.**

Skin examination was unremarkable.

A full beard and very long hair were noted.

He is unable to move his eyes laterally. There is decreased strength in both arms.

3 of 6

BOARD REVIEW DAY 4 INFECTIOUS DISEASE BOARD REVIEW 2024

#41 **Strength of his leg muscles did not decrease with repetitive contractions.**

Basic laboratory work and chest X-Ray were unremarkable.

A head CT scan with contrast was unremarkable.

Lumbar puncture: opening pressure, cell count, glucose and protein were normal.

4 of 6

BOARD REVIEW DAY 4 INFECTIOUS DISEASE BOARD REVIEW 2024

#41 **Which one of the following is the most likely etiology of his paralytic clinical syndrome?**

A) Tick paralysis

B) Guillain-Barre

C) Organophosphate poisoning

D) Botulism

E) Myasthenia gravis

5 of 6

BOARD REVIEW DAY 4 INFECTIOUS DISEASE BOARD REVIEW 2024

#42 **48-year-old asymptomatic man presents with newly diagnosed HIV infection.**

His initial HIV RNA is 280,000 c/ml and CD4 count 65 cells/ul.

Other labs are normal; Genotype is Wild-type virus.

1 of 4

BOARD REVIEW DAY 4 INFECTIOUS DISEASE BOARD REVIEW 2024

#42 **Hepatitis panel reveals:**

- **HBVsAg neg**
- **HBsAb neg**
- **HBcAb +**
- **HBV DNA neg (<1000)**

4 months ago, he started on DTG + TAF/FTC;

He did well: with HIV RNA <20 and CD4 Count 270 cells/ul.

He has heard about injectable ARV therapy on TV and would like to try such a regimen.

2 of 4

BOARD REVIEW DAY 4 INFECTIOUS DISEASE BOARD REVIEW 2024

#42 **What would you recommend?**

A) Cabotegravir alone

B) Rilpivirine alone

C) Cabotegravir-rilpivirine

D) Stay on current regimen: this patient should not be given a long-acting regimen with the drugs currently available

3 of 4

BOARD REVIEW DAY 4 INFECTIOUS DISEASE BOARD REVIEW 2024

#43 **A 28-year-old man is newly found to have HIV infection. Initial work-up reveals he's asymptomatic with a normal physical exam.**

Labs demonstrate:

- **Normal CBC, electrolytes, and LFTs**
- **HIV RNA 23,000**
- **CD4 count 379 cells/uL**
- **Genotype: reverse transcriptase (RT) M184V**

1 of 3

BOARD REVIEW DAY 4 INFECTIOUS DISEASE BOARD REVIEW 2024

#43 **He prefers a one-pill, once-daily oral regimen. Which regimen do you recommend starting?**

A) Abacavir/lamivudine/dolutegravir

B) Tenofovir AF/emtricitabine/bictegravir

C) Tenofovir AF/emtricitabine/darunavir/ritonavir

D) Tenofovir AF/emtricitabine/elvitegravir/cobicistat

E) Tenofovir DF/lamivudine/efavirenz

2 of 3

BOARD REVIEW DAY 4 INFECTIOUS DISEASE BOARD REVIEW 2024

#44 **A 37-year-old man with a history of intravenous drug use and HIV infection appeared in the emergency room with fever and pulmonary infiltrates.**

He is diagnosed with tuberculosis by sputum smear microscopy and started on conventional 4 drug antituberculosis therapy.

Two weeks later, he was started by another physician on abacavir-lamivudine- and double-dose dolutegravir.

1 of 5

BOARD REVIEW DAY 4 INFECTIOUS DISEASE BOARD REVIEW 2024

#44 **His CD4 was 60 cells/μL, and his viral load was 100,000 copies/μL at the time ART was started.**

Eight weeks after starting ART (10 weeks after starting anti-TB therapy), he returns with new fever.

Chest X-ray shows more extensive infiltrates, a new pleural effusion, and new mediastinal adenopathy.

2 of 5

BOARD REVIEW DAY 4 INFECTIOUS DISEASE BOARD REVIEW 2024

#44 **The sputum specimens are negative for AFB. Bronchoscopy shows no pneumocystis, fungus, or bacteria on direct smear, but the GeneXpert MTB/RIF remains positive for TB (rifampin resistance not detected).**

The original culture has now been reported as positive for *M. tuberculosis*; phenotypic susceptibility testing results are pending.

3 of 5

BOARD REVIEW DAY 4 INFECTIOUS DISEASE BOARD REVIEW 2024

#44 **This worsening clinical syndrome most likely represents:**

A) Drug-resistant tuberculosis

B) Abacavir hypersensitivity syndrome

C) BAL negative pneumocystis pneumonia

D) Immune reconstitution syndrome

E) A drug interaction between INH and abacavir

4 of 5

BOARD REVIEW DAY 4 INFECTIOUS DISEASE BOARD REVIEW 2024

#45 **47-year-old woman started BIC/FTC/TAF 12 months ago as her first regimen (Bictegravir, emtricitabine, Tenofovir disoproxil fumarate).**

Initial: HIV RNA 28,000 c/ml (Wild-type virus).

CD4 count 450 cells/ul.

Current: HIV RNA <20 c/mL / CD4+ count 930 /uL.

1 of 4

BOARD REVIEW DAY 4 INFECTIOUS DISEASE BOARD REVIEW 2024

#45 **Since starting her current regimen her weight has increased from 145 lbs to 171 lbs.**

Fasting glucose 101 mg/dl. HbA1c 5.9.

Diet and exercise have not been effective.

She is bothered by the weight gain and wants something done to reduce her weight.

2 of 4

BOARD REVIEW DAY 4 INFECTIOUS DISEASE BOARD REVIEW 2024

#45 **In addition to diet and exercise, you recommend:**

A) No other interventions at this time

B) Changing ARV to non-TAF, non-InSTI regimen

C) Start Metformin 500 mg twice daily

D) Start Semaglutide, ramp up dose to 1.0 mg SQ weekly

3 of 4

BOARD REVIEW DAY 4 INFECTIOUS DISEASE BOARD REVIEW 2024

#46 **A 40-year-old man with no significant past medical history presents in December with complaints of fever, headache, and stiff neck.**

His symptoms started 10 days ago and has not responded to analgesic therapy – in fact, his headache has worsened over the last several days.

He lives alone in a mobile home and has recently seen a number of mice and rats in his home, but he denies any bites from these rodents.

He takes no medications and has received all of his vaccinations.

1 of 4

BOARD REVIEW DAY 4 INFECTIOUS DISEASE BOARD REVIEW 2024

#46 **On examination, his temperature is 101°F. He is awake, alert, and oriented. He has meningismus and shotty cervical adenopathy.**

Genital examination reveals some pain on palpation of his left testes. Abdominal examination is normal.

Laboratory studies reveal a WBC count of 3,000/mm^3 and his platelet count is 80,000/mm^3. Lumbar puncture shows an opening pressure of 210 mm H_2O, WBC count of 200/mm^3 (95% lymphocytes), glucose of 45 mg/dL, and protein of 250 mg/dL.

CSF Gram stain is negative.

2 of 4

BOARD REVIEW DAY 4 INFECTIOUS DISEASE BOARD REVIEW 2024

#46 **Which of the following is the most likely cause of this patient's meningitis?**

A) Mumps virus

B) Measles virus

C) Lymphocytic choriomeningitis virus

D) Leptospira interrogans

3 of 4

BOARD REVIEW DAY 4 INFECTIOUS DISEASE BOARD REVIEW 2024

#47 **A 25-year-old man without HIV infection was receiving every other month injections of cabotegravir for HIV pre-exposure prophylaxis (PrEP).**

He missed 2 consecutive injections due to work travels and was evaluated showing HIV antigen/antibody test +, HIV-1 immunoblot +, HIV RNA 120,000, and HIV genotype is pending.

1 of 3

BOARD REVIEW DAY 4 INFECTIOUS DISEASE BOARD REVIEW 2024

#47 **What do you recommend?**

A) Restart cabotegravir PrEP
B) Change to tenofovir DF/emtricitabine PrEP
C) Start tenofovir AF/emtricitabine/bictegravir
D) Start tenofovir AF/emtricitabine + darunavir/ritonavir

2 of 3

BOARD REVIEW DAY 4 INFECTIOUS DISEASE BOARD REVIEW 2024

#48 **A 50-year-old man with untreated HCV presented with a 6-week history of ulcerating skin lesions.**

He relates a history of injection drug use of both cocaine and fentanyl over this time period.

On physical exam, he is afebrile.

1 of 4

BOARD REVIEW DAY 4 INFECTIOUS DISEASE BOARD REVIEW 2024

#48 **Skin exam reveals multiple small, painful ulcerations on his chest, neck, arms, and legs, most but not all of which are adjacent to areas where he has injected various street drugs.**

There is no purulence, odor, or surrounding erythema.

Punch biopsy showed nonspecific inflammation and subcutaneous necrosis, without vasculopathy.

2 of 4

BOARD REVIEW DAY 4 INFECTIOUS DISEASE BOARD REVIEW 2024

#48 **What is the most likely cause of these ulcers?**

A) Pyoderma gangrenosum
B) Polyarteritis nodosum
C) Xylazine
D) Porphyria cutanea tarda
E) Cryoglobulinemia

3 of 4

BOARD REVIEW DAY 4 INFECTIOUS DISEASE BOARD REVIEW 2024

#49 **A 71-year-old man with HIV transfers care to you with a history of taking and failing "nearly all HIV medications including T20 (enfuvirtide)."**

He currently takes tenofovir alafenamide (TAF)/emtricitabine (FTC) + etravirine + darunavir + ritonavir with a CD4 15 and HIV RNA 233,140 copies/ml.

You send an HIV genotype, phenotype, and tropism test. The tropism test returns "dual/mixed virus."

1 of 3

BOARD REVIEW DAY 4 INFECTIOUS DISEASE BOARD REVIEW 2024

#49 **In addition to optimizing his antiretroviral regimen, you recommend:**

A) Adding maraviroc
B) Adding double dose maraviroc
C) Adding enfuvirtide
D) Adding fostemsavir

2 of 3

BOARD REVIEW DAY 4 2024

#50 **A 35-year-old sexually active heterosexual man wants to reduce his risk of HIV and asks about taking HIV pre-exposure prophylaxis (PrEP) "only when needed."**

Which do you recommend?

A) None, PrEP not recommended

B) Daily tenofovir disoproxil fumarate (TDF)/emtricitabine

C) TDF/emtricitabine "on demand" (2 pills 24 hours before sex, then one 24 hours later and one 48 hours later)

D) TAF/emtricitabine "on demand"

E) Cabotegravir "on demand"

1 of 2

BOARD REVIEW DAY 4 2024

#51 **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 2024

#51 **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 2024

#51 **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 2024

#52 **A 30-year-old woman is admitted to the hospital with seizures and hallucinations.**

Two weeks prior to this admission, she was hospitalized with fever, confusion, and headaches.

A CSF analysis at that time showed 160 WBCs/mm^3 with 89% lymphocytes and HSV-1 PCR was positive.

MRI showed a T2-weighted lesion in the right temporal lobe.

1 of 6

BOARD REVIEW DAY 4 2024

#52 **She was diagnosed with herpes simplex encephalitis (HSE) and was discharged to a skilled nursing facility to complete a 3-week course of intravenous acyclovir (10 mg/kg every 8 hours).**

She initially did well, with resolution of fever and normalization of mentation.

On the day prior to re-admission, she was noted to be paranoid (believed the nurses were poisoning her) and on the day of admission had a generalized seizure.

2 of 6

BOARD REVIEW DAY 4 INFECTIOUS DISEASE BOARD REVIEW 2024

#52 **On exam, she is afebrile, and her neck is supple.**

Choreoathetoid movements of both hands are noted.

She is oriented only to person.

Routine laboratory testing including chemistry panel and CBC are within normal limits.

3 of 6

BOARD REVIEW DAY 4 INFECTIOUS DISEASE BOARD REVIEW 2024

#52 **MRI showed slight improvement in the right temporal lobe with no new lesions, Lumbar puncture is performed with 27 WBC/mm^3, 66% lymphocytes.**

CSF protein and glucose are normal. PCR for HSV was negative.

4 of 6

BOARD REVIEW DAY 4 INFECTIOUS DISEASE BOARD REVIEW 2024

#52 **Which of the following is the most likely diagnosis?**

A) Acyclovir neurotoxicity

B) Anti-N-methyl-D-aspartate receptor (NMDAR) encephalitis

C) Acute disseminated encephalomyelitis (ADEM)

D) Relapsed HSV encephalitis

E) CNS vasculitis

5 of 6

40

Pharyngitis Syndromes Including Group A Strep Pharyngitis

Dr. Karen Bloch

40 - Pharyngitis Syndromes and Group A Strep

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

IDBR INFECTIOUS DISEASE BOARD REVIEW AUGUST 17-21, 2024

Pharyngitis Syndromes Including Group A Strep Pharyngitis

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

7/1/2024

IDBR INFECTIOUS DISEASE BOARD REVIEW AUGUST 17-21, 2024

Disclosures of Financial Relationships with Relevant Commercial Interests

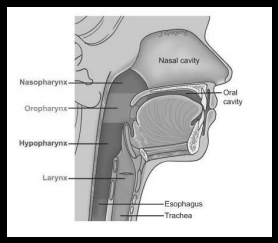
- **None**

Think Like a Realtor

Think Like A Realtor

Location
Location
Location

Pharyngitis

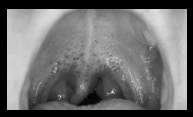


- Micro-neighborhoods
- Regional differences

Case 1

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 erythema & petechiae
Neck-Tender bilateral anterior LAN



Labs:
Rapid strep antigen test negative

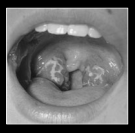
Question 1

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 in adults (even untreated)

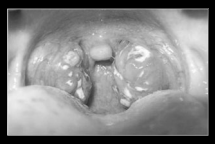
Differentiating Pharyngitis

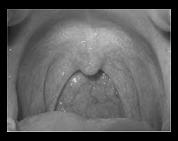
GAS
- Sudden onset
- Fever
- Lymphadenopathy
- Exposure to contact with streptococcal pharyngitis

Viral pharyngitis
- The 3 C's
  - Conjunctivitis
  - Coryza
  - Cough
- Other symptoms
  - Diarrhea
  - Ulcerative stomatitis
  - Hoarseness

Differentiating Pharyngitis

GAS VS **Viral pharyngitis**





How Specific are Clinical Findings?

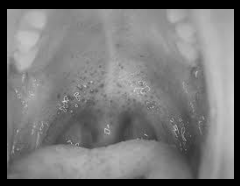
- Modified CENTOR score
  - Can't cough
  - Exudate
  - Nodes
  - Temperature
  - OR age <15 yr (+1) or >44 years (-1)

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

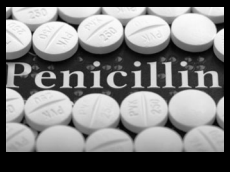


Laboratory Diagnosis

- 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

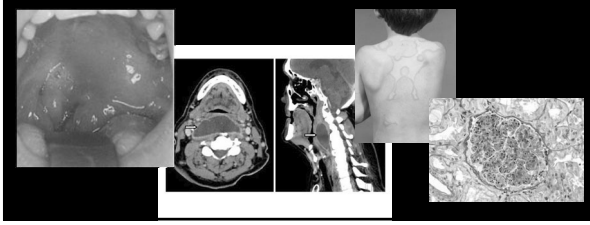


PCN Allergic:

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

Secondary Complications

- Infectious complications
- Immunologic complications



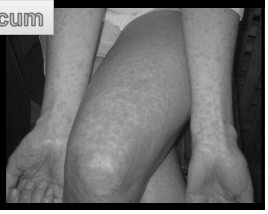
Pharyngitis and….

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

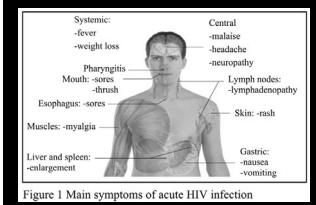
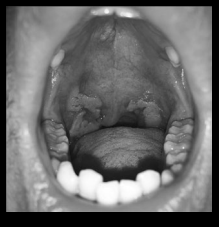


Figure 1 Main symptoms of acute HIV infection

- Secondary syphilis



Pharyngitis after Receptive Oral Intercourse

Neisseria gonorrhoeae	Herpes simplex virus
• Highest risk MSM • Diagnose by nucleic acid amplification test of pharyngeal swab	• HSV-1 or 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

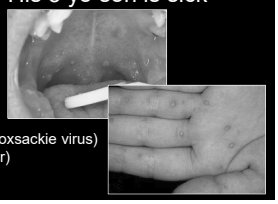
Adenovirus

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



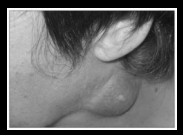
- Caused by enteroviruses (most common Coxsackie virus)
- More common in kids (often serve as vector)

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

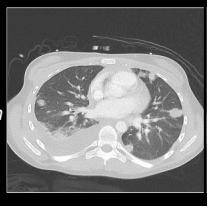
- Uncommon in the US
- Transmission through ingestion (or rarely inhalation)
  - Inadequately cooked game
  - Contaminated water
  - Rodent contamination
- Exudative tonsillitis, suppurative LAN
- Treatment: streptomycin, doxycycline or quinolone

Pharyngitis and Chest Pain

- 20 yo college student with sore throat, fever and chills. 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

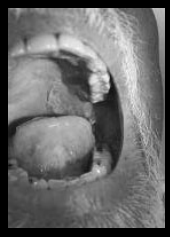


Pharyngitis & TNF-alpha inhibitors

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

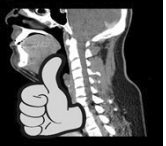
Oropharyngeal Histoplasmosis

- Can mimic oral malignancy
- Denotes disseminated disease



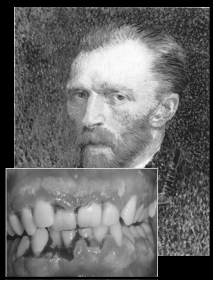
Extra-Tonsillar Infections: 1

- 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



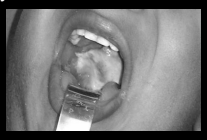
Extra-Tonsillar Infections: 3

- 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

- A 32-year-old woman is seen for a bad sore throat 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.

- T 100.2F; P 126; BP 118/74.
- 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.

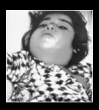
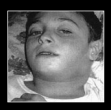
Question 3

The most likely diagnosis is?

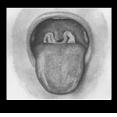
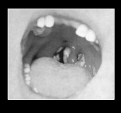
A. Streptococcal pharyngitis
B. Kawasaki disease
C. Vincent angina
D. Diphtheria
E. Candida

Buzz words and Visual Associations

Bull neck:

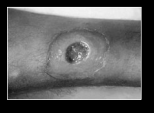




Grey pseudomembrane: extends onto palate or uvula; bleeds when scraped

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

40 - Pharyngitis Syndromes and Group A Strep

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

41

HIV-Associated Opportunistic Infections II

Dr. Rajesh Gandhi

41 – HIV-Associated Opportunistic Infections

Speaker: Rajesh Gandhi, MD

IDBR INFECTIOUS DISEASE BOARD REVIEW AUGUST 17-21, 2024

HIV-Associated Opportunistic Infections II

Rajesh T. Gandhi, MD
Massachusetts General Hospital
Professor of Medicine, Harvard Medical School

7/1/2024

IDBR INFECTIOUS DISEASE BOARD REVIEW AUGUST 17-21, 2024

Disclosures of Financial Relationships with Relevant Commercial Interests

- **None**
- **Acknowledgement: Dr. Henry Masur for slides**

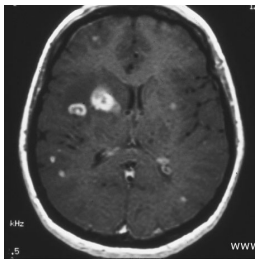
HIV Associated Opportunistic Infections: Part 2

- Opportunistic CNS Infections: Brain Lesions
- Opportunistic CNS Infections: Cryptococcal Meningitis
- Mycobacterial Infections
- Immune Reconstitution Inflammatory Syndrome

Question #1

PREVIEW QUESTION

- 50 yo M with HIV (CD4 40, HIV RNA 600,000 not on antiretroviral therapy) presents with fever, headache.
- Northeast US, no travel; no animal or TB exposures
- MRI: ring enhancing lesions; no midline shift
- Serum toxoplasma IgG +. CSF: no WBC, normal protein, toxoplasma (toxo) PCR pending
- You recommend
  A. Brain biopsy
  B. Meningeal biopsy
  C. Initiate anti-toxo therapy; if no response in 2 weeks, brain biopsy
  D. Vancomycin, cefepime, metronidazole



Brain Lesions in People with HIV (PWH)

- MRI with contrast favored over CT (CT without contrast may miss lesions)
- Clues:
  - Toxoplasma: multiple ring enhancing lesions, often involving basal ganglia; serum toxoplasma IgG positive (reactivation)
  - Primary CNS lymphoma: large solitary focal brain lesion; may cross corpus callosum; increased FDG PET uptake; B cell lymphoma; CSF EBV PCR+. CD4 cell count <50
  - Tuberculoma: consider in person from endemic area with contrast enhancing lesions, basilar meningitis
  - Progressive multifocal leukoencephalopathy (PML): asymmetric non-enhancing lesions in subcortical white matter without mass effect

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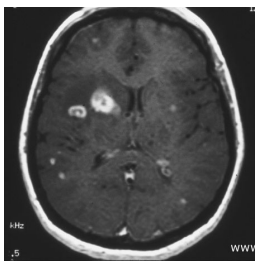
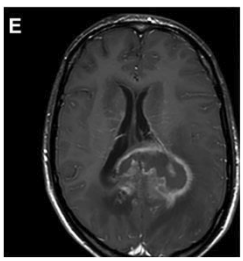
Toxoplasma Encephalitis



Primary CNS Lymphoma



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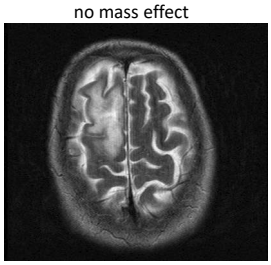
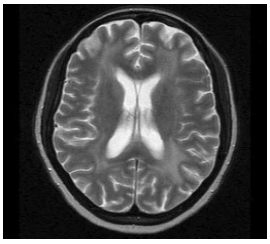
PML: Asymmetric white matter changes adjacent to cortical ribbon, no mass effect



HIV Encephalitis: bilateral symmetric white matter changes



www.idimages.org. Contributed by Dr. Vince Marconi

Evaluation of CNS Mass Lesions in People with HIV/AIDS

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

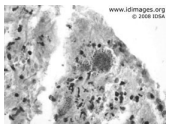
Radiologic Results
- Non-specific although certain features suggestive
- Look for Extra CNS lesions for biopsy

Laboratory Studies to Perform
- Serology: Toxo IgG
- Serum Cryptococcal Ag and Histoplasma Ag
- Blood culture - AFB
- CSF - Cryptococcal Ag
  - PCR (EBV, CMV, Toxoplasma, JC virus)

Response to Empiric Therapy

Toxoplasma Encephalitis (TE)

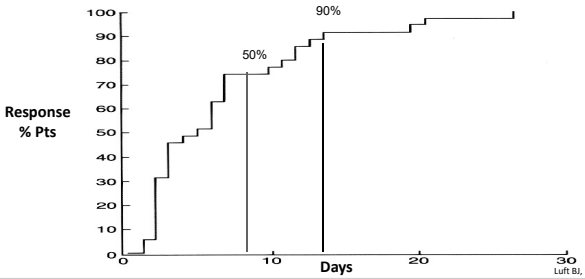
- Caused by protozoan, *Toxoplasma gondii*
- Reactivation of latent tissue cysts
- Highest risk is in PWH with CD4 count <100
- May present with headache, confusion, weakness, fever
- Diagnosis:
  - Serum toxoplasma IgG usually positive; negative serology makes TE unlikely
  - MRI: ring-enhancing lesions, often involving basal ganglia
  - CSF toxoplasma PCR: high specificity (96-100%); sensitivity 50-60% (negative PCR does not rule out TE)
  - Empiric diagnosis: clinical, radiographic improvement with anti-toxoplasma therapy; if no response by about 2 weeks, consider brain biopsy



https://clinicalinfo.hiv.gov/en/guidelines/hiv-clinical-guidelines-adult-and-adolescent-opportunistic-infections/toxoplasma-gondii?view=full

Time to Neurologic Response for Toxoplasma Encephalitis

35 Patients with TE Treated with Clindamycin - Pyrimethamine



Luft BJ, NEJM 1993

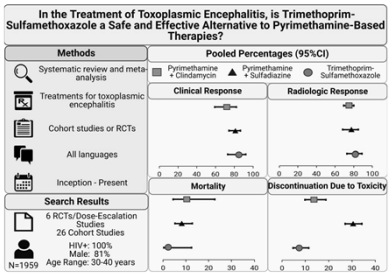
Therapy for Toxoplasma Encephalitis

- **Preferred Regimen**
  - Sulfadiazine plus pyrimethamine plus leucovorin (PO only)
    - May be unavailable or excessively expensive
  - Trimethoprim-sulfamethoxazole (PO or IV)
  - In patients with sulfa allergy, sulfa desensitization should be attempted
- **Alternative Regimens – for those who cannot tolerate sulfonamides**
  - Clindamycin plus pyrimethamine (and leucovorin)
  - Atovaquone +/- Pyrimethamine (and leucovorin)

Note: Initiate antiretroviral therapy when patient is tolerating anti-toxoplasma therapy (usually within a week or two after starting anti-toxoplasma therapy)

https://clinicalinfo.hiv.gov/en/guidelines/hiv-clinical-guidelines-adult-and-adolescent-opportunistic-infections/toxoplasma-gondii?view=full

Compared with Sulfa-Pyrimethamine, Trim-sulfa has similar response rate, lower toxicity



Prosty C, CID, 2023

Adjunctive Therapies for Toxoplasma Encephalitis

- Corticosteroids
  - Not routine
  - Only if mass effect, increased intracranial pressure/symptoms/signs
- Anticonvulsants
  - Should not be given prophylactically
  - Only if patients have seizures

Primary Prevention of Toxoplasmosis in People with HIV

- **Indication**
  - Positive Toxoplasma IgG and CD4 <100 cells/uL
- **Drugs**
  - First Choice
    - TMP-SMX (one double strength tablet daily)
  - Alternatives
    - Other dosing regimens for TMP/SMX
    - Dapsone-Pyrimethamine (with leucovorin)
    - Atovaquone +/- Pyrimethamine (with leucovorin)

https://clinicalinfo.hiv.gov/en/guidelines/hiv-clinical-guidelines-adult-and-adolescent-opportunistic-infections/toxoplasma-gondii?view=full

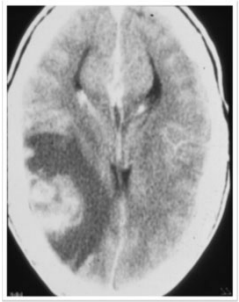
Primary Prevention of Toxoplasmosis in PWH

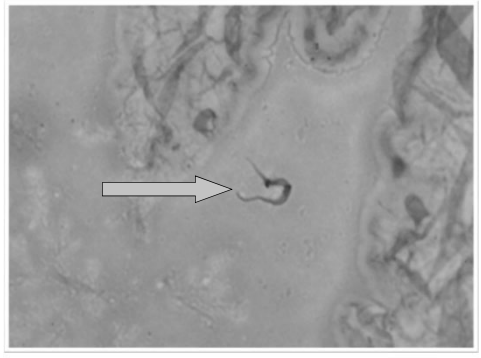
- For patients with CD4<200 who are on TMP-SMX or atovaquone for PCP prophylaxis
  - Nothing more is needed
- For patient on Aerosol Pentamidine or Dapsone for PCP prophylaxis
  - If on dapsone: add pyrimethamine (plus leucovorin)
  - If on Aerosol pentamidine because cannot take TMP-SMX: not protected-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

https://clinicalinfo.hiv.gov/en/guidelines/hiv-clinical-guidelines-adult-and-adolescent-opportunistic-infections/toxoplasma-gondii?view=full

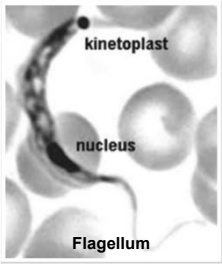
Case

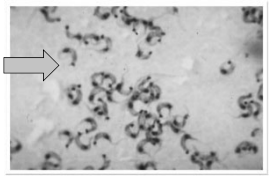
- A 39-year-old female from Brazil presents to ED with a seizure.
  - HIV Ag/Ab is positive
  - CD4 = 20/µL
  - VL = 100,000 copies/µL
- She is started on sulfadiazine and pyrimethamine.
- After 10 days, she has not improved, and a brain biopsy is performed





Trypanosoma cruzi in Blood Smear and CSF (Chagasic Encephalitis in PWH)





Badero et al, AIDS THERAPY, 4th Ed
DiazGranados C, Lancet ID, 2009

HIV Associated Opportunistic Infections: Part 2

Opportunistic CNS Infections: Cryptococcal Meningitis

Question #2

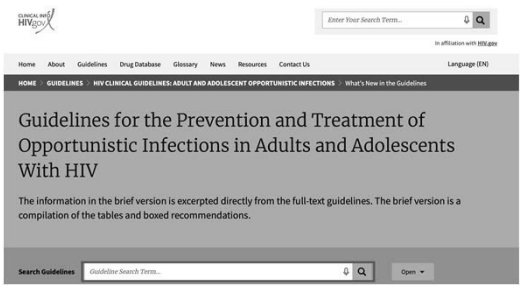
PREVIEW QUESTION

- 50-yo woman with HIV (CD4 20, HIV RNA 500,000) presents with fever and headache. Not on antiretroviral therapy (ART). Diagnosed with cryptococcal meningitis
- Started on induction therapy (liposomal amphotericin plus 5FC)
- When should she be started on ART?
  - A. Start ART at the same time as anti-fungal therapy
  - B. About 4 weeks after starting anti-fungal therapy
  - C. 6 months after starting anti-fungal therapy
  - D. After completing a full course of maintenance anti-fungal therapy

HIV-Associated Cryptococcal Meningitis

- Usually presents with subacute onset of confusion, lethargy
- Neck stiffness and photophobia only occur in 25%
- May be accompanied by non-CNS manifestations: pneumonia, skin lesions, prostate infection
- CD4 Count <100 cells/uL in 90% of patients
- CSF: minimal abnormalities or lymphocytic pleocytosis with elevated protein.
- Opening pressure > 25 cm H_20 in 60-80% of patients (be sure to measure)
- Serum and CSF cryptococcal antigen positive in almost all patients.
- Blood cultures positive for cryptococcus in 60%

https://clinicalinfo.hiv.gov/en/guidelines/hiv-clinical-guidelines-adult-and-adolescent-opportunistic-infections/cryptococcosis?view=full



https://clinicalinfo.hiv.gov/en/guidelines/hiv-clinical-guidelines-adult-and-adolescent-opportunistic-infections/whats-new

Therapy of Cryptococcal Meningitis

Liposomal Ampho B plus **Flucytosine***	**3-4 mg/kg daily** **25 mg/kg QID**	→ 2 weeks	Induction
Fluconazole 800 mg po qd**		→ 8 weeks	Consolidation
Fluconazole 200 mg po daily***		→ ≥ 52 weeks	Maintenance

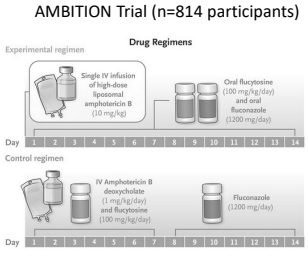
*5FC Associated with earlier sterilization CSF, fewer relapses, improved survival

**For clinically stable patients with negative CSF cultures, dose can be reduced to 400 mg daily

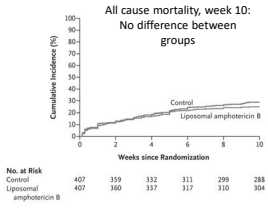
*** Stop after 12 m total therapy if CD4 >100- 150 x >3m , asymptomatic, VL <50 copies

Single-dose Liposomal AmB with Fluconazole/5FC

AMBITION Trial (n=814 participants)



Jarvis JN et al, NEJM, 2022



Adverse events less frequent in single-dose AmB group

Management of Cryptococcal Meningitis

- For flucytosine, therapeutic drug monitoring indicated. Toxicities: marrow suppression, hepatitis, diarrhea. Renal elimination: monitor kidney function
- Successful induction therapy = clinical improvement and negative CSF culture
- India ink and CSF CrAg frequently positive at Week 2: not indicative of failure
- Monitoring of cryptococcal antigen titers not recommended
- In patients with symptoms of elevated intracranial pressure and opening pressure >25 cm: remove CSF to reduce pressure by half or <20cm H20
  - Lumbar drain or VP shunt may be needed if pressures remain elevated
- Not routinely recommended: Corticosteroids, Mannitol, Acetazolamide

https://clinicalinfo.hiv.gov/en/guidelines/hiv-clinical-guidelines-adult-and-adolescent-opportunistic-infections/cryptococcosis?view=full

Dexamethasone Did Not Reduce Mortality and Was Associated with More Adverse Events and Disability

ORIGINAL ARTICLE

Adjunctive Dexamethasone in HIV-Associated Cryptococcal Meningitis

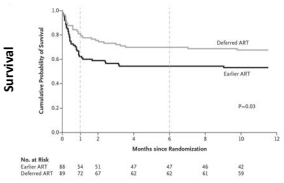
J. Beardsley, M. Wolbers, F.M. Kibengo, A.-B.M. Ggayi, A. Kamali, N.T.K. Cuc, T.Q. Binh, N.V.V. Chau, J. Farrar, L. Merson, L. Phuong, G. Thwaites, N. Van Kinh, P.T. Thuy, W. Chierakul, S. Siriboon, E. Thiansukhon, S. Onsanit, W. Supphamongkholchaikul, A.K. Chan, R. Heyderman, E. Mwinjiwa, J.J. van Oosterhout, D. Imran, H. Basri, M. Mayxay, D. Dance, P. Phimmasone, S. Rattanavong, D.G. Lalloo, and J.N. Day, for the CryptoDex Investigators*

NEJM, 2016

When to Start ART for Cryptococcal Meningitis

- DHHS OI Guidelines recommend ART initiation 4-6 weeks after initiation of antifungal therapy
- Some experts start ART earlier (at 2-4 weeks after initiation of anti-fungal therapy) based on evolving data with close monitoring

COAT trial: early ART (1-2 wks) associated with higher mortality than delayed ART (5 wk)



Boulware D et al, NEJM, 2014
https://clinicalinfo.hiv.gov/en/guidelines/hiv-clinical-guidelines-adult-and-adolescent-opportunistic-infections/cryptococcosis?view=full
Gandhi RT et al, IAS USA Guidelines, JAMA 2022

Preventing Disease
(Pre-emptive Therapy for Cryptococcal Ag+/Low CD4)

- **Recommendation:**
  - Screen patients with CD4 count < 100 with serum cryptococcal antigen
    - Frequency: 2.9% if CD4 <100, 4.3% if CD4 < 50
    - Positive serum CrAg predicts development of disease
- **If Positive: Perform LP and Blood Cultures to determine Rx**
  - If CSF positive or serum LFA is >=640
    - Treat like cryptococcal meningitis/disseminated (Ampho/5FC)
  - If CSF negative
    - Treat with fluconazole 400mg or 800mg x6 months

https://clinicalinfo.hiv.gov/en/guidelines/hiv-clinical-guidelines-adult-and-adolescent-opportunistic-infections/cryptococcosis?view=full

HIV Associated Opportunistic Infections: Part 2

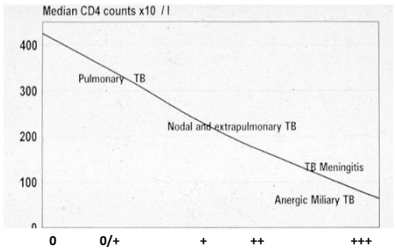
Mycobacterial Infections

Tuberculosis in PWH: Highlights

- High risk of TB reactivation in PWH: ≈5-10% per year; may occur even when CD4 count >200
- Screen PWH for latent TB (tuberculin skin test, TST, or IGRA); if CD4 count low, repeat TB screening after immune reconstitution on ART
- TB prophylaxis: positive TST (>5 mm) or IGRA; close contact of person with infectious TB
- When to start ART in people with HIV and TB
  - CD4 count <50: start within 2 weeks of TB therapy
  - CD4 count >50: start within 2-8 weeks of TB therapy (most would start sooner)
  - TB Meningitis: high mortality; start ART once TB meningitis under control and at least 2 weeks after initiating TB treatment; close monitoring needed
- Prednisone may prevent paradoxical TB immune reconstitution inflammatory syndrome

https://clinicalinfo.hiv.gov/en/guidelines/hiv-clinical-guidelines-adult-and-adolescent-opportunistic-infections/mycobacterium?view=full Torok et al, CID, 2011; Meintjes NEJM, 2018

Extrapulmonary TB and High Organism Load More Common in PWH with Low CD4 Count



Jones et al, Am Rev Respir Dis, 1993; Perlman et al, CID, 1997

Question #3

- 45-yo man with HIV (CD4 11, HIV RNA 300,000) presents with fever, diarrhea and weight loss.
- He is initiated on dolutegravir + tenofovir/emtricitabine
- Two weeks later, he develops markedly enlarged supraclavicular lymph node
- Biopsy shows necrotizing granulomas and AFB; cultures grow MAC
- You recommend:
  A. Stop ART and initiate treatment for MAC
  B. Continue ART; initiate treatment for MAC
  C. Start steroids and stop all other treatments

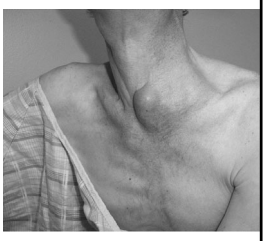


Image from Riddell J, J Translational Med, 2007

Mycobacterium Avium Intracellulare Complex

- **Epidemiology**
  - Ubiquitous in the environment
- **Transmission**
  - Inhalation, ingestion
- **Risk factors**
  - CD4 < 50, HIV RNA >1000
- **Clinical Manifestations of Disseminated MAC**
  - Fever, sweats, wasting, diarrhea, lymphadenopathy, hepatosplenomegaly
  - Rare as cause of lung disease
  - Labs: elevated alkaline phosphatase, anemia

https://clinicalinfo.hiv.gov/en/guidelines/hiv-clinical-guidelines-adult-and-adolescent-opportunistic-infections/disseminated?view=full

Diagnosis

- Compatible symptoms and signs along with isolation of MAC from cultures of blood, lymph node or other normally sterile sites
- MAC may be detected in respiratory or GI tract but routine screening of these sites and pre-emptive therapy for MAC is not recommended

https://clinicalinfo.hiv.gov/en/guidelines/hiv-clinical-guidelines-adult-and-adolescent-opportunistic-infections/disseminated?view=full

Treatment for MAC

- **Specific Therapy**
  - Clarithromycin or Azithromycin + Ethambutol
    - Rifabutin, fluoroquinolone or amikacin as a 3rd or 4th drug, particularly if severe disease ("high burden of organisms")
    - Beware drug interactions with clarithromycin or rifabutin (azithromycin has fewer drug interactions)
    - Perform susceptibility testing on MAC isolate
- **Antiretroviral Therapy**
  - Start as soon as possible after diagnosis, preferably at the same time or within a few days of initiation of anti-mycobacterial therapy

https://clinicalinfo.hiv.gov/en/guidelines/hiv-clinical-guidelines-adult-and-adolescent-opportunistic-infections/disseminated?view=full

~~Primary MAC Prophylaxis~~

- Primary prophylaxis against disseminated MAC disease is NOT recommended if ART initiated immediately

https://clinicalinfo.hiv.gov/en/guidelines/hiv-clinical-guidelines-adult-and-adolescent-opportunistic-infections/disseminated?view=full

Speaker: Rajesh Gandhi, MD

HIV Associated Opportunistic Infections: Part 2

Immune Reconstitution Inflammatory Syndrome

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 recent initiation of therapy for OI
  - High pathogen load
- **Clinical Features**
  - Characterized by fevers and worsening of the underlying OI or tumor
  - May "unmask" disease at previously unrecognized site or lead to paradoxical worsening of a known OI
  - Usually occurs 4-8 weeks after ART initiation but may manifest earlier or later

Pathogens Commonly Associated with IRIS

- Mycobacterium avium complex
- Mycobacterium tuberculosis
- Cryptococcus neoformans
- Reported with virtually all opportunistic infections and tumors

Mycobacterial IRIS

PATHOGEN	TYPICAL/CHARACTERISTICS OF THE DISEASE
Mycobacterium tuberculosis	Worsening lung infiltrates, lymphadenitis, CNS tuberculomas
MAC	Lymphadenitis; pulmonary and abdominal disease

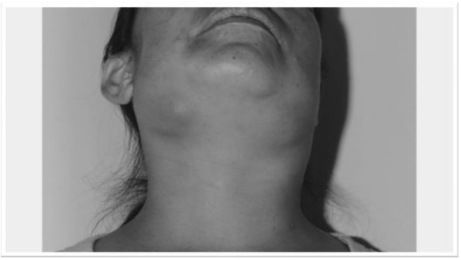
Cecil Textbook (French and Meintjes)

Examples of IRIS

PATHOGEN	TYPICAL/CHARACTERISTICS OF THE DISEASE
Cryptococcus neoformans	Worsening meningitis (may have brisk CSF pleocytosis)
Pneumocystis jiroveci	Exacerbation of pneumonia
Cytomegalovirus (CMV)	Vitritis
JC polyomavirus/PML	Worsening white matter changes; enhancement, edema
Human herpesvirus 8/Kaposi Sarcoma	Rapid progression of existing and/or new KS lesions
Varicella-zoster virus	Dermatomal or multidermatomal zoster; rarely myelitis

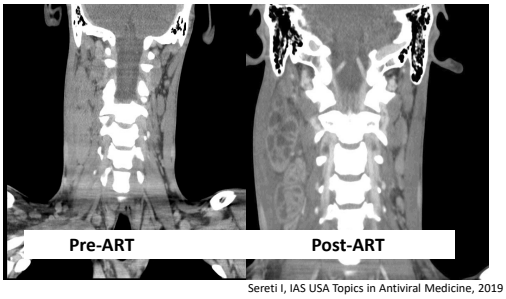
Cecil Textbook (French and Meintjes)

Immune Reconstitution Inflammatory Syndrome (Mycobacterium avium complex)



Sereti I, IAS USA Topics in Antiviral Medicine, 2019

MAC IRIS in Patient with HIV



Sereti I, IAS USA Topics in Antiviral Medicine, 2019

Management of IRIS

- **Reassess Diagnosis**
  - Evaluate for concurrent, additional OIs and tumors
- **Treat IRIS**
  - Continue ART
  - Continue treatment of identified pathogen
  - NSAIDS or Corticosteroids
    - Prednisone 20-40mg qd x 4-8 weeks

Summary

Multiple causes of brain lesions in people with advanced HIV; response to empiric therapy makes dx of toxoplasma encephalitis

New guidelines for induction, consolidation and maintenance therapy for cryptococcal meningitis; deferring ART for about 4 weeks appropriate

TB reactivation may occur even when CD4 count >200; MAC Prophylaxis no longer recommended when ART started quickly

Immune Reconstitution Inflammatory Syndrome may occur after almost all opportunistic infections or tumors: paradoxical worsening or unmasking of subclinical disease

42

Syndromes that Masquerade as Infections

Dr. Karen Bloch

42 – Syndromes that Masquerade as Infections

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

Syndromes that Masquerade as Infections

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

7/1/2024

Disclosures of Financial Relationships with Relevant Commercial Interests

- **None**

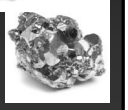
ID Board Content

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
  - Sometimes focal abnormality
    - 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”

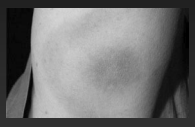
You say…..

YERSINIA (gastroenteritis)

Test taking tip

I say ”Bull’s-eye rash”

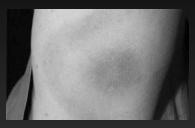
You say…..



Test taking tip

I say ”Bull’s-eye rash”

You say…..

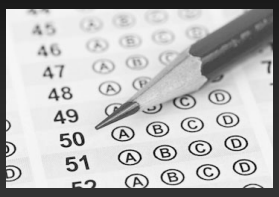


Lyme disease
(or Erythema migrans or STARI)

My Approach to Mimics

- Think like an Internist
- The key is recognition, not treatment
- This talk will emphasize illustrative cases
- Goal 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

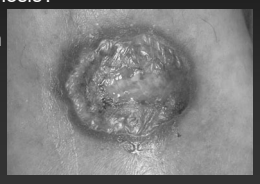
Sweet Syndrome is *most* likely to occur in a patient with which of the following illnesses?

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

Question 3

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

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



But this being boards…..

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 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

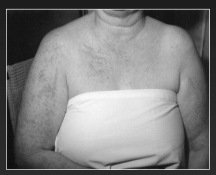
PREVIEW QUESTION

- A 39-year-old woman is admitted for 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

PREVIEW QUESTION

- 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.

PREVIEW QUESTION

Question 5

PREVIEW QUESTION

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

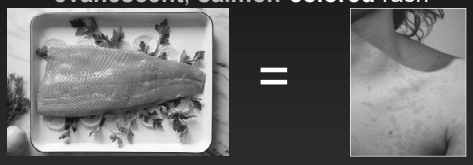
Adult Still's Disease (Adult Onset JRA)

Yamaguchi Criteria: (5 features with 2 major criteria)

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

Adult Still's Disease

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



Koebner phenomenon (rash at pressure sites)

Case 6

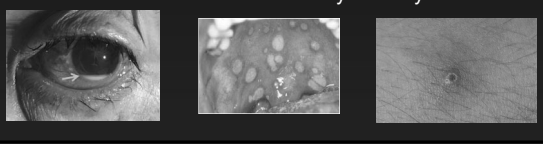
PREVIEW QUESTION

- A 24-year-old man was referred by the ED for evaluation of ulcers of the mouth and penis. He was born 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 painful ulcers on the oral mucosa.
- There is a 0.5cm ulcer on the penis.

PREVIEW QUESTION

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

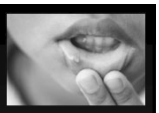


Question 6

PREVIEW QUESTION

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

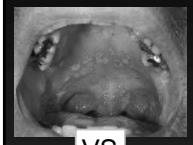
Behçet's disease



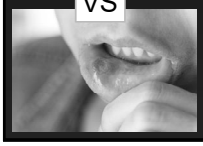
Pleomorphic vasculitis diagnosed clinically

- 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 (abdomenal pain, bloody diarrhea)
  - Aseptic meningitis
  - Arterial and venous thrombosis

Behçet's disease



VS



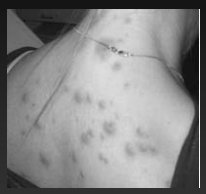
- Ulcers is the buzz word, but the trick is differentiation from infectious causes (HSV, coxsackie, etc)
- Additional Clues
  - Recurrence
  - Ocular findings
  - Pathergy (needle or IV site)

Case 7

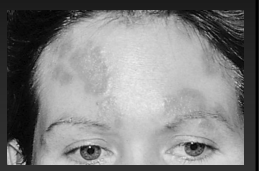
- A 38-year-old woman with AML is admitted with fever. She underwent induction chemotherapy 2 weeks prior, complicated by neutropenic fever that resolved with marrow recovery.
- She presents with a 1-day history of fever without localizing symptoms.
- Exam: T 101.4; P 98, Otherwise unremarkable.
- CBC 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 infiltrates of neutrophils without evidence of vasculitis; stains for organisms negative.

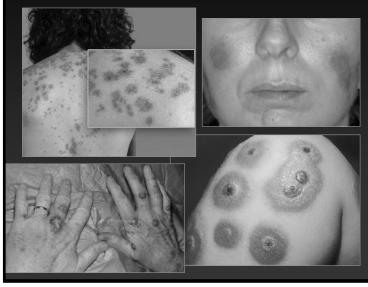
Question 7

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

Sweet Syndrome

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

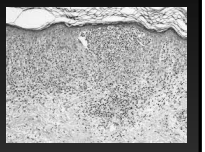
Skin Lesions in Sweet Syndrome



- 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)

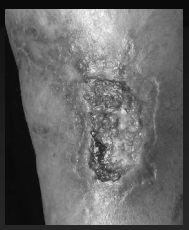


- Be suspicious in patients with malignancy (esp AML), IBD, recent URI, vaccination, pregnancy, or colony stimulating factor use in preceding 2 weeks

Case 8

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

- Exam:
  T 100.2
  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?

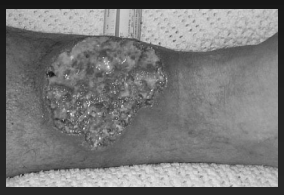
A. Ulcerative colitis
B. Cutaneous leishmaniasis
C. Amebic colitis
D. Cutaneous blastomycosis
E. Squamous cell cancer

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

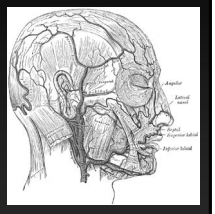
Question 9

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

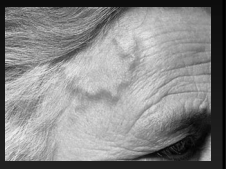
Giant Cell Arteritis

- 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:



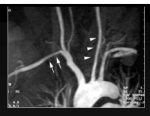
FUO in a patient >50 years PLUS

- 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 stiffness 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

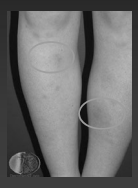
- A 37-year-old female presents with fever and joint pain. She is a long-distance runner and in excellent health.
- Three weeks prior she noted R knee pain after a long run. She was treated with a steroid injection with transient improvement, but subsequently developed bilateral ankle pain and redness. 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

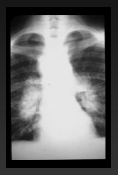
Question 10

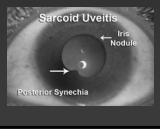
Which of the following is most likely to be diagnostic?

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

Sarcoidosis

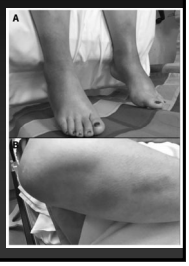
- Extra-pulmonary disease in ~1/3 of cases
- Lofgren Syndrome
  - Only form of sarcoid that is a clinical diagnosis
  - Triad of hilar LAN, acute arthritis, EN
  - Women, ankles (>90%), fevers common
- BUZZ WORDS
  - Hilar LAN, EN, uveitis, parotid enlargement
  - Non-caseating granulomas
  - Aseptic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



Erythema nodosum

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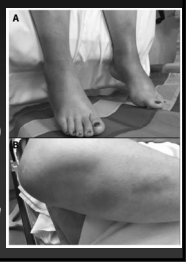
- Drugs: sulfonamides, Penicillins
- Oral contraceptives
- Sarcoid (Lofgren's syndrome)
- Ulcerative colitis (or Crohn's or Bechet's)
- Microbes:
  - EBV, Hep B/C
  - *Streptococci*, *Bartonella,* TB, *Mycoplasma*
  - Endemic fungi



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:

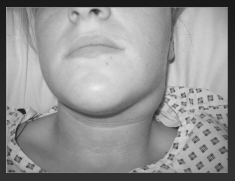
A. Hereditary angioneurotic edema
B. Familial Mediterranean fever
C. Systemic lupus erythematosus
D. Crohn's disease
E. Acute intermittent porphyria

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

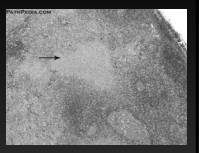
- A 26-year-old medical student presents with fever and cervical adenopathy.
- She was completely well until 9 days ago when she had the acute onset of fever and vague neck discomfort. She had no sore throat and no dental or scalp problems.



- 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

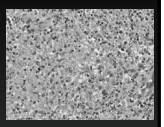
Which one of the following is the most likely diagnosis?

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

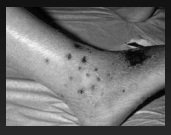


- Diagnosis by pathology:
  - necrotizing histiocytic infiltrate (not neutrophils) and fragments of nuclear debris.
- Buzz words and associations:
  - Acute onset fever and cervical adenopathy in young woman
  - Atypical lymphocytes (mono-like syndrome)
  - Path: necrotizing adenitis with histiocytosis

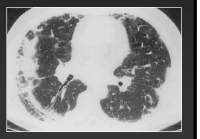
Case 13

- 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

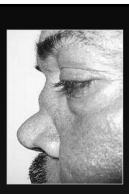
- Buzz words and associations:
  - Longstanding asthma
  - New infiltrates and eosinophilia (>10%) as steroids tapered.
  - Rash (tender nodules on extensor surfaces, purpura, ecchymosis, necrosis)
  - Fever UNCOMMON (until late)

Case 14

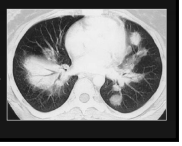
- A 38-year-old man is seen for a 6-week history of cough, intermittent fever and night sweats.
- He has had nasal stuffiness for 4-5 months with occasional epistaxis.
- He lives in Philadelphia, and 6 months ago traveled to Cincinnati on business.
- He has no pets and takes only an OTC decongestant.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

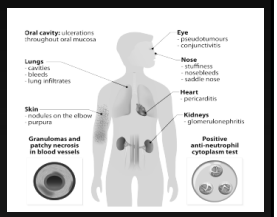


Question 14

- The diagnosis will most likely be supported by which of the following?
  A. c-ANCA
  B. Anti-glomerular basement membrane Ab
  C. Urine toxicology screen
  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

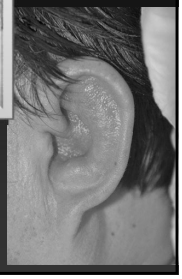
- Dx:
  Suggestive: Positive ANCA (~85% sensitivity)
  IFA: c-ANCA.
  ELISA: anti-proteinase 3 (PR3-ANCA)
  Diagnostic: Biopsy

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?

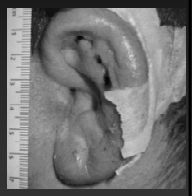
A. Malignant otitis externa
B. Leprosy
C. Granulomatosis with polyangiitis
D. Relapsing polychondritis
E. Congenital syphilis

Relapsing Polychondritis

--Immune-mediated condition.

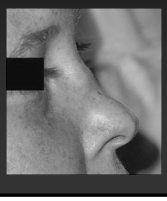
--Inflammation of cartilaginous structures, particularly ears, but also nose, eyes, joints, and airways.

--Clinical diagnosis.



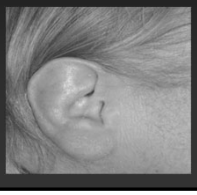
Saddle-nose Deformity

– 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



42 – Syndromes that Masquerade as Infections

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

43

Non-AIDS-Defining Complications of HIV/AIDS

Dr. Michael Saag

43 - Non-AIDS-Defining Complications of HIV/AIDS

Speaker: Michael Saag, MD

Non AIDS-Defining Complications of HIV/AIDS

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

7/1/2024

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

  - None

CASE 1

PREVIEW QUESTION

- 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

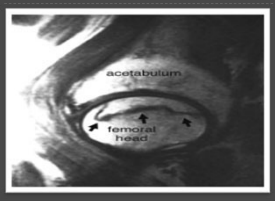
QUESTION #1

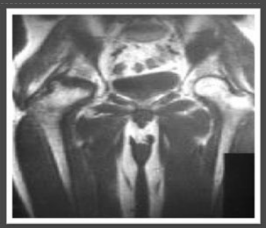
PREVIEW QUESTION

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

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

Osteonecrosis





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

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

Avascular necrosis in HIV

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

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

CASE 2

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

CASE 2: Exam

- VS: T 98.2 P 79 BP 112/73
- RR 16, O2 sat 97%
- Pertinent findings
- Neuro: CNII-XII intact, strength 1+ all extremities except 4+ hand/wrist and ankles.
- NI reflexes. Alert, oriented.

CASE 2: Labs

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

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

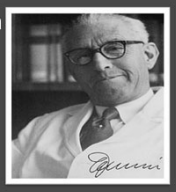
QUESTION #2

Which of the following is the most likely diagnosis?

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

Fanconi syndrome

- Type II RTA
- Generalized proximal tubule dysfunction
- Hypophosphotemia, renal glucosuria, hypouricemia, aminoaciduria
  - Not all have present at once
- Osteomalacia can occur
- Recovery is the rule; can take months



CASE 3

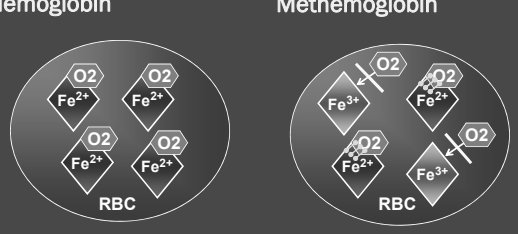
- 35 year old man presents with complaints of increasing fatigue, headache, SOB / DOE
- HIV diagnosed 4 mos ago with PCP; intolerant to TMP/SMX
- Now on TAF / FTC / BIC + PCP Prophylaxis with Dapsone
- Claims adherence to all meds;
  "Doesn't miss a dose!"
- Normal PE
- Pulse Ox 85%; CXR no abnormalities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

QUESTION #3

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

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

Hemoglobin and Methemoglobin



CASE 4:

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 #1:

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

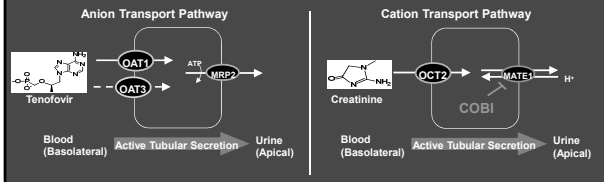
- Started on TAF/FTC+ Dolutegravir; No other medications
- Returns 4 weeks later, labs unchanged except creatinine now 1.3 mg/dl (eGFR 55)

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

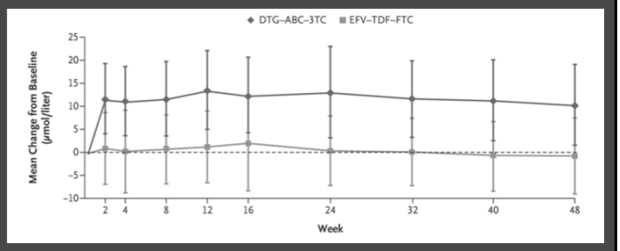
Tenofovir and COBI Interact with Distinct Renal Transport Pathways



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

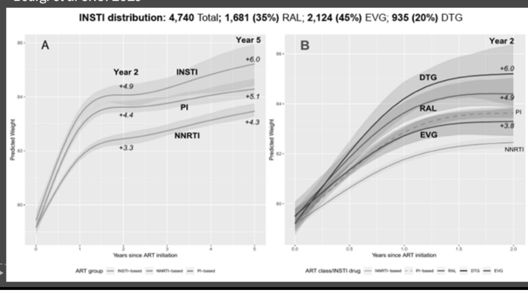
- 48 yo Male presents with newly diagnosed HIV infection
- Asymptomatic
- **Initial: HIV RNA 160,000 c/ml**
  CD4 count 221 cells/ul
- Other labs are normal; Started on ARV Rx with DTG + TAF/FTC
- Returns for a 3 month follow up visit
- **HIV RNA < 20 c/ml; CD4 390 cells/ul**

QUESTION # 9

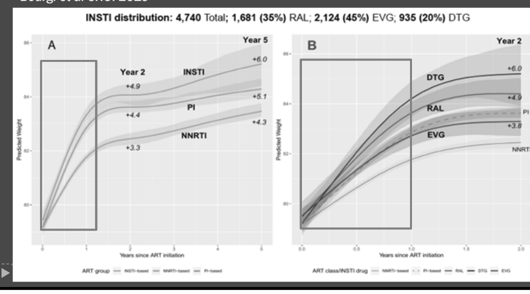
Which of the following will most likely be present on his 3 month visit from use of dolutegravir:

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

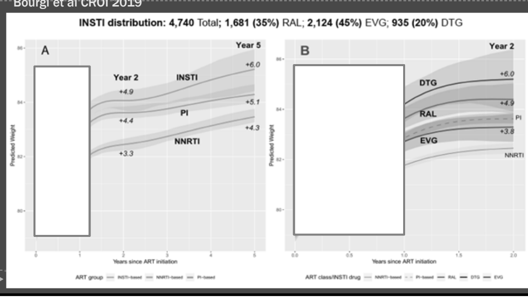
Change in Weight Overtime – NA-ACCORD
Bourgi et al CROI 2019



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

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

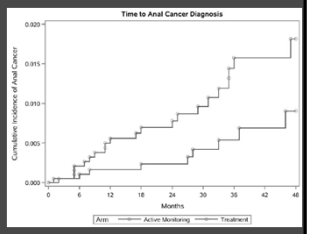
QUESTION # 11

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%

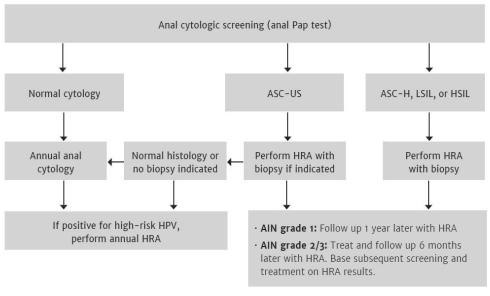
- **30 anal cancers diagnosed** in median f/u of 25.8 months
  - 9 in Treatment arm (173/100,000 PY)
  - 21 in Active Monitoring arm (402/100,000 PY)
- 8 study-related serious AEs:
  - 7 in treatment arm (3 pain, 3 abscess, 1 skin ulceration)
  - 1 in monitoring arm (infection)



Anal dysplasia

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

Figure 1. Follow-up of Anal Cytologic Screening Results



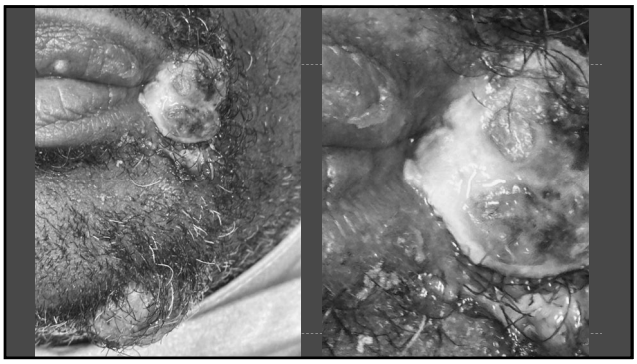
Recommendations: Screening

- ☑ 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)

7/31/2024 NYSDOH AIDS Institute Clinical Guidelines Program

CASE 12

- 30 yo Male presents with new lesions on his buttocks, groin, back, and face
- MSM; reports fever
- Denies sexual activity in the last 12 weeks
- HIV RNA 68,000 c/ml (off ARV now)
  CD4 count 250 cells/ul
- UDS + methamphetamine



QUESTION # 12

In addition to STI screening and Mpox culture, which of the following would you do?

A. Treat for molluscum contagiosum
B. Start tecovirimat at this visit
C. Wait for cultures, if positive for mpox, start tecovirimat
D. No specific mpox Rx; give JYNNEOS vaccine now instead
E. Administer Benzathine Penicillin

44

Encephalitis Including West Nile and Rabies

Dr. Allen Tunkel

44 – Encephalitis including West Nile and Rabies

Speaker: Allan Tunkel, MD

Encephalitis Including West Nile and Rabies

Allan R. Tunkel, MD, PhD, MACP
Professor of Medicine and Medical Science
The Warren Alpert Medical School of Brown University

7/1/2024

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

  - None

ENCEPHALITIS Definitions

- Encephalitis
  - Inflammation of brain parenchyma with neurologic dysfunction
  - Gold standard is pathologic examination and testing of brain tissue
  - Usually based on clinical, laboratory, and imaging
- Encephalopathy
  - Altered consciousness (confusion, disorientation, behavioral changes, cognitive impairment) ± inflammation
  - Usually metabolic or toxic conditions

ENCEPHALITIS Epidemiology

- ~5 cases/100,000 population annually in US from 1990-2017
- >1 million cases annually worldwide
  - Rabies
  - Measles
  - Japanese encephalitis virus

ENCEPHALITIS Etiology

- California Encephalitis Project (CEP) reviewed 1,570 cases over 7-year period (CID 2006;43:1565)
- Confirmed or probable etiology in 16%
  - 69% viral
  - 20% bacterial
  - 7% prion
  - 3% parasitic
  - 1% fungal
- Possible etiology in 13%

ENCEPHALITIS Etiology

- Australian Childhood Encephalitis Study (CID 2020;70:2517)
- 287 children with confirmed encephalitis
- 57% infectious (confirmed/probable)
- 25% immune-mediated
- 17% unknown

Reasons Etiology not Identified

- Undiscovered pathogens
- Uncommon presentation by common pathogens
- Common presentation by uncommon pathogens
- Wrong test
- Wrong sample
- Wrong timing
- Not an infection

General Approach

- Can't test for everything
- Epidemiologic and clinical clues
- General diagnostic studies
- Neuroimaging clues
- Consider noninfectious etiologies

Tunkel et al. Clin Infect Dis 2008;47:303
Venkatesan et al. Clin Infect Dis 2013;57:1114
Bloch et al. Clin Infect Dis 2023;doi.org/10.1093/cid/ciad306

CASE #1

PREVIEW QUESTION

- 50-year-old man presents with a several day history of fever, headache, and personality change with progression to confusion
- On exam, temperature is 101ºF; he is disoriented and unable to follow commands
- CT scan of the head without contrast is negative
- CSF analysis reveals a WBC of 80/mm^3 (95% lymphs), glucose 70 mg/dL (serum 100 mg/dL), protein 120 mg/dL; Gram stain is negative

CASE #1

PREVIEW QUESTION

- Acyclovir is initiated
- MRI with gadolinium reveals enhancement in the left temporal lobe
- Results of initial cerebrospinal fluid (CSF) polymerase chain reaction (PCR) for HSV-1 and HSV-2 return negative
- After 3 days, the patient is now oriented to name and follows simple commands

QUESTION #1

PREVIEW QUESTION

What is the next step in the management of this patient?

A. Perform a brain biopsy of the left temporal lobe
B. Obtain new CSF for HSV PCR testing
C. Send serum for HSV IgG antibodies
D. Repeat brain MRI
E. Discontinue acyclovir

CASE #1 (Continued)

- Repeat CSF analysis on day #4 reveals that the PCR is now positive for HSV-1
- The patient continues to improve and completes a 14-day course of acyclovir
- One month later, he presents again with fever and confusion
- CSF analysis reveals a WBC count of 30/mm^3 (all lymphocytes) with normal glucose and mildly elevated protein; CSF PCR tests for HSV-1 and HSV-2 are negative

QUESTION #2

Which of the following is the most likely reason for his second presentation of encephalitis?

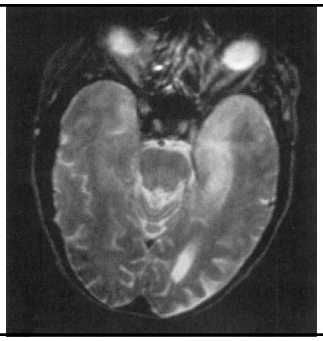
A. Relapse of herpes simplex encephalitis
B. Development of acyclovir-resistant herpes simplex encephalitis
C. Development of autoimmune encephalitis
D. Acyclovir neurotoxicity

Herpes Simplex Encephalitis

- Epidemiology
  - Among the most severe of all human viral infections of brain; >70% mortality with no or ineffective therapy
  - Accounts for 10-20% of encephalitis viral infections
  - Occurs throughout the year and in patients of all ages
  - Described following whole brain irradiation or following a neurosurgical procedure
  - Majority in adults caused by HSV-1
- Clinical features
  - Fever, personality change, dysphasia, autonomic dysfunction

Herpes Simplex Encephalitis

- Electroencephalography
  - Sensitivity of ~84%
  - Periodic lateralizing epileptiform discharges (PLEDs)
- Neuroimaging
  - Computed tomography (lesions in 50-75% of patients)
  - Magnetic resonance imaging (>90% of cases)
- Brain biopsy
  - Inflammation with widespread hemorrhagic necrosis
  - Intranuclear inclusions (50% of patients)
  - Reserve for patients not responding to acyclovir therapy



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Herpes Simplex Encephalitis

- Cerebrospinal fluid (CSF) findings
  - Lymphocytic pleocytosis (mean of 100 cells/mm^3)
  - Presence of red blood cells (25% never have RBCs)
  - Elevated protein
  - Normal in 5-10% of patients on first evaluation
- CSF Polymerase Chain Reaction
  - Sensitivity 98%
  - Specificity 94%
  - Positive predictive value 95%
  - Negative predictive value 98%
  - If negative, may need new CSF sample in 3-7 days

Herpes Simplex Encephalitis

- Acyclovir is the antiviral agent of choice
  - Mortality of 19% at 6 months
  - Mortality of 28% at 18 months
  - Morbidity ~50%
- Dosage in adults is 30 mg/kg/day in 3 divided dosages (in those with normal renal function) for 14-21 days
- No added benefit on oral valacyclovir (3-month course) after standard course of acyclovir

Other Herpesviruses

- Varicella-zoster virus
  - Can occur without rash (zoster sine herpete)
  - Focal neurologic deficits and seizures
  - CSF PCR; lower sensitivity in those with vasculopathy so also check CSF antibodies
  - MRI/MRA large vessel vasculitis and ischemia
  - Acyclovir (however, no controlled studies) + ?corticosteroids (if vasculopathy)
- Epstein-Barr virus
  - Encephalitis and/or transverse myelitis
  - Serologic testing; CSF PCR (may have false-positives)

Other Herpesviruses

- Human herpesvirus 6
  - Immunocompromised patients, but seen in children
  - CSF PCR (sensitivity >95%); high rate of detection in healthy adults (PPV only 30%)
  - Ganciclovir or foscarnet
- Cytomegalovirus
  - Immunocompromised (especially HIV)
  - Evidence of widespread disease
  - CSF PCR (sensitivity 82-100%; specificity 86-100%)
  - MRI may reveal subependymal gadolinium enhancement and non-specific white matter changes
  - Ganciclovir + foscarnet

CASE #2

- 72-year-old man presents in late August with complaints of fever, chills, and weakness beginning 1 week earlier; on the day of admission, he becomes confused
- He lives in central New Jersey, where he and his wife have a horse farm; they often noted mosquito and tick bites
- On presentation, he is somnolent and unable to provide a complete history, although denies headache and stiff neck

CASE #2

- T 103.1ºF, P 110, RR 16, BP 110/70 mmHg
- No rash or petechiae, neck supple, no adenopathy, lungs clear, heart without murmurs, abdomen normal
- On neurologic exam, he is oriented to person only. Cranial nerves intact. Motor strength 4/5 UE, and 3/5 LLE and 2/5 RLE. Sensation intact. Reflexes diminished in LE

QUESTION #2

Which of the following tests is most likely to establish the etiology of this patient's encephalitis?

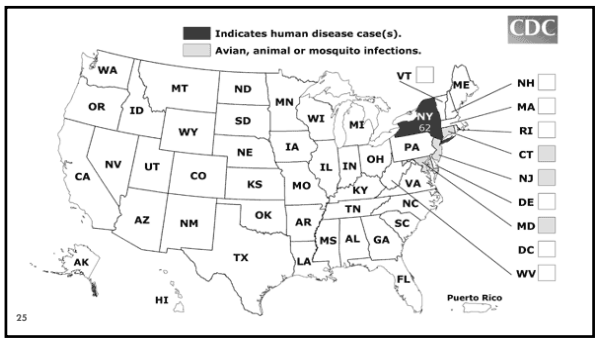
A. Serum IgM
B. Serum polymerase chain reaction
C. Cerebrospinal fluid IgM
D. Cerebrospinal fluid polymerase chain reaction
E. Brain MRI

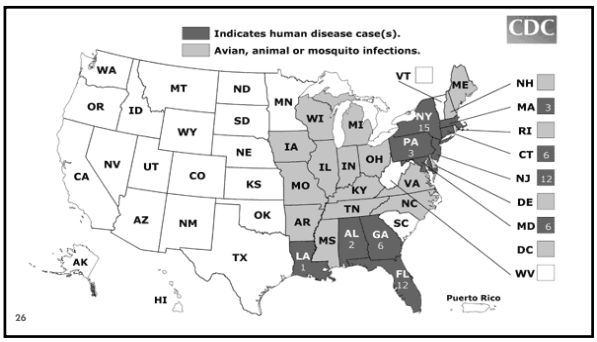
West Nile Virus (WNV) Encephalitis

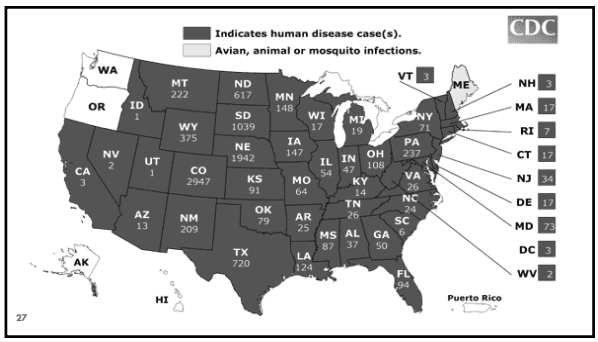
- First US cases reported in 1999 in New York City
- Birds are main reservoirs
- Mosquito vector
- Other modes of transmission
  - Transplanted organs
  - Blood transfusions
  - Breast milk
  - Transplacental
  - Occupational

44 – Encephalitis including West Nile and Rabies

Speaker: Allan Tunkel, MD







WNV Human Cases Reported To CDC

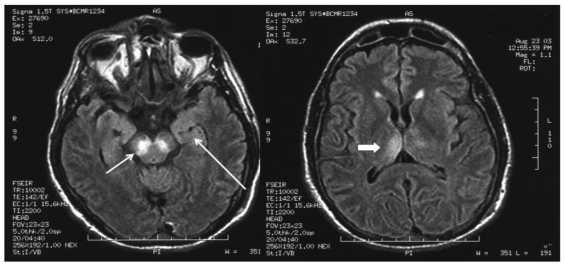
Year	Total Human Cases	Neuroinvasive	Deaths
2007	3630	1227	124
2009	720	386	32
2011	712	486	43
2012	5674	2873	286
2014	2122	1283	85
2018	2544	1594	137
2019	971	633	60
2021	2911	2008	227
2023 (through 1/9/2024)	2406	1599	

West Nile Virus Clinical Syndromes

- No clinical illness or symptoms (~80%)
- West Nile Fever (~20%)
- Severe WNV Disease (1 in 150)
  - Meningitis (37%)
  - Encephalitis/Meningoencephalitis (53%)
  - Poliomyelitis-like flaccid paralysis (7%)

West Nile Virus Encephalitis

- Diagnosis
  - Serum IgM antibody (8-14 days of illness onset)
  - CSF reveals lymphocytic pleocytosis and elevated protein; glucose is normal
  - CSF IgM (positive in >90%)
  - CSF PCR (<60% sensitivity)
  - Neuroimaging



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West Nile Virus Encephalitis

32

- Therapy
  - Supportive
  - Ribavirin, interferon alpha, and IVIG don't work

Other Arboviruses

33

- St. Louis encephalitis virus
  - Mosquito vector; bird reservoir
  - Endemic in western US; periodic outbreaks in eastern US
  - Urinary symptoms early; SIADH (one-third of cases)
  - Serology; CSF IgM
- Japanese encephalitis virus
  - Most common cause of mosquito-borne encephalitis worldwide (SE Asia, China, India, Nepal, Korea, Japan)
  - Mainly children; rice fields where vectors breed
  - Seizures and parkinsonian features; poliomyelitis-like flaccid paralysis
  - Serology; CSF IgM

Other Arboviruses

34

- Powassan virus
  - Tick vector (Ixodes scapularis in NE); rodent reservoir; New England
  - Prevalence among animal hosts and vectors increasing
  - Parkinsonism, involvement of basal ganglia and thalamus common
  - Serology; CSF IgM; metagenomic sequencing
- Tickborne encephalitis virus
  - Tick vector, rodent reservoir; drinking unpasteurized milk or cheese; solid organ transplantation; rituximab
  - Eastern Russia, central Europe
  - Poliomyelitis-like paralysis
  - Serology; CSF IgM
  - Anti-TBE immune globulin for post-exposure prophylaxis

Other Arboviruses

35

- La Crosse virus
  - Mosquito vector; chipmunk and squirrel reservoir
  - Midwest and eastern US; woodlands
  - 2nd most common arbovirus in US
  - Serology; CSF IgM; SIADH (~20%)
- Eastern equine encephalitis virus
  - Mosquito vector; bird reservoir in North America; organ transplantation
  - Primarily Atlantic and Gulf coast states
  - Abrupt onset with fulminant course; seizures common
  - High case-fatality rate (50-70%)
  - Serologic testing
  - High CSF WBC count (>1000 cells/mm^3)

Measles Virus

36

- Acute disseminated encephalomyelitis
  - Usually 1-2 weeks after exposure; incidence 1 per 1,000 infections
  - Fever, fatigue, headache, nausea, vomiting
- Inclusion body encephalitis
  - Unvaccinated children and adults; immunocompromised
  - Symptoms 1-6 months after exposure; decreased consciousness, focal signs, seizures
- Subacute sclerosing panencephalitis
  - 6-10 years after infection (range 3-35 years)
  - Behavioral changes, cognitive impairment at presentation
  - Myoclonus, seizures, neurologic deterioration (coma and death) later

BioFire FilmArray

37

Bacteria	Viruses	Fungi
Escherichia coli K1	Cytomegalovirus	*Cryptococcus neoformans/gatti*
Haemophilus influenzae	Enterovirus	
Listeria monocytogenes	Herpes simplex virus 1	
Neisseria meningitidis	Herpes simplex virus 2	
Streptococcus agalactiae	Human herpesvirus 6	
Streptococcus pneumoniae	Human parechovirus	
	Varicella zoster virus	

Metagenomic Next-Generation Sequencing

- Consider for encephalitis cases in which no cause identified
- Allows unbiased or agnostic pan-species molecular diagnostics
- In one study of 204 patients (58 with meningitis or encephalitis), NGS identified an infectious cause in 22% not identified by clinical testing (Wilson et al. NEJM 2019;380:2327).
- Possible role in testing of enigmatic cases

CASE #3

39

- 36-year-old man is on a hiking trip in northern California and is bitten on his lower leg by a skunk
- Upon presentation, he is afebrile and has several puncture wounds on his right lower extremity
- You irrigate with wounds with soap and povidone iodine, and administer a tetanus booster
- He has never been vaccinated against rabies

QUESTION #3

40

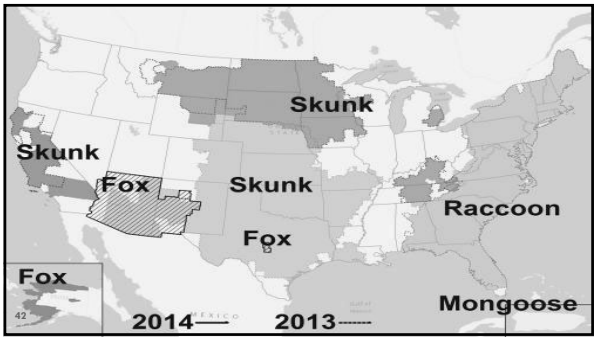
In addition to administration of rabies vaccine, what is the most appropriate management?

A. Rabies immune globulin at the bite sites
B. Rabies immune globulin in the deltoid muscle
C. Rabies immune globulin in the buttocks
D. Rabies immune globulin intraperitoneally
E. Nothing further is indicated

Rabies

41

- Transmitted by bite of infected animal
  - Dogs are principal vector (98% of cases) worldwide
  - May be transmitted after unrecognized bites by bats
- Rare and sporadic in US – 125 cases from 1960-2018
  - 36 (28%) attributed to dog bite during international travel
  - 89 acquired in US; 62 (70%) attributed to bats
- Worldwide in distribution (50,000-100,000 annual deaths)
- Incubation period 20-90 days



44 – Encephalitis including West Nile and Rabies

Speaker: Allan Tunkel, MD

Rabies

43

- Encephalitic (furious) form (80%)
  - Agitation alternating with lucidity
  - Hypersalivation
  - Hydrophobia
  - Bizarre behavior
  - Disorientation, stupor, coma, death
- Paralytic (dumb) form
  - Ascending paralysis; early muscle weakness
  - Later cerebral involvement

Rabies

44

- Diagnosis
  - Culture and RT-PCR of saliva
  - Immunofluorescent detection of viral antigens and RT-PCR in nuchal biopsy
  - CSF antibodies and RT-PCR
  - Brain biopsy (antigen detection/Negri bodies)
- Therapy
  - Supportive
  - Milwaukee Protocol has failed in 26 cases
  - Post-exposure prophylaxis (rabies immune globulin at bite site and vaccine)

CASE #4

45

- 22-year-old woman with no significant past medical or psychiatric history develops headache and low-grade fever followed by confusion and hallucinations
- On presentation, she is afebrile and disoriented; she has evidence of abnormal movements of her mouth and face
- CSF analysis reveals a WBC count of 20/mm^3, with normal glucose and protein
- Brain MRI is normal

CASE #4

46

- EEG reveals diffuse slowing
- CSF Gram stain and cultures, and PCR for HSV are negative
- A diagnosis of autoimmune encephalitis is considered, and appropriate studies sent
- CSF returns positive for antibodies to the NR1 subunit of the N-methyl-D-aspartate receptor
- Corticosteroids and IV immune globulin are initiated

QUESTION #4

47

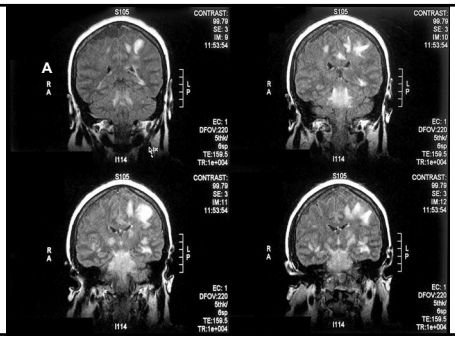
Which of the following studies should now be performed?

A. CT scan of the chest
B. CT scan of the abdomen
C. Carotid ultrasound
D. Renal ultrasound
E. Transvaginal ultrasound

ENCEPHALITIS
Noninfectious Etiologies

48

- Acute disseminated encephalomyelitis (ADEM)
  - 10-15% of encephalitis cases in US
  - Post-infectious
  - Symptoms 2-4 weeks after trigger
  - MRI bilateral asymmetric T2 hyperintensity in subcortical and deep white matter
  - Corticosteroids
- Anti-N-methyl-D-aspartate receptor (Anti-NMDAR) encephalitis



Anti-NMDAR Encephalitis

- Neuronal antibody-associated encephalitis
- In California Encephalitis Project, this entity exceeded that of any single viral entity in children and was also seen in adults
- Female to male ratio of about 8:2
- 37% of patients younger than 18 years at presentation

Anti-NMDAR Encephalitis

- Abnormal behavior (psychiatric symptoms)
- Cognitive dysfunction
- Seizures
- Movement disorders (orofacial dyskinesias)
- Decreased level of consciousness
- Autonomic instability
- May be associated with ovarian teratoma (in ~50% of patients older than 18 years)

Anti-NMDAR Encephalitis

- CSF analysis
  - Mild pleocytosis (median WBC 23/mm^3); normal glucose and protein
  - Specific IgG antibodies to GluN1 subunit of the NMDAR in CSF and serum
  - Viral causes of encephalitis (e.g., HSV) are associated with development of NMDAR antibodies

Anti-NMDAR Encephalitis

- Neuroimaging
  - Abnormal in 50%, but nonspecific
  - T2 and FLAIR hyperintensity (hippocampi, cerebellar or cerebral cortex, frontobasal and insular regions, basal ganglia, brainstem)
- EEG
  - Diffuse or focal slowing
  - Occasional superimposed epileptic activity

Anti-NMDAR Encephalitis

- Therapy
  - First-line
    - Corticosteroids
    - Intravenous immunoglobulin
    - Plasma exchange
  - Second-line
    - Rituximab or cyclophosphamide
  - Female patients should be evaluated for ovarian teratoma; if present, remove
- 75% of patients have mild sequelae or fully recover; relapse in up to 24%

44 – Encephalitis including West Nile and Rabies

Speaker: Allan Tunkel, MD

45

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

Dr. Rajesh Gandhi

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

Speaker: Rajesh Gandhi, MD

IDBR INFECTIOUS DISEASE BOARD REVIEW AUGUST 17-21, 2024

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

Rajesh T. Gandhi, MD
Massachusetts General Hospital
Professor of Medicine, Harvard Medical School

7/1/2024

IDBR INFECTIOUS DISEASE BOARD REVIEW AUGUST 17-21, 2024

Disclosures of Financial Relationships with Relevant Commercial Interests

- **None**

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

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

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

Case 1

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

SH: Three months before, she travelled to Ecuador, where she stayed in an ecotourism hotel near a river. No known fresh- or salt-water exposure. Reported seeing several kinds of insects and receiving several bites. No known animal exposures or tick bites.

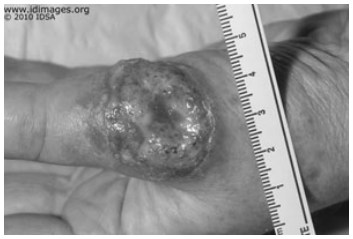
Contributed by Rojelio Mejia, MD

Differential Diagnosis

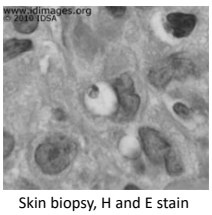
PE: Patient appeared well. T 98.1.

Raised ulcerated lesion on thumb with a violaceous border

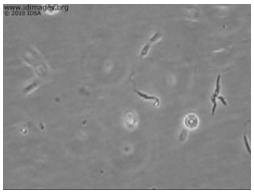
A. Cutaneous leishmaniasis
B. *Mycobacterium marinum*
C. Sporotrichosis
D. Pyoderma gangrenosum
E. Tularemia



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



Skin biopsy, H and E stain

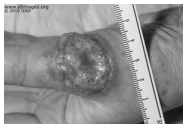


Culture of skin biopsy tissue in Schneider's medium

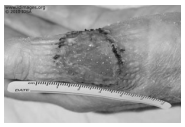
45 – Photo Opportunity I: Photos and Questions to Test Your Board Preparation

Speaker: Rajesh Gandhi, MD

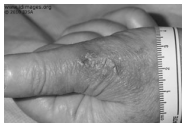
Treated with liposomal amphotericin



One week after treatment



Follow-up at 3 months



Differential Diagnosis

- ***Mycobacterium marinum*:** patient did not have known fresh- or salt-water exposure; she did not have nodular lymphangitis
- **Sporotrichosis:** no known exposures to soil or thorn; she did not have nodular lymphangitis
- **Pyoderma gangrenosum:** patient did not have known inflammatory bowel disease or other underlying pre-disposing condition; ulcerative PG usually occurs on lower extremities, trunk
- **Tularemia:** no animal or tick exposure; no systemic symptoms; no adenopathy

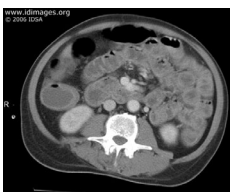
Case 2

- A man in his fifties presented with diarrhea, nausea, and vomiting of three days' duration.
- He had recently been discharged from another hospital where he had received a one-week course of iv steroids for back pain.
- **Past medical history:** spinal stenosis. Medication: prednisone
- **Social history:** Immigrated to the US from the Caribbean two decades ago; returned to visit one year ago.
- **PE:** Temp 98.6. Mild epigastric tenderness. Remainder of exam normal

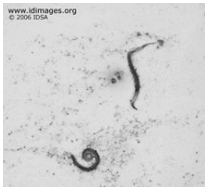
Case 2 (continued)

- **Past medical history:** WBC 12,000 (neutrophils 43%, bands 38%, lymphocytes 10%). Creatinine 1.8
- Clinical course:
- Patient received iv fluids because of concern for acute gastroenteritis and dehydration.
- On hospital day 3, developed lethargy and fever (temp 102.4).
- Shortly thereafter, developed respiratory failure and Klebsiella was isolated from blood cultures (4/4 bottles) and cerebrospinal fluid

Abdominal CT:
colonic wall inflammation



Gram stain of sputum

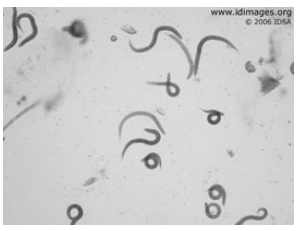


A. Salmonella bacteremia
B. Strongyloides hyperinfection syndrome
C. Amebic infection
D. Ascariasis
E. Fascioliasis

Strongyloides hyperinfection syndrome

- May occur during immunosuppression, even short courses of steroids
- Accelerated autoinfection
- Larval migration in GI tract, lungs, skin and, at times, other organs
- Migration of filariform larva may be associated with entry of enteric bacteria (eg, gram-negative sepsis, meningitis)
- Peripheral eosinophilia absent

Iodine stain of stool showed Strongyloides

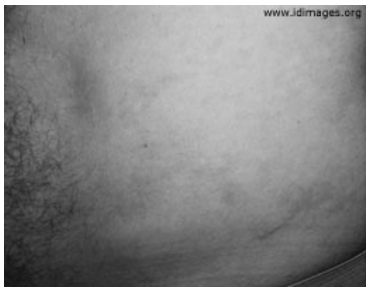


45 – Photo Opportunity I: Photos and Questions to Test Your Board Preparation

Speaker: Rajesh Gandhi, MD

Larva currens: Cutaneous Strongyloidiasis

- Serpiginous urticarial rash caused by the dermal migration of filariform larvae
- Rash may move rapidly: 5-10 cm per hour



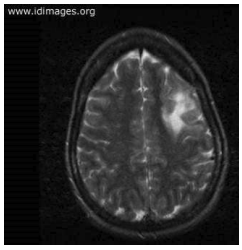
Case 3

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

Contributed by Wendy Yeh, M.D.

The most likely diagnosis is:

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

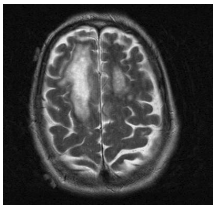


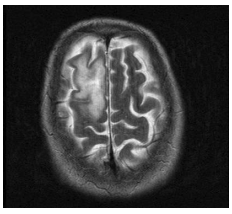
MRI: Abnormal T2 signal involving white matter, left fronto-parietal region. No enhancement, edema, mass effect

Progressive multifocal leukoencephalopathy

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

PML





Contributed by Vince Marconi, M.D.

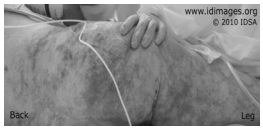
Differential diagnosis

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

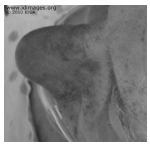
Case 4

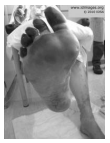
60 yo M was well until day of admission when he developed lethargy and confusion. Over the course of the day, his hands and feet grew cold and numb and he developed a rash.

SH: He lives in a rural area (mountain-lion territory) and drinks well-water. He has a history of alcohol use disorder. He rides horses and has dogs, one of whom bit him a few days before.



PE: T 102. Nonblanching, nonpalpable, purpuric patches on head, trunk, thighs; puncture wounds on dorsal aspect of hand; edema, cyanosis of nose.





A. *E. coli* 0157:H7
B. *Yersinia pestis*
C. *Pasteurella*
D. *Capnocytophaga*
E. Leptospirosis

Capnocytophaga canimorsus

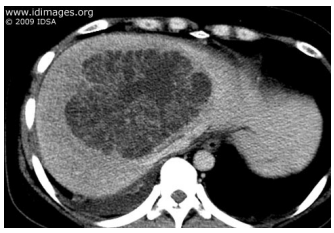
- Blood cultures positive for *C. canimorsus*
- Facultative, fastidious gram-negative bacillus found in the mouth of dogs, cats.
- Risk factors: male sex, dog-bite, alcohol abuse, asplenia, immunosuppression
- Septicemia: 20-40% have a rash (maculopapular, progressing to purpura fulminans)

Differential diagnosis

- ***E. coli* 0157:H7:** abdominal cramping, diarrhea; fever typically absent
- ***Yersinia pestis:*** usually presents as bubonic plague, with regional lymphadenitis
- ***Pasteurella**:* may follow cat or dog bit; usually presents with cellulitis; septicemia uncommon
- **Leptospirosis:** contact with urine or tissue of infected animals; in acute phase, pt may have conjunctival suffusion; purpura fulminans, as in this case, would be unusual

Case 5

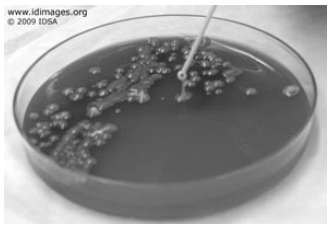
- A woman from China in her 40s developed fever, epigastric pain, and nausea. One week later, she was brought to ED with confusion and fever.
- T 101°F. Right upper quadrant abdominal tenderness
- Abdomen CT: 10 cm hypoattenuated liver lesion



What is the diagnosis?

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

Culture from liver aspirate



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

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

Speaker: Rajesh Gandhi, MD

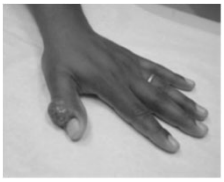
Klebsiella liver abscess

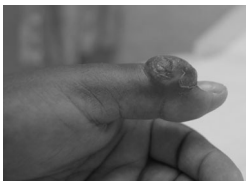
- Hypermucoid strain of Klebsiella pneumoniae associated with a distinctive clinical syndrome in Southeast Asia that includes primary liver abscess, bacteremia, and metastatic infection
- Risk factors: diabetes and Asian ancestry
- Colonies exhibit extreme "stickiness" on agar plates ("hypermucoviscosity phenotype")
  - Positive String test: "string" of > 5 mm when loop used to stretch a colony on an agar plate

Case 6

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

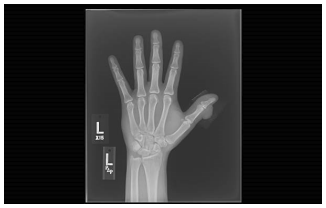
Afebrile. 2 x 2 x 2 cm firm lesion on his thumb, without discoloration, purulent discharge, fluctuance, or bleeding





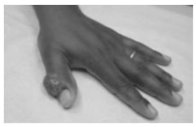
Creatinine and LFTs normal. Glucose 158. WBC 4.2 (normal differential).

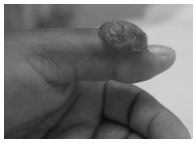
X-ray: fungating soft tissue lesion on dorsal aspect of distal thumb; no underlying bone or joint abnormality



What is the diagnosis?

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

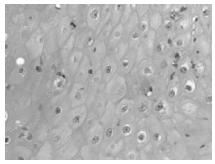




Contributors: Drs. Isaac Bogoch, Rajesh Gandhi

Follow-up

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



Appearance consistent with ecythma contagiousum

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

Speaker: Rajesh Gandhi, MD

Orf (contagious ecthyma)

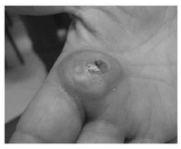
- Zoonotic infection caused by a dermatropic parapox virus (ds DNA) of goats and sheep
- Transmitted by contact with infected animal or fomites
  - Animal handlers; children after visiting petting zoos, livestock fairs
  - Clusters reported after Eid, other festivities involving lamb sacrifice (Passover,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

Orf (continued)

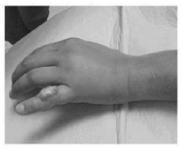
- 3-7 d incubation period.
- Macule or papule → nodule with red center, white halo and peripheral erythema → ulcerative lesion → regenerative papilloma.
- Most resolve in 4-8 wk
- Human-to-human transmission has not been reported
- Protective immunity incomplete; persons can be infected multiple times

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

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



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

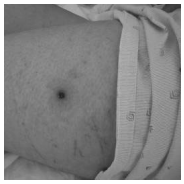


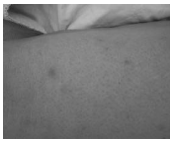
Case 7

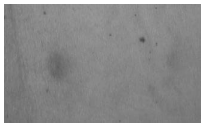
- 50 yo F was well until 7 days prior to admission when she noted "bite" on left thigh. Lesion enlarged over several days. Four days prior to admission, developed fatigue, arthralgias, myalgias, fever, headache. On admission (July), developed generalized rash on extremities, trunk, back.
- **SH:** Lived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

Does this patient most likely have:

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







Rickettsialpox

- Caused by *Rickettsia akari*, member of spotted fever group of rickettsiae.
- Transmitted to humans by mouse mite
- NYC outbreak in1980s; high seroprevalence (16%) in IDUs in Baltimore
- After bite of infected mite, *R. akari* proliferates resulting in papule, ulcerates to form eschar
- 3-7 days later, high fever, chills and headache.
- 2-3 days after onset of fever, generalized papulovesicular rash (not involving palms, soles)
- Diagnosis: serologic testing. Treatment: doxycycline

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

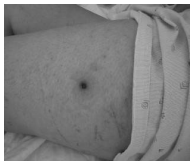
Speaker: Rajesh Gandhi, MD

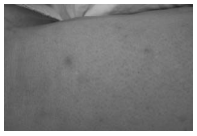
Rickettsialpox vs. Chickenpox

	Rickettsialpox	Chickenpox
Eschar	Yes	No
Lesions in crops	No	Yes
Number of lesions	Relatively sparse (20-40)	Many
Mature lesion	Papulovesicle	Vesicle

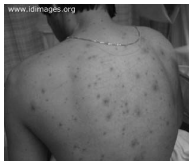
Case contributed by Karen Thomas, M.D. and Leena Gandhi, M.D.

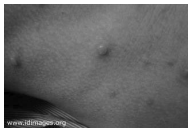
Rickettsialpox





Chickenpox





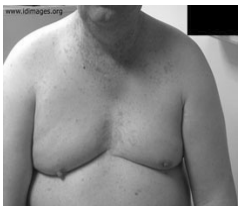
Case 8

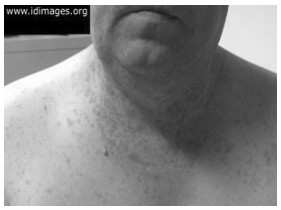
- Man in his 40s was well until 5 days before presentation when, in mid-spring, he developed headache. Two days later, he developed non-productive cough, throat discomfort and his eyes became watery and red.
- On 5th day of illness, while traveling to New England from Midwest, he developed a rash on face, upper arms & chest.
- Lived in Midwest with wife, teenagers, dog. Monogamous. Denied illicit drug use. Travels throughout US for work.

Contributed by Drs. Jessica Haberer, Justin Chan, Rochelle Walensky

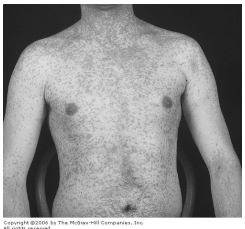
T 101. Diffuse erythematous, blanching maculopapular rash on face, trunk and arms. Conjunctival injection. Exam otherwise normal.

WBC 3.3. Platelets normal.



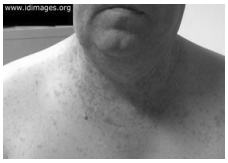


Rash in a different patient with the same infection



Differential Diagnosis

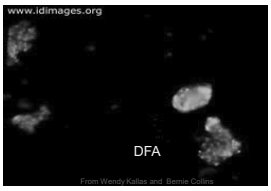
A. Syphilis
B. Scarlet fever
C. Parvovirus infection
D. Measles
E. Rocky mountain spotted fever



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

Speaker: Rajesh Gandhi, MD

- Placed on airborne precautions
- Testing for influenza negative
- Nasal specimen positive for measles virus by direct fluorescent antibody (DFA)
- Measles IgM and IgG antibodies positive



Person in airport he was in had been diagnosed with measles of same genotype (imported case)

Measles

- Acute febrile rash illness
- Airborne virus, contagious from several days before to several days after appearance of rash.
- Incubation period: 10-14 d from exposure to rash
- Prodromal sx: fever, cough, coryza, conjunctivitis
- Koplik spots may appear toward end of prodromal symptoms, just before rash
- Rash typically begins on face; then spreads down body to involve trunk and then extremities. Lasts 5-6 days.

Case 9

Previously healthy man in his seventies presented with 2 weeks of fever, headaches, myalgias and 5 days of nonproductive cough, dyspnea, and fevers

Epidemiologic history

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

Case (cont.)

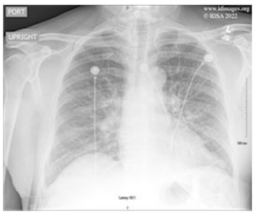
Physical Examination

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

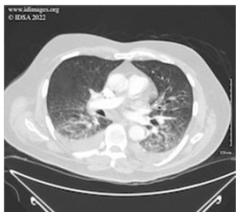
Studies

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

Studies



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



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

Clinical Course Prior to Diagnosis

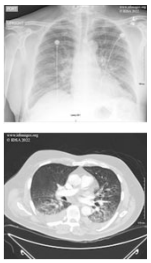
- Patient was admitted with diagnosis of community-acquired pneumonia.
- He was started on azithromycin and ceftriaxone.
- He was initially requiring minimal supplemental oxygen, however, his respiratory status worsened requiring high flow nasal canula at 20 L with fractional inspired oxygen of 80% saturation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

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

Speaker: Rajesh Gandhi, MD

What is the diagnosis?

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



Follow-up

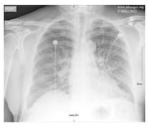
- Hantavirus IgG and IgM serologies were positive.
- Patient improved and his symptoms resolved.

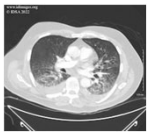
Hantavirus cardiopulmonary syndrome (HCPS): Clues

- Most cases are in southwestern US; first recognized in Four Corners region
- Transmitted by rodent reservoir, often in rural settings
- Febrile illness, bilateral interstitial infiltrates, and respiratory compromise requiring oxygen within 72 hours of hospitalization.
- Cardiopulmonary phase characterized by capillary leak, hemoconcentration (elevated hemoglobin/hematocrit), shock, pulmonary edema
- Diagnostic test: serologic assays

Final Diagnosis

•Hantavirus Cardiopulmonary Syndrome (HCPS)





Contributed by Dr. Dave Patel

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

46

Antiretroviral Therapy for Special Populations

Dr. Roy Gulick

46 – What Could Be on the Exam About COVID

Speaker: Roy Gulick, MD

What Could Be on the Exam About COVID

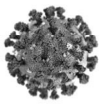
Roy Gulick, MD, MPH
Rochelle Belfer Professor in Medicine
Chief, Division of Infectious Diseases
Weill Cornell Medicine

7/1/2024

Disclosures of Financial Relationships with Relevant Commercial Interests

- **None**

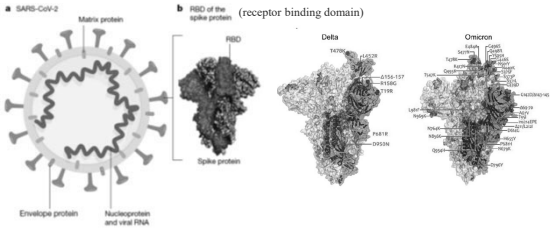
Outline – COVID-19



- Virology
- Clinical
- Treatment
- Prevention

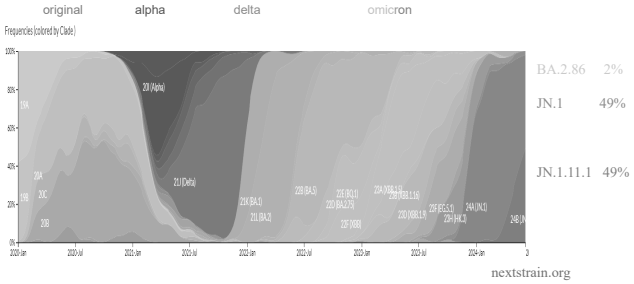
Virology

COVID-19 Structure



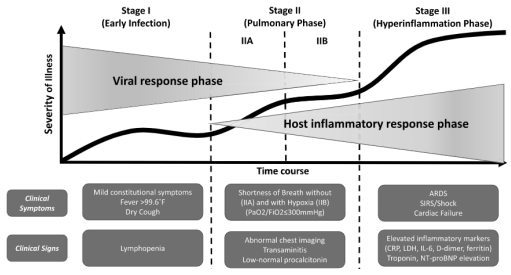
Krammer Nature 2020;586:516-527
Annavajhala Nature 2021;597:703-708

SARS-CoV-2 Variants: Global (1/20→6/24)



Clinical

COVID-19: Clinical Course



Marks and Gulick, Ann Intern Med 2023;176:ITC145-ITC160

What's the strongest risk factor for progression of COVID-19 to severe disease?

1. Older age
2. Diabetes, heart disease, or other comorbidities
3. Race/ethnicity
4. Vaccine status
5. Being infected with an omicron variant

What's the strongest risk factor for progression of COVID-19 to severe disease?

1. Older age
2. Diabetes, heart disease, or other comorbidities
3. Race/ethnicity
4. Vaccine status
5. Being infected with an omicron variant

U.S. CDC: Risk for Severe COVID-19

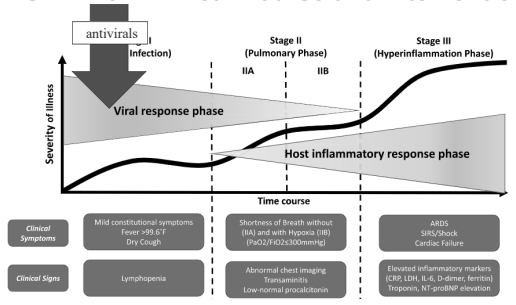
- **Older age** remains the strongest risk factor
  - Compared with age 18-29, risk of death (vaccinated/unvaccinated individuals in 2020-2022) is:
    - 25X ↑ for age 50-64
    - 60X ↑ for age 65-74
    - 140X ↑ for age 75-84
    - 340X ↑ for age >85
- **Comorbidities** 1.3-2.9X ↑
- **Racial/ethnic minorities**, compared to Non-Hispanic Whites, have ↑ SARS-CoV-2 infections, hospitalizations, ICU admissions, death
- **Unvaccinated or not up-to-date with vaccines** www.cdc.gov (4/15/24)
- Risk ↓ with omicron variants

Treatment

46 – What Could Be on the Exam About COVID

Speaker: Roy Gulick, MD

COVID-19: Clinical Course and Interventions



Marks and Gulick, Ann Intern Med 2023;176:ITC145-ITC160

NIH COVID-19 Treatment Guidelines – Outpatients (2/29/24)

All Patients

- Symptom management should be initiated for all patients (AIII).
- The Panel **recommends against** the use of **dexamethasone**[g] or other systemic corticosteroids (**AIIb**), unless these agents are being used to treat an underlying condition (**AIII**).

Patients Who Are at High Risk of Progressing to Severe COVID-19[b,c,d]

Preferred therapies. Listed in order of preference:

- **Ritonavir-boosted nirmatrelvir (Paxlovid)**[e] (**AIIa**). Start as soon as possible and within 5 days of symptom onset. See footnote on drug-drug interactions.[f]
- **Remdesivir**[e,g] (**BIIa**). Start as soon as possible and within 7 days of symptom onset.

Alternative therapy. For use when the preferred therapies are not available, feasible to use, or clinically appropriate:[h]

- **Molnupiravir**[e,i] (**CIIa**). Start as soon as possible and within 5 days of symptom onset.

https://www.covid19treatmentguidelines.nih.gov/

Nirmatrelvir/ritonavir: Drug Drug Interactions

- Ritonavir inhibits CYP3A during rx (5 days) and 2-3 days after rx
  - Some medicines should not be coadministered: e.g. rivaroxaban, amiodarone, rifampin, tadalafil (for pulmonary hypertension)
  - Others may need to be dose-reduced or temporarily stopped: e.g., atorvastatin, rosuvastatin

- Useful resources:
  - **NIH** COVID-19 Treatment Guidelines
  - **IDSA** Management of Drug Interactions: Resource for Clinicians
  - **University of Liverpool** COVID-19 Drug Interaction Checker

https://www.covid19treatmentguidelines.nih.gov/
https://www.idsociety.org/practice-guideline/covid-19-guideline-treatment-and-management/management-of-drug-interactions-with-nirmatrelvirritonavir-paxlovid/
https://www.covid19-druginteractions.org/

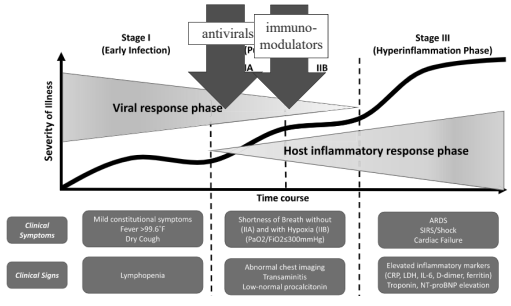
What's the treatment of choice for COVID-19 with hypoxia?

1. Nirmatrelvir-ritonavir
2. Remdesivir
3. Dexamethasone
4. 1 and 2
5. 2 and 3

What's the treatment of choice for COVID-19 with hypoxia?

1. Nirmatrelvir-ritonavir
2. Remdesivir
3. Dexamethasone
4. 1 and 2
5. 2 and 3

COVID-19: Clinical Course and Interventions



Marks and Gulick, Ann Intern Med 2023;176:ITC145-ITC160

46 – What Could Be on the Exam About COVID

Speaker: Roy Gulick, MD

NIH COVID-19 Treatment Guidelines – Inpatients (2/29/24)

Hospitalized and Requires Conventional Oxygen

Clinical Scenario	Antiviral or Immunomodulator Therapy Recommendation
Patients who require minimal conventional oxygen	**Remdesivir**[a,f] (BIIa)
Most patients	Use **dexamethasone plus remdesivir**[f] (BIIa). If remdesivir cannot be obtained, use **dexamethasone (BI)**.
Patients who are receiving dexamethasone and who have rapidly increasing oxygen needs and systemic inflammation	Add 1 of the following immunomodulators:[g] *Preferred* • **PO baricitinib (BIIa)** • **IV tocilizumab (BIIa)** *Alternatives (Listed in Alphabetical Order)* • **IV abatacept (CIIa)** • **IV infliximab (CIIa)**

https://www.covid19treatmentguidelines.nih.gov/

NIH COVID-19 Treatment Guidelines – Inpatients (2/29/24)

Hospitalized and Requires MV or ECMO

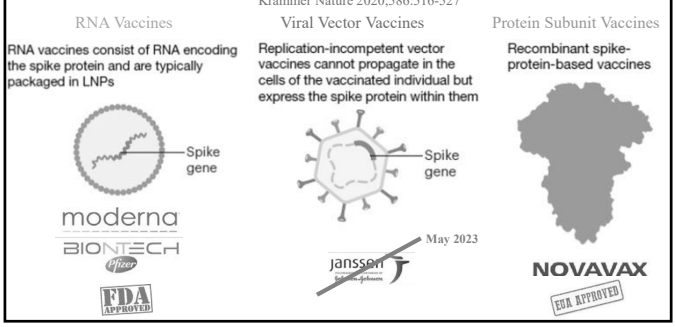
Clinical Scenario	Antiviral or Immunomodulator Therapy Recommendation
All patients	**Dexamethasone** should be administered to all patients (**AI**). If not already initiated, promptly add 1 of the following immunomodulators:[g] *Preferred* • **PO baricitinib (AI)** *Preferred Alternative* • **IV tocilizumab (BIIa)** *Additional Alternatives (Listed in Alphabetical Order)* • **IV abatacept (CIIa)** • **IV infliximab (CIIa)** Add remdesivir to 1 of the options above in certain patients (for examples, see footnote).[f]

https://www.covid19treatmentguidelines.nih.gov/

Prevention

COVID-19 Vaccines

Krammer Nature 2020;586:516-527



COVID-19 Vaccines

Billions of vaccine doses given globally

Benefits of vaccination outweigh risks; serious adverse events are rare

Side Effects

- **Most common:** fever, HA, fatigue, myalgias, pain at injection site X 1-2 days
- **Myocarditis / pericarditis:** rare (~1/5000-1/100,000)
  - more common in men: late teens-early 20s
  - mild; most recover fully
- **Anaphylaxis:** rare (1/200,000)
  - related to PEG/polysorbate(?)
  - more common in women, 80-86% had history of allergies, 24% had history of anaphylaxis
  - most within 15 minutes (one outlier at 20 hours)

www.CDC.gov 9/12/23

- **Uptake remains suboptimal** (2023-4 vaccine: 23% of US adults; 42% >65 yo as of 5/24)

COVID-19: 5 Questions They Could Ask

1. What leads to SARS-CoV-2 variants?	MUTATIONS IN THE SPIKE PROTEIN
2. What are important risk factors for COVID-19 progression?	↑AGE and IMMUNOSUPPRESSION
3. What characterizes severe COVID-19?	HYPOXIA
4. Who should receive outpatient treatment for COVID-19?	PEOPLE WITH RISK FACTORS FOR SEVERE DISEASE
5. What is the preferred outpatient regimen for COVID-19?	NIRMATRELVIR-RITONAVIR

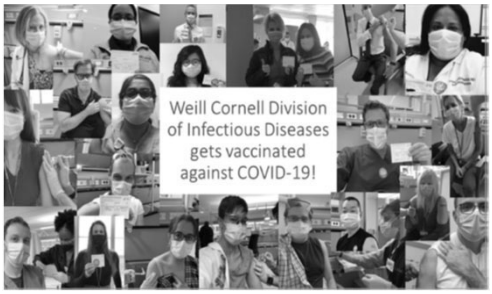
46 – What Could Be on the Exam About COVID

Speaker: Roy Gulick, MD

COVID-19: 5 MORE Questions They Could Ask

6. What drugs interact with nirmatrelvir-ritonavir?	DRUGs METABOLIZED THROUGH CYTOCHROME P450 3A4 ENZYMES (E.G. AMIODARONE, RIFAMPIN)
7. What is the preferred regimen for inpatients with COVID-19 and hypoxia?	DEXAMETHASONE + REMDESIVIR
8. How do you manage a patient with rapidly progressive hypoxia or needing mechanical ventilation?	DEXAMETHASONE + A SECOND IMMUNOMODULATOR (BARICITINIB OR TOCILIZUMAB)
9. How do COVID-19 mRNA vaccines work?	MRNA TRANSCRIBED TO SPIKE PROTEIN THAT PROVOKES AN EFFECTIVE IMMUNE RESPONSE
10. What's the most important serious side effect of COVID-19 mRNA vaccines?	MYOCARDITIS

Acknowledgments: Thanks to multiple colleagues who shared their ideas and slides.



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Weill Cornell Medicine

Agenda Day 5: Wednesday, August 21, 2024

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

47

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

Dr. Henry Chambers

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

Speaker: Henry F. Chambers, MD

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

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

7/1/2024

Disclosures of Financial Relationships with Relevant Commercial Interests

- **Merck: Data Monitoring Committee (member); Stock**
- **Moderna: Stock**

Topics for Discussion

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

Diagnosis of Endocarditis

Clinical Signs and Symptoms

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

Arch Intern Med. 2009;169:463-473

Q1. Which one of the following statements is correct?

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

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

Speaker: Henry F. Chambers, MD

Microbiology

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

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

Clin Infect Dis. 2023;77:518 and Clin Infect Dis. 2024; 78:964-967

Weaknesses of Modified Duke Criteria

- Reduced sensitivity for diagnosis of PVE, CIED-related endocarditis
- Reduced sensitivity for culture-negative endocarditis
- Poorly validated in pediatric populations
- Newer imaging modalities and molecular diagnostics not included in criteria
- Uncertainty about "possible" cases

2023 Duke-ISCVID Criteria for Diagnosis of Endocarditis

Definite pathologic diagnosis	Definite Clinical Diagnosis	Possible Clinical Diagnosis
Microorganisms identified on cardiac tissue, vegetation, graft, device OR Vegetation, leaflet destruction, or adjacent cardiac tissue showing inflammatory changes	Two major criteria OR Five minor criteria OR One major plus three minor criteria	Three minor criteria OR One major plus one minor criteria

Rejected endocarditis: criteria for definite or possible endocarditis are not met **OR** firm alternative diagnosis established OR lack of recurrence with < 4 days antibiotic therapy

2023 Duke-ISCVID Major Criteria

Positive blood cultures	Imaging	Surgical
Typical microorganisms* from 2 separate blood cultures OR Non-typical organisms in 3 or more separate blood cultures OR + PCR for Coxiella burnetti, Bartonella, T whipplei; Coxiella phase I IgG antibody titer >1:800, IFA IgG titer for Bartonella ≥ 1:800	+ ECHO/Cardiac CT 1) Vegetation, leaflet perforation, aneurysm, abscess, pseudo-aneurysm, fistula OR 2) New regurgitation c/w prior imaging OR 3) NEW PVE dehiscence + PET/CT PV, device, or graft	Evidence of IE by direct inspection at surgery

**Staphylococcus aureus*, viridans group streptococci, *Streptococcus gallolyticus*, HACEK species (*Hemophilus* species, *Aggregatibacter*, *Cardiobacterium*, *Eikenella*, *Kingella*), *E. faecalis*, *S. lugdunensis*, *Granulicatella*, *Gamella*, *Abiotphia* and in addition for PVE CoNS, *C. acnes*, Corynebacterium, Serratia

2023 Duke-ISCVID Minor Criteria

- Predisposition: previous IE, PV, h/o valve repair, CHD, more than mild valve regurgitation or stenosis, CIED, hypertrophic cardiomyopathy, IVDU
- Fever, documented temperature >38.0°C (>100.4°F)
- Vascular phenomena: systemic arterial emboli, septic pulmonary emboli, mycotic aneurysm, intracranial hemorrhage, conjunctival hemorrhages, or Janeway lesions, cerebral or splenic abscess
- Immunologic phenomena: glomerulonephritis, Osler nodes, Roth spots, or rheumatoid factor
- Positive blood cultures that do not meet major criteria, OR +PCR/NGS for typical organism from sterile body site
- + PET/CT of PV, graft, or device within 3 mo of implantation
- New regurgitant murmur on exam and echocardiography unavailable

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

Speaker: Henry F. Chambers, MD

Performance of New vs Old Duke Criteria

Sensitivity

True Positive Definition	2000 Criteria	2023 Criteria
Definite	76	84
Definite + Possible	93	99

Specificity

True Negative Definition	2000 Criteria	2023 Criteria
Rejected	74	60
Rejected + Possible	85	83

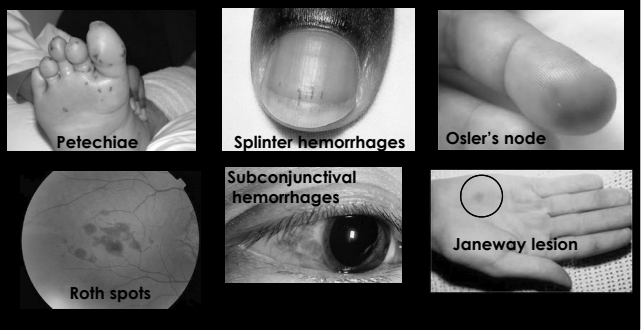
Chambers, et al. Duke Infective Endocarditis Criteria 3.0 for the Clinician: Defining What Is Possible. Clin Infect Dis. 2024, in press

What about "Possible" IE Cases?

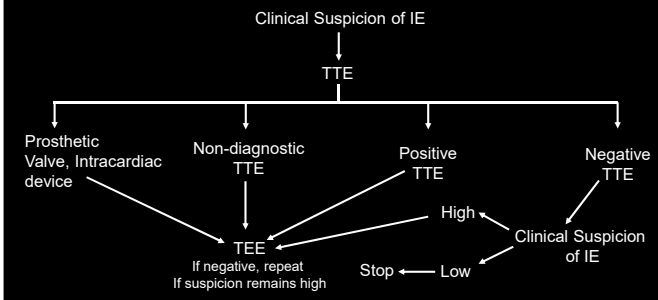
	2000 Criteria	2023 Criteria
% of all cases classified as possible	18-38	15-34
% of all possible cases that were true IE	41-52	30-36

Chambers, et al. Duke Infective Endocarditis Criteria 3.0 for the Clinician: Defining What Is Possible. Clin Infect Dis. 2024, in press

Microvascular/Immunologic Phenomena



Role of Echocardiography



European Heart Journal (2015) 36, 3075–3123

Harmonic TTE vs TEE for Diagnosis of IE

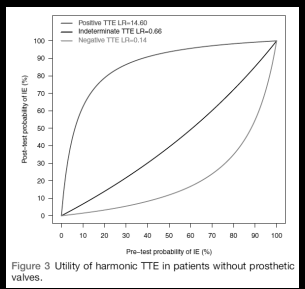


Figure 3 Utility of harmonic TTE in patients without prosthetic valves.

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

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

Native Valve Endocarditis

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

Speaker: Henry F. Chambers, MD

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

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

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

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

Native Valve Staph. aureus IE

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

No gentamicin, no rifampin

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

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

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

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

Treatment of VGS and Strep. gallolyticus Native Valve Endocarditis

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

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

Speaker: Henry F. Chambers, MD

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

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

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

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

Enterococcal Endocarditis

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

*Limited data that 2 weeks of gent is sufficient

HACEK Organisms

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

Antimicrobial Therapy of HACEK Endocarditis

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

Empirical Therapy for Endocarditis While Awaiting Culture Results

- Vancomycin 60 mg/kg/d in divided doses + ceftriaxone 2 gm Q24h
- Severe penicillin allergy: Vancomycin + aztreonam 2 gm q8h

Oral Therapy of Endocarditis

Principles Of Antimicrobial Therapy

- The regimen should kill the pathogen
- A prolonged course of therapy (i.e., weeks not days)
- Intensive dosing to ensure adequate drug exposure
- Source control

POET Trial of Oral Therapy

- Noninferiority trial, 10% margin, left-sided endocarditis, IV vs partial oral
- Streptococci, Enterococcus faecalis, Staph. aureus, coag-negative staphylococci
- All patients given IV antibiotics for at least 10 days
- Primary outcome: composite of all-cause mortality, unplanned cardiac surgery, embolic events, or relapse within 6 mo.

N Engl J Med 2019;380:415

Outcomes: POET Trial of Oral Therapy

1954 assessed for eligibility

↓

1554 excluded (428 no Duke criteria)

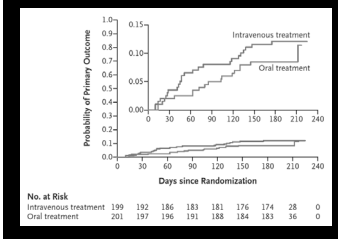
↓

400 randomized

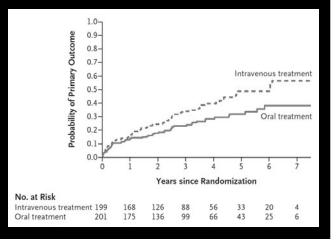
Outcome	IV (N=199)	PO (N=201)
Mortality	13 (6.5%)	7 (3.5%)
Unplanned surgery	6 (3.0%)	6 (3.0%)
Embolic event	3 (1.5%)	3 (1.5%)
Relapse	5 (2.5%)	5 (2.5%)

N Engl J Med 2019;380:415

Outcomes: POET Trial of Oral Therapy



N Engl J Med 2019;380:415



N Engl J Med 2019;380:1373

Culture-Negative Endocarditis

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

Speaker: Henry F. Chambers, MD

Culture-Negative Endocarditis

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

Culture-Negative Scenarios

- **Coxiella burnetii (Q fever)**: Direct or indirect animal contact, hepatosplenomegaly, abnormal or prosthetic valve. Doxycycline + hydroxychloroquine >1 yr.
- **Bartonella**: Homeless, indolent, valve normal or abnormal, louse vector. **Rx:** 6 wks doxycycline plus two wks gentamicin or plus 2 wks rifampin if valve resected (otherwise 3 months more of doxy)
- **Tropheryma whippeli:** Indolent, protracted course with arthralgias, diarrhea, malabsorption, weight loss, CNS involvement

Tools for Diagnosis of Culture-Negative Endocarditis

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

Prosthetic Valve and Device-Related Endocarditis

Q5. A 72 y/o man s/p AV replacement with a bioprosthetic valve for bicuspid AV with insufficiency. He reports sore throat, cough, congestion, fever, chills, sweats and malaise for 3 days

- Exam: T 100.2º F, Pulse 85 , BP 130/70mm Hg, RR 16
  - HEENT: oral cavity and tonsils red and swollen, no lymphadenopathy
  - Lungs: clear
  - Heart: No murmur
  - Skin: no rash
- Rapid rapid strep, rapid flu both negative

Q5. What is the best approach for managing this patient?

1. Obtain throat culture and prescribe Pen VK while awaiting results
2. Obtain throat culture and give a script for Pen VK to be filled if culture is positive for GAS
3. Prescribe azithromycin for treatment of acute URI
4. Obtain blood cultures and await results
5. Obtain blood cultures and initiate therapy with vancomycin, gentamicin, and rifampin

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

Speaker: Henry F. Chambers, MD

Microbiology of PVE

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

Adapted from Karchmer and Chu, UpToDate, 2020

Diagnosis of PVE

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

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

Antimicrobial Therapy of PVE

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

Cardiac Implantable Device Infections

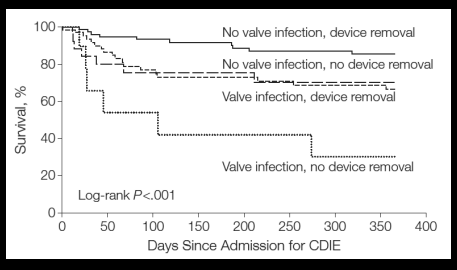
(permanent pacemakers, defibrillators)

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

Cardiac Implantable Device Infection Types

- Pocket site/generator only : ~ 60%
  - Blood culture positive <50%
  - Pocket infection or generator/lead erosion
- Occult bacteremia/fungemia: ~7-30%
- Lead infection +/- endocarditis: ~10-25%
- PET-CT may detect localized infection if work-up is inconclusive

Survival with and without Device Removal

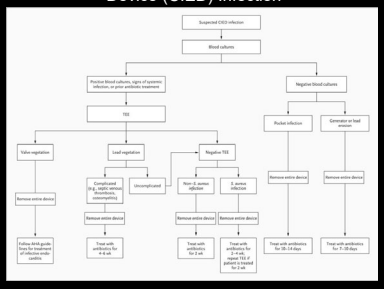


Athan, JAMA. 2012; 307:1727-1735

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

Speaker: Henry F. Chambers, MD

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



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

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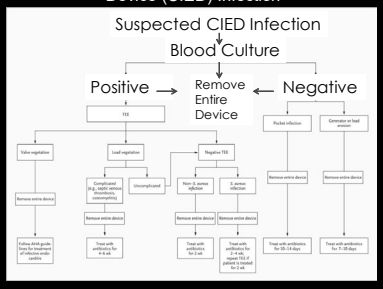


Baddour LM et al. N Engl J Med 2012;367:842-849 The NEW ENGLAND JOURNAL of MEDICINE

AHA Guidelines for Management of Cardiac Implantable Device Infections

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

Circulation 2010;121:458-77

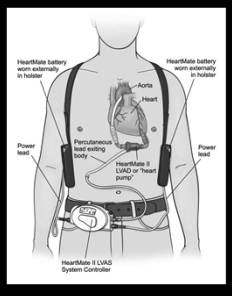
AHA Guidelines for Device Reimplantation

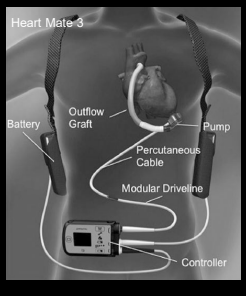
- Determine if reimplantation necessary
- New device on contralateral side
- ≥72h negative BC before reimplantation
- If IE: reimplant ≥ 14d after original removal
- Antibiotic prophylaxis: 1h before implantation, none thereafter

Main Take-home Points

- Duke-ISCVID criteria is a valuable tool for assessing the likelihood of endocarditis
- TTE is acceptable to rule out endocarditis if of high quality and in a low probability setting
- Use a tried-and-true regimen, avoid aminoglycoside combination therapy for NVE
- Think prior antibiotics and Bartonella in culture-negative endocarditis
- Any fever is a patient with a prosthetic valve is endocarditis until proven otherwise

Infection of Ventricular Assist Devices





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

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Types of VAD Infections

- VAD-specific infections – occurs only in LVAD patients
  - Pump pocket/cannula infections
  - Pocket infections
  - Driveline exit site infections (superficial or deep)
- VAD-related infections- risk of LVAD infection increased
  - Bloodstream infections (VAD-related, IV catheter/non-VAD related)
  - Endocarditis (pump or cannula, native valve)
  - Mediastinitis, sternal wound infections
- Non-VAD infections

Ann Cardiothorac Surg 2021;10:233; Clinical Transplantation 2019;33:e13552.

Microbiology of VAD-Specific Infections

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

Clinical Transplantation 2019;33:e13552.

Management and Therapy

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

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

Antimicrobial Therapy

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

Clinical Transplantation 2019;33:e13552; Open Forum Infect Dis. 2020 Nov 16;8(1):ofaa532
Ann Cardiothorac Surg 2021;10(2):233-239

IE Prophylaxis after Dental Procedures

YES

- Prosthetic cardiac valve or material
  - Presence of cardiac prosthetic valve
  - Transcatheter implantation of prosthetic valves
  - Cardiac valve repair with devices, including annuloplasty, rings, or clips
  - Left ventricular assist devices or implantable heart
- Previous, relapse, or recurrent IE
- CHD
  - Unrepaired cyanotic congenital CHD, including palliative shunts and conduits.
  - Completely repaired congenital heart defect with prosthetic material or device, whether placed by surgery or by transcatheter during the first 6 mo after the procedure
  - Repaired CHD with residual defects at the site of or adjacent to the site of a prosthetic patch or prosthetic device
  - Surgical or transcatheter pulmonary artery valve or conduit placement such as Melody valve and Contegra conduit
- Cardiac transplant recipients who develop cardiac valvulopathy

NO

- Implantable electronic devices such as a pacemaker or similar devices
- Septal defect closure devices when complete closure is achieved
- Peripheral vascular grafts and patches, including those used for hemodialysis
- Coronary artery stents or other vascular stents
- CNS ventriculoatrial shunts
- Vena cava filters
- Pledgets

Circulation. 2021;143:e963-e978

Which Dental Procedures?

YES

All dental procedures that involve manipulation of gingival tissue or the periapical region of teeth or perforation of the oral mucosa

NO

Anesthetic injections through noninfected tissue, taking dental radiographs, placement of removable prosthodontic or orthodontic appliances, adjustment of orthodontic appliances, placement of orthodontic brackets, shedding of primary teeth, and bleeding from trauma to the lips or oral mucosa

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

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IE Prophylaxis Regimens

Situation	Agent	Adults	Children
Oral	Amoxicillin	2 g	50 mg/kg
Unable to take oral medication	Ampicillin OR	2 g IM or IV	50 mg/kg IM or IV
	Cefazolin or ceftriaxone	1 g IM or IV	50 mg/kg IM or IV
Allergic to penicillin or ampicillin—oral	Cephalexin*† OR	2 g	50 mg/kg
	Azithromycin or clarithromycin OR	500 mg	15 mg/kg
	Doxycycline	100 mg	<45 kg, 2.2 mg/kg >45 kg, 100 mg
Allergic to penicillin or ampicillin and unable to take oral medication	Cefazolin or ceftriaxone†	1 g IM or IV	50 mg/kg IM or IV

Single dose
30-60 min
before Procedure

Other Stuff

Valve Surgery with Stroke

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

Am Heart J 2019;216:102-112

Pan-Scanning

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

Fever during Therapy of Endocarditis

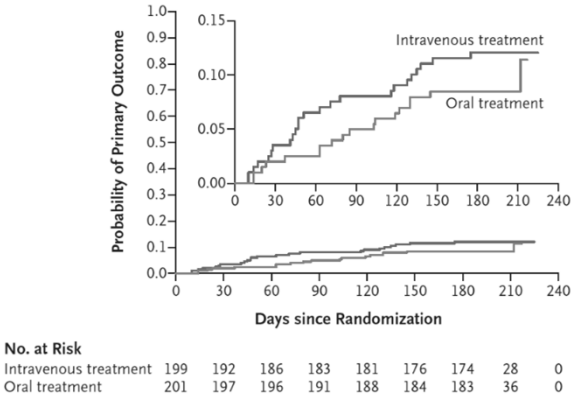
- Very common, lasts into the second week, a concern in PVE
- Cause (if one is found, often it is not)
  - Abscess: valve ring or elsewhere
  - Septic pulmonary emboli, pleural effusion
  - Another infection (e.g., IV site, fungal superinfection)
  - Polymicrobial endocarditis
  - Drug fever
- Work-up: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

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

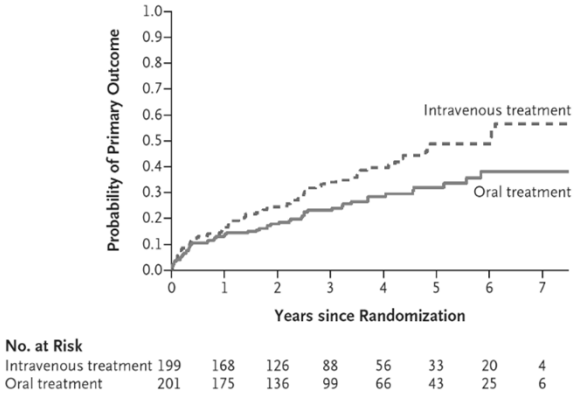
Speaker: Henry Chambers, MD

Enlarged Slides: 35, 49

Outcomes: POET Trial of Oral Therapy



N Engl J Med 2019;380:415



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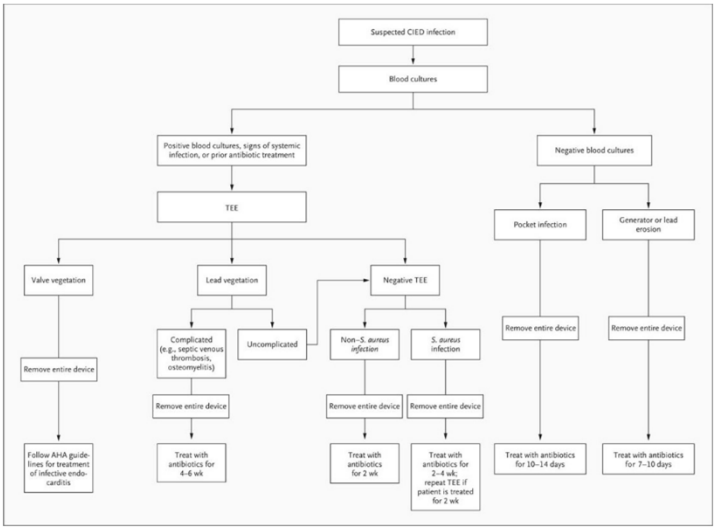

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47 – Endocarditis of Native and Prosthetic Devices, and Infections of Pacers and Ventricular Assist Devices

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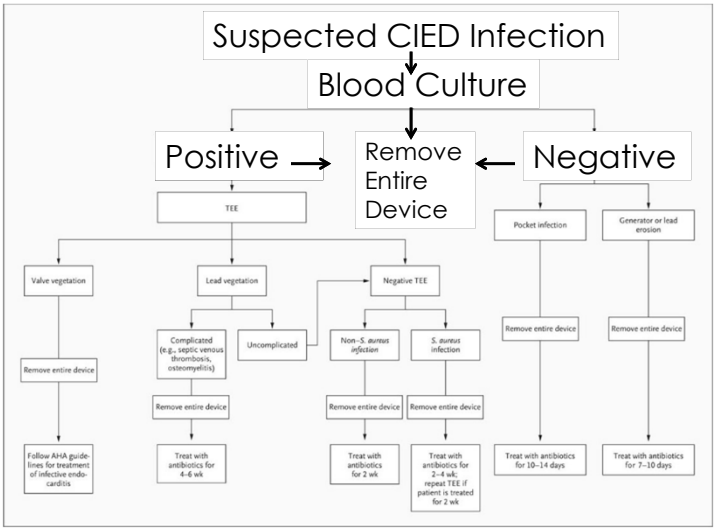

* Baddour LM et al. N Engl J Med 2012;367:842-849

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48

Photo Opportunities II: Images You Should Know for the Exam

Dr. John Bennett

48 – Photo Opportunities II You Should Know for Exam

Speaker: John Bennett, MD

Photo Opportunities II: You Should Know for Exam

John E. Bennett, MD
Bethesda, Maryland

7/1/2024

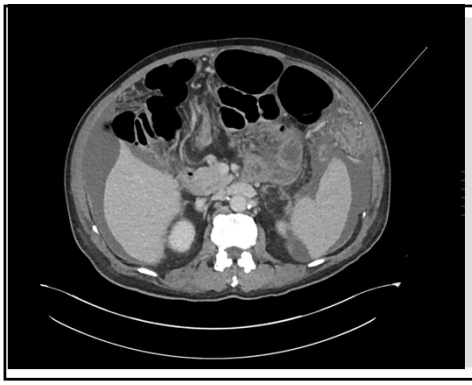
- **Disclosures of Financial Relationships with Relevant Commercial Interests**

  - None

Case 1. Indolent peritonitis

courtesy of Prishanya Pillai, MD. Georgetown University Hospital

◦ A 37 yr old woman was admitted with a three month history of fatigue, night sweats and a 30 pound weight loss. She had been previously healthy, working as a nurse now and in the Philippines prior to moving to the USA 5 years ago. She had no history of alcohol or illicit drug use and lived with her husband and two young children in Baltimore. Her physical examination was normal except for a temperature of 38C, pallor and abdominal distention with shifting dullness. Lab work found Hgb 6.1 gm/l, WBC 8.7, creatinine 1.5, albumin 3.3 and normal LFT. Pericentesis found WBC 2500 with 70% lymphs, albumin 2.9 g/l, negative cytology and negative acid fast stain. Abdominal-pelvic CT found enlarged mesenteric nodes, ascites, thickened peritoneum with "caking" (see photo and arrow) and a 6.5 cm diameter enlarged left ovary. Finding were consistent with metastatic tumor in the peritoneum, likely ovarian in origin.



. The most sensitive diagnostic test would be which of the following

A. Culture and smear of ascitic fluid for mycobacteria and fungi
B. Culture and pathology of peritoneal tissue for mycobacteria and fungi
C. Culture and pathology of needle aspirate of enlarged abdominal lymph node
D. Laparoscopic biopsy of ovarian mass
E. PCR for TB

Tuberculous peritonitis

◦ Tuberculous peritonitis often resemble ovarian cancer.

◦ Abdominal CT can have peritoneal granulomatous inflammation ("caking")

◦ Culture and smear of ascites has low sensitivity.

◦ PCR value unsure . May not provide susceptibility

◦ Culture of peritoneal biopsy tissue =most sensitive method

◦ Needle biopsy of the node or ovarian mass appear unnecessary.

◦ Empirical therapy for tuberculous peritonitis if biopsy of peritoneal tissue shows granuloma

Case 2. Asymptomatic lung masses

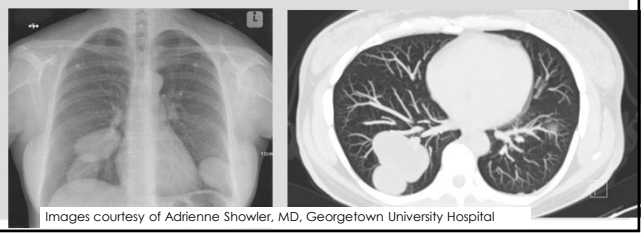
◦ A 30 yr old woman from Los Angeles was referred to you because a chest xray done because of cough and fever, found to be due to COVID-19. Abnormalities were confirmed on a chest CT done later, after the symptoms had resolved. She is currently asymptomatic, living in Los Angeles with her husband and three children and working in retail. She grew up in rural Peru but has not returned since moving to the USA 15 years go. She is taking no medications, has never smoked and has only traveled around California in the last decade. Routine laboratory work is normal. A bronchalveolar lavage was negative on cytopathology and culture for bacteria, fungi and mycobacteria

48 – Photo Opportunities II You Should Know for Exam

Speaker: John Bennett, MD

The history and images are highly suggestive of what diagnosis?

A. Cysticercosis
B. Echinococcosis
C. Paragonimiasis
D. Coccidioidomycosis
E. Paracoccidioidomycosis



Images courtesy of Adrienne Showler, MD, Georgetown University Hospital

Echinococcosis (Echinococcus granulosis) Hydatic lung disease

- Clinical picture is highly consistent.
- Endemic In rural Peru
- can progress in the lung or liver without symptoms for many years.
- Aspiration or biopsy may release protoscolices into the pleura, leading to numerous new lesions. Referral to a medical center familiar with surgical management of the disease is indicated.
- Rounded, dense, well circumscribed lung lesions would not be characteristic of the other listed diagnoses

Case 3, FEVER AND RASH

A 30 year-old man from El Salvador, living in the United States for 10 years, returned to United States from visiting family in a residential area of San Salvador for two weeks. On the second day home, he had the onset of fever, headache, muscle ache, and retrobulbar pain. He had some nausea but no abdominal pain, diarrhea or constipation.

The symptoms persisted, but he did not seek medical attention until the third day of illness, when a diffuse petecchial, non pruritic rash appeared on his arms and upper chest. The home he stayed at in San Salvador was in the city and had no pets. Children and adults in the family were healthy. Physical examination was negative except for fever of 102F, rash and two tender occipital lymph nodes. No nuchal rigidity was found. Labs revealed a WBC = 1.6 with a normal differential and no atypical lymphs, platelets 60,000, Normal blood chemistries and chest x-ray.

The most likely source of infection

A. Food
B. Mosquito
C. Flea
D. Another human
E. Animal urine

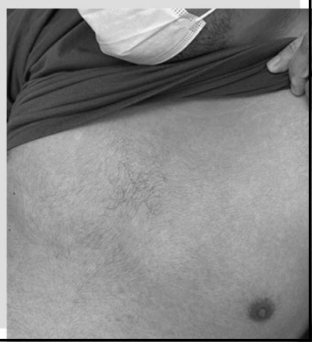


Photo courtesy of Glenn Wortmann, Washington Hospital Center

- Correct answer B . Mosquito (Dengue)

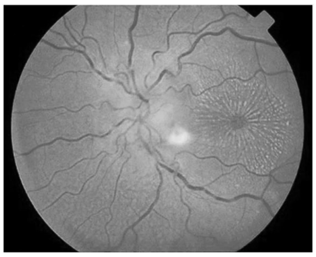
- Rash after several days of fever, myalgia ,headache. Thrombocytopenia , leukopenia common. Diagnosis early in the infection by PCR or NS1 antigen. Treatment supportive.
- Dengue is more of an urban disease than malaria. Aedes aegypti mosquito breeds in small urban pools of water, as in old auto tires, near human habitation and to bite in the daytime, particularly in the early morning and late afternoon. The incubation period is usually 4-7 days but can be up to 14 days.
- Animal urine (leptospirosis) : rash and leukopenia are against the diagnosis
- Rat fleas(murine typhus) uncommon in Central America and the rash is usually more subtle.
- Food (typhoid) The rash of rose spots,is much less extensive
- Another human: (measles) rash is different. No conjunctivitis, cough, coryza

Case 4. Rapid visual loss one eye

- A 20 yr old woman graduate student from Washington, DC presented in January with the acute onset of vision loss in her right eye, with a "black hole" in the middle and blurred images around the scotoma. She had no ocular pain and normal vision in her left eye. She was not sexually active, taking no medications and no recent travel outside the local area. She did some hiking in local parks but was not aware of tick bites. She lived alone with a kitten and a goldfish. She occasionally ate raw sushi and beef tartar. Routine laboratory work was normal. . Funduscopic examination found blurring of the disc and retinal edema in the macula.

48 – Photo Opportunities II You Should Know for Exam

Speaker: John Bennett, MD



Which of the following pathogens is most likely:

*A.*Toxoplasma gondii
B. Bartonella henselae
C. Treponema pallidum
D. Toxocara cati
E. Anisakis

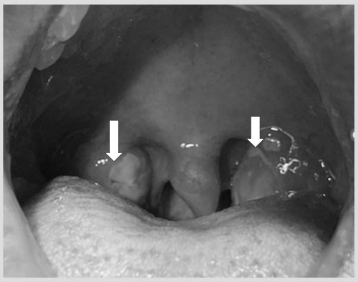
Bartonella henselae

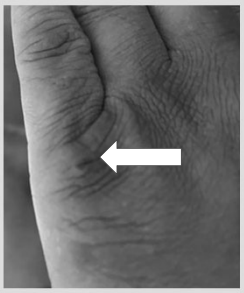
- Bartonella henselae: small a tender swollen draining lymph node. Also encephalitis, neuroretinitis in previously healthy
- Bacillary angiomatosis more often immunosuppressed
- Diagnosis is usually made by serology.
- Acute ocular toxoplasmosis from eating poorly cooked meat. Fluffy exudative lesions with overlying vitritis
- Toxocara causes single inflammatory mass from a larva embedded in the eye, sometimes mistaken for retinoblastoma. Young children accidentally ingesting cat feces are at risk.
- Syphilis can present in the eye in many ways but her sexually history is not suggestive.
- Anisakis (raw fish) causes stomach lesions that do not spread to the eye.

Case 5. Pharyngitis and popular skin lesions

- A 23 yr old man presented to the emergency department with 18 days of severe sore throat, not improving despite injection of ceftriaxone and a course of azithromycin given him in emergency room visits 2 and 14 days prior. Rapid strep tests on a throat swab had been negative at prior visits. In addition four pustular lesions had appeared in the prior two days, scattered over his trunk and extremities. He had felt feverish at night but not taken his temperature. He lived in downtown Washington DC, worked in retail, had sex with men and had no recent travel, medications, or illicit drugs. On exam, he had severe tonsilitis, temperature of 38.5C, prominent submental lymph nodes and four skin lesions like the one to be shown. His routine labs were normal

Courtesy of TARA PALMORE, MD





Which of the following is likely to be most helpful?

A. throat swab
B. Rapid HIV test
C. Urine NAAT
D. Serology for syphilis
E. Blood culture

Throat swab for Mpox PCR

- A throat swab for Mpox DNA . MSM. Pustular skin lesion . Possible receptive oral sex. Skin bx for PCR also possible
- Tecovirimat treatment.
- Notify health department for contact tracing and vaccine candidates
- Throat swab for herpes simplex ? localization to the posterior oropharynx and this severity is unusual.
- Throat swab or NAAT for gonorrhea and Chlamydia trachomatis ? Prior antibiotics.
- A 4th generation test for HIV is indicated but there is no rash and severe tonsillitis is unusual for acute retroviral syndrome.
- Syphilitic chancres can occur in the mouth but would not be this painful

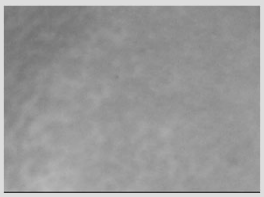
48 – Photo Opportunities II You Should Know for Exam

Speaker: John Bennett, MD

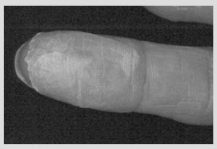
Case 6. Post-op complication

A 64 year old woman presented in the emergency room with fever, nausea, sore throat, muscle pain, headache and several loose stools over the past 24 hours. She had been in good health and was recovering well after functional endoscopic nasal surgery done 9 days ago for chronic sinusitis. She lived in downtown Chicago with her husband, a dog, a kitten and her 5 year old granddaughter, who was just recovering from several days of cough and fever. The patient had no recent travel and was taking no medications. On examination she had a temperature of 38.9C, pulse 109 and BP 86/45. She had a diffuse erythematous rash. Routine labs were notable for a creatinine of 3.1 mg/dl, WBC 14,900 and platelets of 112,000. She was given three liters of saline with little improvement in her blood pressure, admitted to intensive care and began requiring oxygen support.

Rash on her back



Clue: finger 2 weeks later



◦ The most likely pathogen was which of the following:

A. Streptococcus pyogenes
B. Staphylococcus aureus
C. Capnocytophaga canimorsus
D. Bartonella henselae
E. COVID-19

Staphylococcal toxic shock

- Staphylococcal toxic shock can follow nasal surgery
- Post operative nasal packing has been thought to contribute.
- Symptoms often appear a week or so after surgery but can be delayed.
- Hypotension, fever, renal failure, myalgias, abdominal pain, nausea, vomiting and diarrhea are common. Sinus pain not worse than usual post-op. Desquamation later.
- Toxin 1-producing Staphylococcus aureus in nasal discharge. Blood culture neg.
- Rx: antistaphylococcal beta lactam plus linezolid. Clindamycin may be useful but macrolide resistance is a concern.
-

◦ Streptococcus pyogenes toxic shock. Infection obvious. Acute rheumatic fever – no shock

◦ Capnocytophaga sepsis: no dog bite. Spleen intact.

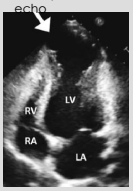
◦ Bartonella henselae does not cause hypotension.

◦ COVID-19 multisystem inflammatory syndrome (MIS-A) 2-6 weeks after COVID-19 but the patient not infected. Only granddaughter sick

Case 7. Young man with a stroke

A 26 year old male construction worker from the District of Columbia presented with the acute onset of right-sided weakness. MRI confirmed a stroke in the left MCA. Echocardiography looking for source that might embolize found a ventricular aneurysm and mural thrombus in the apex of the left ventricle. Cardiac MRI confirmed the presence of an apical ventricular aneurysm. EKG found a left anterior fascicular block and right bundle branch block. Review of an EKG taken in the Emergency room two years prior when he was seen after falling off a ladder found that an EKG had shown the same conduction block but the patient had not returned for a scheduled cardiology clinic visit. The patient's past history was unremarkable except that he had lived in rural Bolivia until coming the USA at age 12. HIV testing was negative.

Ventricular aneurysm on echo



Which of the following infections may explain his cardiac disorder?

a. Leishmaniasis
b. Trypanosomiasis
c. Cysticercosis
d. Toxoplasmosis
e. Paracoccidioidomycosis

Trypanosomiasis (Chagas' disease)

◦ Chagas' disease) common in many areas of Central and South America
◦ Infection can progress decades after the initial infection
◦ Presents as cardiac or intestinal disease (megacolon, megaesophagus)
◦ Cardiac conduction block is an early sign of cardiac disease.
◦ Myocarditis . Congestive failure . Apical aneurysm, mural thrombus.
◦ Toxoplasmosis can cause myocarditis but almost always in an immunocompromised patient
◦ Cysts of cysticercosis rarely in myocardium. No aneurysm
◦ Visceral leishmaniasis and paracoccidioidomycosis: no myocarditis.

48 – Photo Opportunities II You Should Know for Exam

Speaker: John Bennett, MD

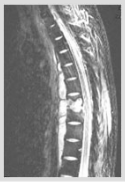
Case 8. Back ache

This 22-year-old college student who lived in India until immigrating to the United States at age 18 years presented with progressive thoracic back pain of three weeks' duration.

No foreign travel in the past year. No unusual food habits. No pets. Lives with healthy sister in an apartment in DC.

The likely portal of entry of this infection is:

A. Lung
B. GI tract
C. Skin
D. Urinary tract



Portal for vertebral osteo=Lung (Pott's)

- Lung: High risk for TB: foreign born. Immigration in past 5 yrs
- GI tract: Brucellosis no recent exposure. Actinomycosis no GI lesion
- Skin: Staphylococcal infection . No IV drug use. No skin lesion. No sepsis. Staph aureus=over half of cases in the USA . Portal not always obvious
- Urinary tract : organisms are rare causes of spondylitis.
- MRI: lesion on both sides of disc suggests infection, not tumor.

Case 9. Managing an epidural abscess

A 55-year-old man is brought to the emergency room because of increasingly severe back pain of two days' duration, precipitated by loading some grain sacks onto his truck.

He has been seen in the past because of obesity, poorly controlled type 2 diabetes mellitus and hypertension.

Admission blood cultures have grown MSSA.

Nafcillin and a TTE have been ordered.

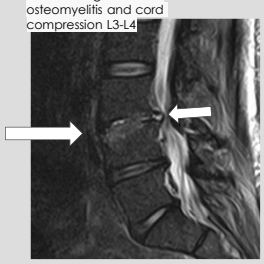
MRI has found osteomyelitis of vertebral bodies T12 and L1, with a contiguous epidural abscess impinging on the spinal cord.

On your examination, temperature is 39°C, pulse 120 and BP 160/90. The patient is alert but has severe back pain. He is unable to walk because of pain but has weakness in both legs and absent deep tendon reflexes in both legs.

Now what?

A. Surgical decompression of the spinal cord
B. Aspiration of the abcess
C. Nafcillin alone
D. Vancomycin alone
E. Dexamethasone

MRI showing vertebral osteomyelitis and cord compression L3-L4

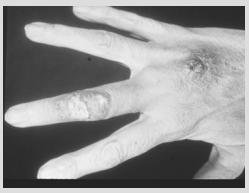


- Answer: surgical decompression of the spinal cord because of neurologic signs
- Aspiration of the abscess is often diagnostic but unable to prevent permanent paraparesis once neurologic signs, such as leg weakness, are present.
- Dexamethasone may decrease inflammation but has no role in this scenario.

Case10. Skin lesions

An otherwise healthy 58-year-old woman who lives in Wisconsin presents with progressive nodular lesions on her right hand. She has recently acquired a kitten. The lesions have been present for approximately six weeks and have increased in number as they have progressed from her finger to the back of her hand She works at a local flower store. She visited Brazil 3 months ago and spent 2 weeks in the Amazon basin. She gives no history of fever or constitutional symptoms.

Her exam is remarkable for several subcutaneous lesions from the right hand extending to the forearm. There is no associated lymphadenopathy or lymphangitic streaking. The lesions are somewhat painful to palpation, and some of these nodules have spontaneously suppurated and drained.



48 – Photo Opportunities II You Should Know for Exam

Speaker: John Bennett, MD

What is the most likely organism?

A. Leishmania brasiliensis
B. Prototheca wickerhamii
C. Bartonella henselae
D. Sporothrix schenckii
E. Mycobacterium marinum

Sporothrix schenckii

Nodular lymphangitis

- Sporotrichosis: thorny plants (flower store)
- Mycobacterium marinum: water, fish tanks
- Cutaneous leishmaniasis: foreign travel
- Nocardia brasiliensis: soil (not listed as a possibility)

Other inoculation lesions
- Bartonella henselae: local cat scratch then local lymphadenitis (axillary, epitrochlear, inguinal)
- Prototheca wickerhamii: soil, water. local verrucous or ulcerated lesion.

Only contiguous spread.

49

Staphylococcal Disease

Dr. Henry Chambers

49 – Staphylococcal Aureus

Speaker: Henry F. Chambers, MD

Staphylococcal Aureus

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

7/1/2024

Disclosures of Financial Relationships with Relevant Commercial Interests

- **Merck: Data Monitoring Committee (member); Stock**
- **Moderna: Stock**

Outline of the Talk

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

Q1. Which one of the following risk factors is most predictive of complicated Staph. aureus bacteremia and mortality?

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

Predictors of Complicated/High Risk SAB*

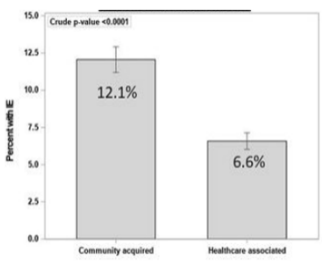
Fowler, et al (OR)	**Liu, et al** (IDSA MRSA)	**van der Vaart, et al** (OR)
Persistent bacteremia (5.6)	Persistent bacteremia	Persistent bacteremia (6.8)
Skin findings (2.04)	Skin findings	Community onset (2.9)
Community onset (3.1)	Prosthetic material	(infected) Prosthetic material (2.3)
Persistent fever (2.2)	Persistent fever	

Complicated/High Risk = mortality, metastatic foci or complicated local infection, embolic stroke, recurrent bacteremia

Fowler, et al. Arch Intern Med. 2003; 163:2066;
Liu, et al. Clin Infect Dis. 2011; 52:e18-55;
van der Vaart, et al. Clin Infect Dis. 2023 Dec 29;ciad784. doi: 10.1093/cid/ciad784

OR = Odds ratio

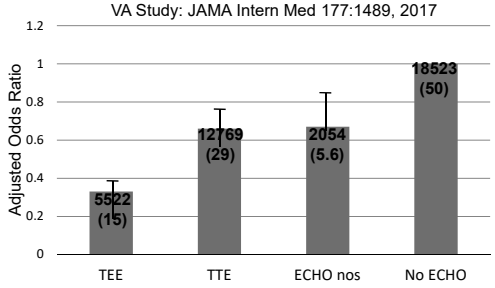
Infective Endocarditis (IE) Prevalence in Community Associated (CA) vs. Heathcare Associated (HCA) S. aureus bacteremia



5549 community cases, 7491 HCA cases in Denmark Registries 2010-18; OFID 2022; 9:ofac647

ECHO and Mortality in S. aureus Bacteremia

VA Study: JAMA Intern Med 177:1489, 2017



Numbers on bars indicate number of patients (%)

Role of Echocardiography for S. aureus Bacteremia

- Prevalence of endocarditis 12%-18% overall
- Depends on the pre-test probability
  - Consider TTE (sensitivity 70%, specificity 95%) in all patients with SAB
  - Obtain TEE (sensitivity 90%, specificity 95%) in high risk patients
    - Embolic events, intracardiac device, IVDU, prior IE
    - Suspected endocarditis, negative TTE

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

FDG-PET/CT in Patients with Staph. aureus Bacteremia

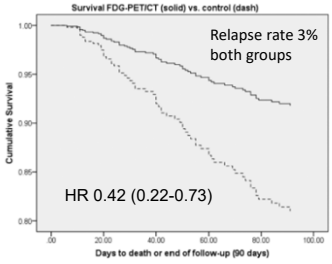
Matched Cohort Study of FDG-PET/CT in Patients with Staph. aureus Bacteremia

Detection of Infected Foci by PET/CT according to Clinically Suspicion

Clinically suspected sites (n=136)		PET/CT + sites (n=217)	
PET/CT +, confirmed	72 (53%)	PET/CT +, clinically unsuspected	145 (69%)
PET/CT -, excluded	64 (47%)	PET/CT +, clinically suspected	72 (31%)

Clin Infect Dis. 2021;73:e3859

Matched Cohort Study of FDG-PET/CT in Patients with Staph. aureus Bacteremia



Clin Infect Dis. 2021;73:e3859

Issues:
--Availability
--Reimbursement
--Observation studies only
--Goals of care?

Q2. A single positive blood culture for Staph. aureus…….

A. Represents contamination in a quarter or more of cases
B. Is associated with a significantly lower relapse rate than presence multiple positive blood cultures
C. Is associated with complicated bacteremia at a rate similar to multiple positive cultures
D. Excludes the need to perform echocardiography to rule out endocarditis
E. Is associated with a lower 60-day mortality than multiple positive blood cultures

Single positive blood culture for S. aureus

- Represents contamination in < 10% of cases
- Follow-up blood cultures will be positive in ~15% of cases in whom half will be afebrile
- Carries similar risks of mortality, relapse, and complicated bacteremia as multiple positive cultures
- Although the risk of endocarditis is less than with multiple positive cultures (~ 4% vs ~14%), an ECHO still should be obtained
- **Always obtain follow-up blood cultures**

Infect Dis 2020;52:207, OFID. 2021;9(2):ofab642

Treatment of MSSA Bacteremia

FDA-approved Antibiotics for SAB

- Penicillin
- Nafcillin/Oxacillin
- Cefazolin
- Vancomycin
- Daptomycin
- Ceftobiprole

AHA Guidelines for S. aureus Native Valve Endocarditis

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

Circulation. 2015; 132:1435

Q3. On day 9 of nafcillin therapy for complicated methicillin-sensitive S. aureus bacteremia the patient has developed new neutropenia (1,000 neutrophils). MICs (µg/ml) of the blood isolate are penicillin 0.12 (S), cefazolin 0.5 (S), vancomycin 1 (S), daptomycin 0.5 (S), ceftaroline 0.5 (S). **Which one of the alternative agents would you recommend?**

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

Tolerability of Cefazolin in Nafcillin-Intolerant Patients for the Treatment of Methicillin-Susceptible *Staphylococcus aureus* Infections

Ankit M. Gandhi,[1,2] Megan D. Shah,[1] Lindsay E. Donohue,[1] Heather L. Cox,[1] and Joshua C. Eby[3]

[1]Department of Pharmacy, University of Virginia Health, Charlottesville, Virginia, USA; [2]National Institutes of Health, Bethesda, Maryland, USA, and [3]Division of Infectious Diseases and International Health, Department of Medicine, University of Virginia Health, Charlottesville, Virginia, USA

Switching to cefazolin after a non-IgE-mediated hypersensitivity reaction to nafcillin is safe

Clin Infect Dis 2021; 73:1650

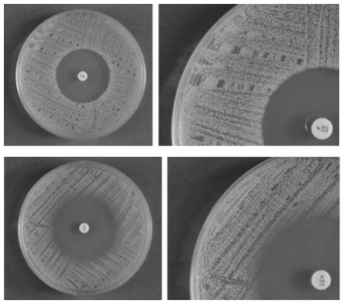
What about Penicillin G for Penicillin-susceptible SAB? Probably Yes

- Confirm susceptibility
  - MIC ≤ 0.025 µg/ml (J Antimicrob Chemother. 2021; PMID: 33615356)
  - MIC ≤ 0.25 µg/ml (CLSI breakpoint) and
    - Negative PCR for beta-lactamase gene (blaZ) or
    - Negative zone test
- References supporting efficacy
  - J Antimicrob Chemother. 2023; PMID: 37596905
  - Int J Antimicrob Agents. 2022; PMID: 35288257
  - Int J Antimicrob Agents. 2019; PMID: 31181352

Zone edge test for β-lactamase

Positive

Negative



MSSA Bacteremia: Cefazolin vs. Antistaphylococcal Penicillins

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

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

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

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

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

Summary: MSSA bacteremia

- An ASP and cefazolin overall preferred agents for definite therapy
  - An ASP is first-line but less well tolerated than cefazolin
  - Observational studies suggest mortality, relapse, and treatment failures rates are similar with cefazolin
  - Anxiety over the inoculum effect, which may adversely impact outcome in a subset of cefazolin-treated patients
  - Start with an ASP until source control established
- Vancomycin, daptomycin if serious beta-lactam allergy or intolerance and possibly for OPAT (daptomycin > vancomycin)
- Ceftriaxone not 1st or 2nd line, should be avoided in patients with endocarditis, more serious infections, complicated/high risk SAB

*ASP = antistaphylococcal penicillin

Treatment of MRSA Bacteremia

First-line choices for MRSA bacteremia

- Vancomycin
  - 30-60 mg/kg/d in 2-3 divided doses
  - Nephrotoxic at higher trough concentrations (15-20 µg/ml)
  - Need for therapeutic drug monitoring
- Daptomycin
  - Non-inferior to vancomycin, better tolerated
  - Potential for emergence of resistance on therapy (mprF mutants), especially in high inoculum infections, poor source control
  - Do not use for primary pneumonia (OK for septic emboli)
  - Some cross-resistance with VISA

Holland et al: JAMA 312:1330, 2014

AHA guidelines for therapy of native valve *S. aureus* endocarditis

- MSSA
  - Nafcillin (or Oxacillin) 2 gm q4h x 6 weeks
  - Cefazolin 2 gm q8h x 6 weeks, allergic or intolerant to naf
  - No aminoglycoside
- MRSA
  - Vancomycin 30-60 mg/kg/d divided q8-12h to achieve ~~trough of 15-20 µg/ml~~ **AUC 400-600 x 6 weeks**
  - Daptomycin ~~6~~ **10** mg/kg q24h x 6 weeks
  - No aminoglycoside

Circulation 2015; 132:1435

AUC = Area under the concentration-time curve

Vancomycin or Daptomycin?

- Meta-analysis, 24 studies, MRSA and MSSA, heavily weighted to retrospective studies
- Microbiological cure (n=1036): favored daptomycin
- Clinical cure (n=888): favored daptomycin
- Relapse (n=878): not significantly different
- Mortality (n=8845): not significantly different
- Adverse events: favored daptomycin

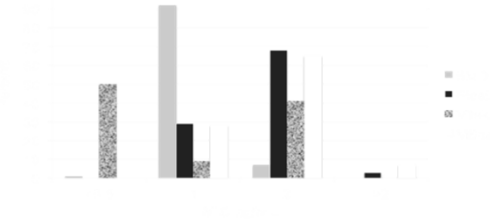
Int J Antimicrob Agents. 2023, 62:106946

Q4. A patient with complicated MRSA bacteremia on day 9 of therapy with daptomycin q48h develops myalgias with a creatinine kinase of 1250 u/L (upper limit of normal 200). The last positive blood culture was on day 3 of therapy. MICs (µg/ml) of the isolate are as follows: vancomycin 2 (S), daptomycin 0.5 (S), dalbavancin 0.25 (S), telavancin 0.5 (S), ceftaroline 1 (S). **Which one of the following would you recommend?**

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

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

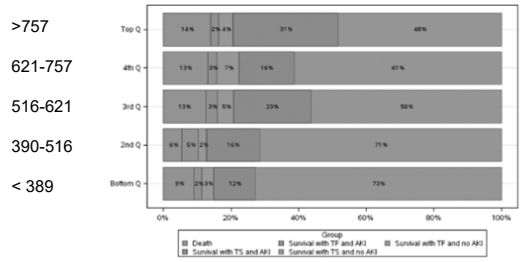
Vancomycin MICs Vary by Method



Int J Antimicro Agent 32:378, 2008

Vancomycin Dosing: Higher AUC Correlates with Worse Outcome

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



Highlights of Modern Vancomycin Dosing for MRSA Infections

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

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

Duration of Therapy for S. aureus BSI

14 days
- UNCOMPLICATED/LOW RISK (~10% of cases)
- Fever resolves by day 3
- Sterile blood culture after 2-3 days (DOCUMENT!)
- Easily removed focus of infection (no DVT)
- No metastatic infection (e.g., osteo)
- Negative echo, no evidence of endocarditis
- No predisposing valvular abnormalities
- (No implanted prosthetic devices, no DM, no immunosuppression)

4-6 weeks +
- COMPLICATED/HIGH RISK
- Failure to meet one or more of above criteria
- Osteomyelitis, endocarditis, epidural abscess, septic arthritis, pneumonia, complicated UTI

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

Outcomes of Partial Oral Antibiotic Treatment for Complicated *Staphylococcus aureus* Bacteremia in People Who Inject Drugs

John A. Wildenthal,[1,3,4] Andrew Atkinson,[2] Sophia Lewis,[3] Sena Sayood,[3,5] Nathanial S. Nolan,[3] Nicolo L. Cabrera,[3] Jonas Marschall,[3] Michael J. Durkin,[3] and Laura R. Marks[3,5]

[1]Medical Scientist Training Program, Washington University in St. Louis School of Medicine, St. Louis, Missouri, USA; [2]Department of Infectious Diseases, Bern University Hospital, Inselspital, University of Bern, Bern, Switzerland; [3]Division of Infectious Diseases, Washington University in St. Louis School of Medicine, St. Louis, Missouri, USA; and [4]Department of Computational and Systems Biology, Washington University in St. Louis School of Medicine, St. Louis, Missouri, USA

Endocarditis*	Epidural abscess	Septic Arthritis	Osteo	+BC, 5+ days*	MRSA
65%	15%	24%	19%	32%	42%

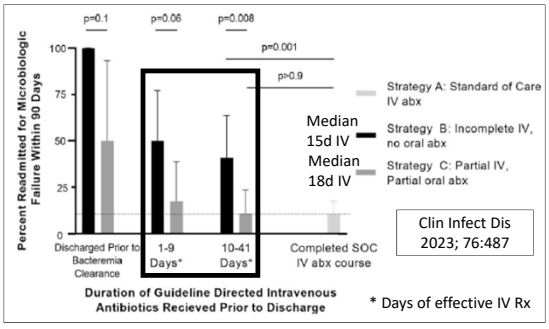
Clin Infect Dis 2023; 76:487

Outcomes of 3 Treatment Strategies

Outcomes	A: Standard of care IV N=122	B: Partial IV Discharged No PO N=36	C: Partial IV Discharged With PO N=69
Death, micro failure @ 90 days of D/C	11%	44%	13%
Readmission @ 90 days of D/C	31%	53%	26%

Clin Infect Dis 2023; 76:487

Readmissions with Treatment Failure



SABATO Trial: Oral (PO) Step-down vs IV Therapy for "Low Risk" SAB

Outcomes	PO (n=108)	IV (n=105)
SAB complication @ 90 days	14 (13%)	13 (12%)
Relapse	3 (3%)	4(4%)
Deep-seated infection	5 (5%)	8 (8%)
Death due to SAB	2(2%)	0
Missing/non-attributable death	8 (7%)/3 (3%)	5(5%)/1 (1%)

Lancet ID. 2024; 2024 Jan 17:S1473-3099(23)00756-9

Oral Therapy of S. aureus Bacteremia

- Only a single randomized clinical trial (RCT), somewhat low in quality
- Observation studies (Obs.) subject to selection bias, confounding by indication
  - Mortality and relapse rates consistently higher with IV!! Really!?
- Role in treatment of and efficacy for endocarditis, endovascular infections, complicated bacteremia, MRSA in particular is emerging
- May be an option for treatment of "low risk" patients, but there is a lack of standard definition
- **Infectious disease consultation strongly recommended for all SAB!**
- Prefer agents with good oral bioavailability: linezolid, TMP/SMX, fluoroquinolone + rifampin, clindamycin, anti-staphylococcal beta-lactam (?)

Combination Therapy of S. aureus BSI

Q5. Which one of the following combinations have been shown to improve mortality of patients with S. aureus bacteremia or native valve endocarditis?

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

Overview of Studies of Combination Therapy for SAB

Regimen	Study	Population	Comments	PMID
Adjunctive rifampin	RCT	MRSA, MSSA	No benefit	1929035 29249276
Adjunctive aminoglycoside	Obs., RCT	MRSA, MSSA	1 d shorter SAB, toxic	Various
Adjunctive dapto	RCT	MSSA	No benefit	32667982
Adjunctive β-lactam + vanco/dapto	RCT	MRSA	↑↑ AKI, higher mortality	32044943
Dapto + ceftaroline	Obs., aborted RCT	MRSA	Low quality data	30858203, 31640977, 31404468
Dapto + fosfomycin	RCT	MRSA	No mortality benefit, ↓ micro failure, ↑ AEs	32725216 32887985

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Dapto + fosfomycin	RCT	MRSA	No mortality benefit, ↓ micro failure, ↑ AEs	32725216 32887985

Consider for salvage therapy, not first line

De-Escalation of Combo Therapy for Complicated MRSA bacteremia

Outcome	Combo (n=66)	Mono (n=74)	P-value
Composite clinical failure	14 (21%)	8 (24%)	0.66
Recurrent bacteremia, 60d	2 (3%)	5 (7%)	0.45
In-patient mortality	1 (2%)	4 (5%)	1
Readmission, 60d	13 (20%)	13 (18%)	0.75
Duration of bacteremia, d	8 (IQR 6-11)	8 (IQR 5-12)	0.33
Adverse drug event	2 (4%)	1 (1)	0.47
Length of stay, d	26 (IQR 20-41)	24 (IQR 16-33)	0.08

Open Forum Infect Dis. 2021 Jun 22;8(7):ofab327.

Take-Home Points

- "Uncomplicated" Bacteremia is uncommon
  - 2 weeks of therapy for "uncomplicated" SAB, otherwise 4-6 weeks
- Community and HCA SAB do not differ in early mortality rates, but the former has a 2-fold increased risk of endocarditis
- Parenteral drugs of choice
  - MSSA: Nafcillin, cefazolin, penicillin
  - MRSA: Daptomycin, vancomycin
- Monotherapy is effective in most cases, reserve combination therapy for MRSA salvage
- Role of oral therapy is an evolving area

Thanks

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Bone and Joint Infections

Dr. Sandra Nelson

50 – Bone and Joint Infections

Speaker: Sandra Nelson, MD

Bone and Joint Infections

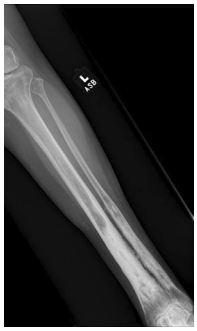
Sandra B. Nelson, MD
Assistant Professor of Medicine
Harvard Medical School

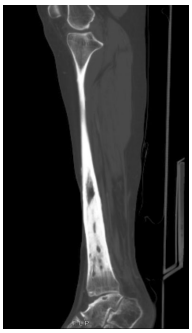
7/1/2024

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

  - None

Osteomyelitis





3

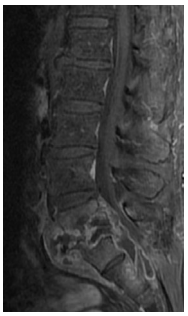
Osteomyelitis: Unifying Principles

- 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 increasingly supported
  - Longer oral suppression in setting of retained hardware

4

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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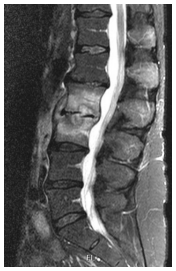
Case #1: Vote

What is the best next step in management?

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

6

Vertebral Osteomyelitis: diagnosis

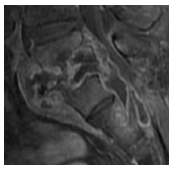


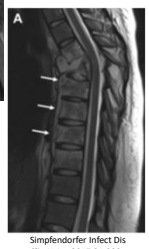
- Imaging pearls
  - MRI best for early infection; plain films and CT for subacute infection
  - Findings: disc hyperintensity, loss of disc height, bone marrow edema, endplate erosions, paraspinal and/or epidural collections
  - Infection almost always involves two contiguous vertebral bodies
- Blood 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 no sepsis or neurologic compromise
  - If negative, repeat percutaneous biopsy or consider open procedure

7

Pott's Disease

- Clinical:
  - 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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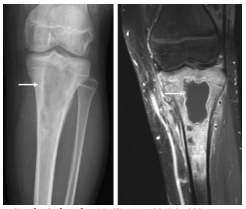
Brodie's Abscess: Subacute hematogenous osteomyelitis

- 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

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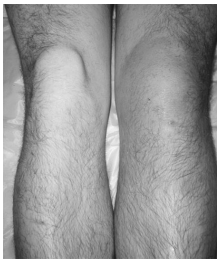
Septic Arthritis



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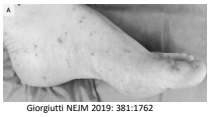
Septic Arthritis: Clinical Pearls

- 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

11

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

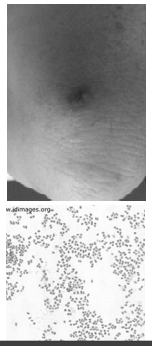


Giorgiutti NEJM 2019: 381:1762

12

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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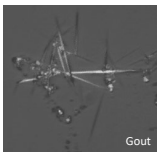
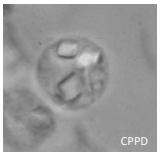
Crystalline arthritis: clinical pearls

- 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
  - Needle-shaped monosodium urate crystals
- Crystalline disease and septic arthritis can coexist (esp. CPPD)
  - CPPD rarely has cell count >30,000
  - CPPD rarely associated with high fever
  - Rhomboid-shaped calcium pyrophosphate dihydrate crystals





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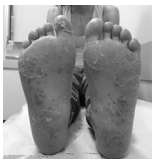
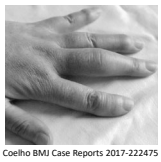
Masquerading as Infection…

- 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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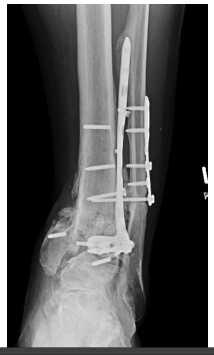
Osteofixation Infections



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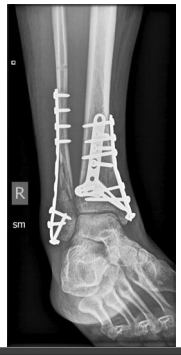
Case #2

- 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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Case #2: Vote

What are your next steps?

A. No surgical debridement; cefazolin for 6 weeks
B. Surgical debridement with hardware removal; 6 weeks of cefazolin
C. Surgical debridement with hardware removal; 6 weeks of cefazolin and rifampin
D. Surgical debridement without hardware removal; 6 weeks of cefazolin and rifampin
E. Surgical debridement with hardware exchange; 6 weeks of cefazolin and rifampin

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Osteofixation Infections

Goals: BOTH 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

20

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

21

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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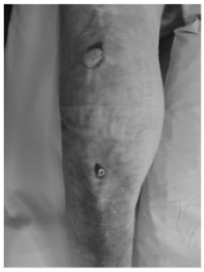
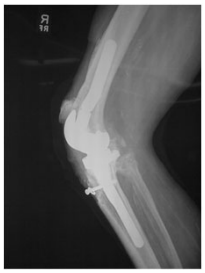
Prosthetic Joint Infection (PJI)





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PJI: Clinical presentations

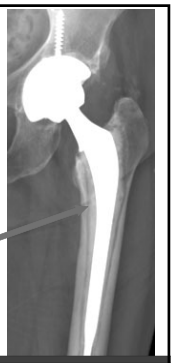
- Early surgical site infection (< 3months)
  - Acute onset of fever, joint pain, swelling
  - Caused by virulent organisms (*Staph aureus*)
- Delayed / Subacute infection (3 – 24 months)
  - Insidious onset of pain; fever is uncommon
  - Less virulent organisms: e.g. Coagulase-negative Staph, Cutibacterium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

24

PJI: 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



25

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	1-6 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	1-6 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

26

Case #3

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

27

Case #3: Vote

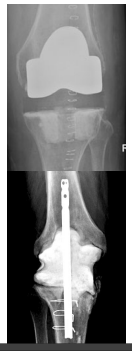
You are asked to provide recommendations about systemic and local antimicrobial therapy for the spacer. She has no antimicrobial allergies. You advise:

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

28

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.

30

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

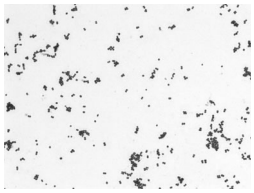
31

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

32

Microbiology of Musculoskeletal Infections



33

Case #5

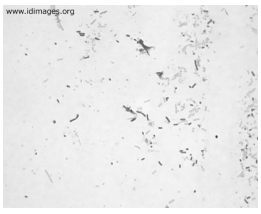
A 56-year-old man with poorly controlled diabetes presents to ED with a one-week history of low-grade fevers and gradually progressive right knee pain and swelling. He traveled to the Dominican Republic one month ago and had no illnesses while traveling. He last saw a dentist six months ago and denies 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.

34

Case #5: Vote

Culture growth at 3 days incubation



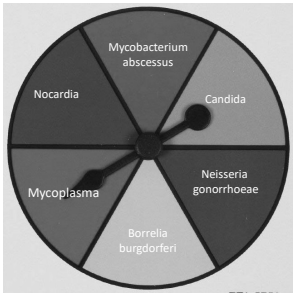
What is the most likely organism?

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

35

Guess the Bug

Musculoskeletal Edition



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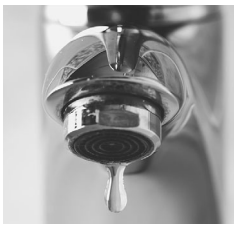
Salmonella Species

- 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

37

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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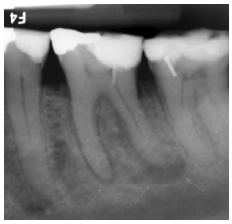
HACEK Organisms



- 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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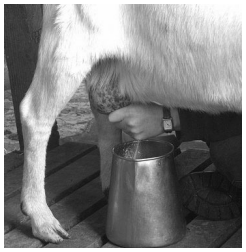
Brucella species



- 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

40

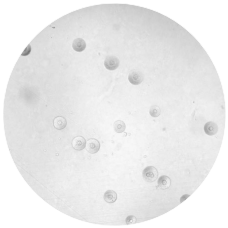
Pasteurella species

- Clinical
  - Direct inoculation (bite)
  - Hematogenous spread
  - Rapid clinical onset
- Epidemiology
  - Exposure to cats/dogs
  - Bite history not always elicited in hematogenous infection

41

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

43

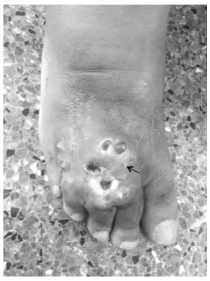
Non-tuberculous mycobacteria

- 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

44

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



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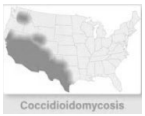
Endemic mycoses

- 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 coccidioides
  - May see concomitant pulmonary infection



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Thank you!

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BR5

Board Review Session 5

Drs. Masur (Moderator), Bennett, Chambers, Mitre, Nelson, and Rose

Board Review: Day 5

Moderator: Henry Masur, MD
Faculty: Drs. Bennett, Chambers, Mitre, Nelson, and Rose

7/1/2024

BOARD REVIEW DAY 5 2024

#53 **A 40-year-old white male was switched to a darunavir+ritonavir+tenofovir (TDF)/emtricitabine regimen, secondary to virologic failure and multiple PI mutations including I50L.**

He presents to the clinic 6 months after the switch for a routine evaluation.

Current CD4 = 350 and VL = <20 copies

1 of 4

BOARD REVIEW DAY 5 2024

#53 **Lipids drawn during the evaluation reveal**

- **Total cholesterol of 260 mg/dL**
- **LDL 130 mg/dL**
- **HDL 35 mg/dL**
- **Triglycerides 1200 mg/dL**

2 of 4

BOARD REVIEW DAY 5 2024

#53 **What is the most appropriate management for his hypertriglyceridemia?**

A) Switch patient to an atazanavir-based regimen

B) Increase exercise regimen

C) Fenofibrate

D) Fat-free diet

3 of 4

BOARD REVIEW DAY 5 2024

#54 **A 77-year-old woman with insulin-dependent diabetes is seen for 4 days of severe right ear pain.**

The pain is worsened by chewing.

She has no previous history of ear problems and has not had fever.

She says that the ear feels wet, and that there is a yellow stain on her pillowcase in the morning.

1 of 5

BOARD REVIEW DAY 5 2024

#54 **On examination, she is afebrile.**

The pinnae appear normal and symmetrical but tugging on the right external ear produces pain.

The right ear canal appears moist and is partially occluded by heaped-up granulation tissue.

The part of the tympanic membrane that can be seen is normal.

2 of 5

BOARD REVIEW DAY 5 INFECTIOUS DISEASE BOARD REVIEW 2024

#54 There is no mastoid tenderness and hearing is grossly normal.

There is mild facial nerve palsy on the right side.

The rest of the exam is unremarkable except for the sequelae of diabetes.

3 of 5

BOARD REVIEW DAY 5 INFECTIOUS DISEASE BOARD REVIEW 2024

#54 Pending culture results, which one of the following antimicrobials is most appropriate for this patient?

A) Ciprofloxacin

B) Amphotericin B

C) Clindamycin

D) Gentamicin ear drops

E) Amoxicillin-clavulanate

4 of 5

BOARD REVIEW DAY 5 INFECTIOUS DISEASE BOARD REVIEW 2024

#55 A 42 yo female who injects drugs is admitted with fever and chest pain of 4 days duration.

Past medical history is positive for several prior episodes of cutaneous abscesses not requiring hospitalization.

She takes no medications and is allergic to sulfa drugs.

There is a 4 out of 6 systolic murmur at the lower left sternal border.

1 of 5

BOARD REVIEW DAY 5 INFECTIOUS DISEASE BOARD REVIEW 2024

#55 Chest x-ray shows multiple bilateral nodular infiltrates consistent with septic pulmonary emboli.

Three blood cultures are drawn, and she is empirically treated with vancomycin and ceftriaxone.

The following day, hospital day 2, all three blood cultures are reported positive for Gram-positive cocci in clusters.

A transthoracic echocardiogram shows a 1.2 cm mobile mass on the posterior leaflet of the tricuspid valve.

2 of 5

BOARD REVIEW DAY 5 INFECTIOUS DISEASE BOARD REVIEW 2024

#55 Two blood cultures are drawn, and the ceftriaxone is discontinued.

The following day, the isolate from the admission blood cultures is identified as methicillin-susceptible Staphylococcus aureus (MSSA), resistant to penicillin, and erythromycin.

Vancomycin is discontinued and cefazolin is administered.

Serial daily blood cultures continue to be positive through hospital day 5. You are asked to see the patient to recommend salvage therapy.

3 of 5

BOARD REVIEW DAY 5 INFECTIOUS DISEASE BOARD REVIEW 2024

#55 Which one of the following drug regimens is most appropriate for treatment of this patient?

A) Cefazolin plus gentamicin

B) Daptomycin

C) Daptomycin plus ceftaroline

D) Nafcillin

E) Vancomycin

4 of 5

BOARD REVIEW DAY 5 INFECTIOUS DISEASE BOARD REVIEW 2024

#56 A 35-year-old male traveled outside of the United States for the first time, going on a safari to Botswana, Africa for 3 weeks.

5 days after returning from Botswana, he developed a fever to 39.1°C for 12 hours and comes to the Emergency Room. He also complains of malaise and headache.

His physical examination is normal. No splenomegaly is detected by physical examination.

1 of 4

BOARD REVIEW DAY 5 INFECTIOUS DISEASE BOARD REVIEW 2024

#56 CBC and chemistry panel are normal.

The astute ER physician finds out the patient did not take his malarone prophylaxis after the first week in Botswana.

The ER physician performs a blood smear for malaria: no parasites are seen by an experienced technician. A rapid test is also negative.

You are asked if additional evaluation for malaria is needed.

2 of 4

BOARD REVIEW DAY 5 INFECTIOUS DISEASE BOARD REVIEW 2024

#56 You recommend?

A) The initial blood smear that is negative rules out malaria as a cause of the fever

B) The initial rapid malaria test that is negative rule out malaria as a cause of fever

C) A rapid antibody test should be performed: together with a negative rapid antigen test, malaria would be ruled out as a cause of fever

D) Further testing with malaria smears and/or rapid test should be done every 12 hours for 2-3 days to rule of malaria

3 of 4

BOARD REVIEW DAY 5 INFECTIOUS DISEASE BOARD REVIEW 2024

#57 A 62-year-old woman enters the hospital and is scheduled for multiple tests to evaluate masses in her colon and liver that are suspected of being neoplastic.

She has previously been well and takes no drugs other than a statin and every other day aspirin.

She is afebrile, has a normal WBC, and her complaints and findings on exam are related to her hepatic lesions.

1 of 4

BOARD REVIEW DAY 5 INFECTIOUS DISEASE BOARD REVIEW 2024

#57 Six years prior to this admission the patient had a left shoulder replacement and two years ago she had a knee replacement.

Both joint replacements were uncomplicated, and she has not had any change in joint function over the past year.

2 of 4

BOARD REVIEW DAY 5 INFECTIOUS DISEASE BOARD REVIEW 2024

#57 For which of the following procedures should this patient receive antimicrobial prophylaxis to avoid infecting one of her prosthetic joints?

A) Bronchoscopy with transbronchial biopsy

B) Extraction of a decayed wisdom tooth

C) Colonoscopy with biopsy of a suspected carcinoma

D) Percutaneous liver biopsy

E) The patient does not need antimicrobial prophylaxis for any procedure

3 of 4

BOARD REVIEW DAY 5 INFECTIOUS DISEASE BOARD REVIEW 2024

#58 **A 16 yr old male high school student from suburban Alexandria, Virginia presented with episodes during the past three months when he felt like his heart was "bursting from his chest" when he was doing push-ups in gym class.**

This went away promptly when he stopped exercising. He said it didn't feel like skipped beats and was not associated with chest pain or dyspnea.

1 of 5

BOARD REVIEW DAY 5 INFECTIOUS DISEASE BOARD REVIEW 2024

#58 **He grew up in Iran, but his family has moved the USA four years previously.**

On exam, he was afebrile and appeared healthy.

A grade 3 systolic and diastolic murmur was heard at the left sternal border.

Echocardiogram found mitral stenosis and regurgitation, with a thickened mitral valve without vegetations and an enlarged left atrium.

2 of 5

BOARD REVIEW DAY 5 INFECTIOUS DISEASE BOARD REVIEW 2024

#58 **EKG showed first degree heart block with a PR interval of 300 msec and no extrasystoles.**

Routine chemistries and CBC were normal but CRP and ESR were elevated.

3 of 5

BOARD REVIEW DAY 5 INFECTIOUS DISEASE BOARD REVIEW 2024

#58 **Which of these tests might be helpful in diagnosis?**

A) Anticardiolipin IgG

B) Anti dsDNA

C) Anti Coxiella burnetii phase 2 IgG

D) Anti streptococcal DNase B

E) PCR on blood for Tropheryma whipplei

4 of 5

BOARD REVIEW DAY 5 INFECTIOUS DISEASE BOARD REVIEW 2024

#59 **A 56-year-old woman with poorly controlled type 2 diabetes mellitus presents with fever, rigors and near syncope. In the Emergency Room she is confused, hypotensive, and febrile to 38.5°C.**

Her WBC is 18,000 with 90% neutrophils.

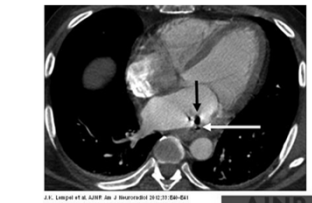
She is given bolus IV fluids for shock, started on vancomycin and piperacillin-tazobactam and admitted.

1 of 5

BOARD REVIEW DAY 5 INFECTIOUS DISEASE BOARD REVIEW 2024

#59 **CT showed air in her left atrium (see figure) and multiple brain abscesses.**

The left atrium shows air in the atrium (black arrow) and the esophagus (white arrow).



2 of 5

BOARD REVIEW DAY 5 INFECTIOUS DISEASE BOARD REVIEW 2024

#59 **Her past history is remarkable for a dental extraction one week prior.**

No prophylaxis was given.

Four weeks prior she had her second catheter radiofrequency ablation for atrial fibrillation.

3 of 5

BOARD REVIEW DAY 5 INFECTIOUS DISEASE BOARD REVIEW 2024

#59 **The most likely cause of this syndrome is:**

A) Aortic valve endocarditis
B) Atriobronchial fistula
C) Atrioesophageal fistula
D) Mucormycosis of the left atrium
E) Atrial myxoma

4 of 5

BOARD REVIEW DAY 5 INFECTIOUS DISEASE BOARD REVIEW 2024

#60 **A woman in her 60s presented with three months of non-productive cough, night sweats and a 10-pound weight loss.**

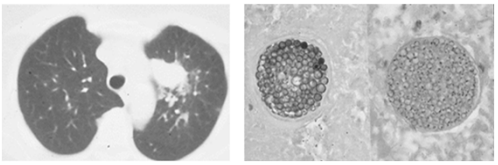
She had received empiric clarithromycin, but the symptoms persisted.

The patient had traveled in the past year to South America, Europe, Arizona, and Australia.

1 of 4

BOARD REVIEW DAY 5 INFECTIOUS DISEASE BOARD REVIEW 2024

#60 **A Chest CT showed a left upper lobe lung nodule. Pathology from a lung biopsy is shown.**



2 of 4

BOARD REVIEW DAY 5 INFECTIOUS DISEASE BOARD REVIEW 2024

#60 **The most likely diagnosis is which of the following?**

A) Histoplasmosis
B) Cryptococcosis
C) *Pneumocystis jirovecii*
D) Coccidioidomycosis
E) Paracoccidioidomycosis

3 of 4

BOARD REVIEW DAY 5 INFECTIOUS DISEASE BOARD REVIEW 2024

#61 **A 25-year-old man who uses injection drugs presents to the hospital with low back pain and tenderness. These symptoms began 3 days earlier.**

He denies lower extremity weakness.

On physical examination, his temperature is 102°F, pulse is 120/minute, and his blood pressure is normal.

The physical exam reveals tenderness on palpation of his lumbosacral spine region. There is no evidence of lower extremity weakness.

1 of 4

BOARD REVIEW DAY 5 INFECTIOUS DISEASE BOARD REVIEW 2024

#61 He undergoes an MRI with contrast of his entire spine, which reveals evidence of discitis at L1-L2 disc space, and evidence of osteomyelitis of the inferior L1 and superior L2 vertebrae, and the presence of a 1 cm ventral epidural abscess.

He is started on therapy with vancomycin and cefepime.

Blood cultures reveal gram-positive cocci, subsequently identified as methicillin-resistant Staphylococcus aureus. Cefepime is discontinued.

2 of 4

BOARD REVIEW DAY 5 INFECTIOUS DISEASE BOARD REVIEW 2024

#61 Which of the following is the most appropriate next step in management?

A) Continue vancomycin and monitor his clinical examination and blood culture results

B) Change therapy to ceftaroline and daptomycin

C) Consult interventional radiology for aspiration of the epidural abscess to obtain microbiologic data

D) Consult neurosurgery for laminectomy and drainage of the epidural abscess

3 of 4

BOARD REVIEW DAY 5 INFECTIOUS DISEASE BOARD REVIEW 2024

#62 A 36-year-old healthy man presents with a 10-month history of ulcerating skin lesions. These initially started on his right ear following a minor trauma.

He subsequently developed similar lesions on his scalp and right wrist. He was given a course of Keflex with no response.

He denies fevers or systemic symptoms but is bothered by the cosmetic appearance of these lesions.

1 of 5

BOARD REVIEW DAY 5 INFECTIOUS DISEASE BOARD REVIEW 2024

#62 He works as a field biologist performing reptile surveys. In the months preceding onset of the initial skin lesion, he was working in Mexico and Guatemala.

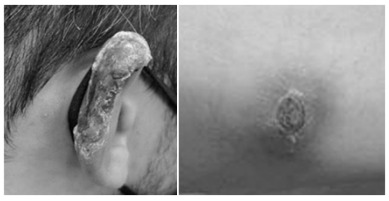
He denies known arthropod assault at the site of the lesions but does note he is frequently bitten by mosquitos and other insects while working in the field.

He is afebrile and vital signs are within normal limits.

2 of 5

BOARD REVIEW DAY 5 INFECTIOUS DISEASE BOARD REVIEW 2024

#62 His skin lesions are shown below.



CBC with differential and CMP are within normal limits. HIV antibody testing is negative.

3 of 5

BOARD REVIEW DAY 5 INFECTIOUS DISEASE BOARD REVIEW 2024

#62 What is the most likely cause of this patient's lesions?

A) Yaws

B) *Leishmania mexicana*

C) *Paracoccidioides brasiliensis*

D) *Pyoderma gangrenosum*

E) *Mycobacterium leprae*

4 of 5

BOARD REVIEW DAY 5 2024

#63 A 46-year-old male with poorly controlled diabetes and obesity presents to the emergency department with fever and erythema involving his left forefoot.

He has had diabetes mellitus for 24 years; his last A1C was 10.4%.

He works in construction and first noted skin breakdown over the medial metatarsophalangeal joint three weeks ago that he attributed to irritation from a new pair of shoes. The day prior to presentation he noted increased pain, swelling, and drainage on his socks.

1 of 5

BOARD REVIEW DAY 5 2024

#63 He takes metformin, semaglutide, atorvastatin, and valsartan.

He does not have a prior history of foot infections. He has no history of MRSA infection.

He lives in Delaware with his wife and two young children, all of whom are well.

In the ED, he was afebrile and normotensive. There was an ulcer involving the medial metatarsophalangeal joint that measured 1.5 wide and 0.6 cm deep. There was moist drainage on the sock but no expressible purulence and no malodor.

2 of 5

BOARD REVIEW DAY 5 2024

#63 The dorsalis pedis pulse was faint, and probe-to-bone test was negative. There was tender erythema that involved the forefoot and midfoot.

Plain films demonstrated no cortical erosion and no soft tissue gas.

ESR and CRP are elevated at 42 mm/Hr and CRP 84 mg/L.

3 of 5

BOARD REVIEW DAY 5 2024

#63 What do you recommend as the best next step?

A) Discharge from the emergency department on oral amoxicillin-clavulanate

B) Hospitalization and initiation of ampicillin-sulbactam after wound cultures are collected

C) Hospitalization and initiation of vancomycin and piperacillin-tazobactam after wound cultures are collected

D) Addition of topical silver sulfadiazine to the wound in addition to systemic antibiotic therapy

E) Surgical evaluation for debridement

4 of 5

BOARD REVIEW DAY 5 2024

#64 A 38-year-old male is evaluated in the emergency room for onset of abdominal pain and vomiting starting 4 hours ago.

He does not have any significant past medical history but has been drinking 4-5 shots of vodka daily for the past 2 years.

On examination, his temperature is 100.1°F, pulse 100, blood pressure is 140/80 and respiration of 18. Liver is palpable 1 cm below right costal margin and there is pain on deep palpation at the epigastrium.

1 of 5

BOARD REVIEW DAY 5 2024

#64
- WBC 9,000 cells/L
- Hemoglobin 14 g/dl
- amylase 450 (nl 23-85) U/L,
- lipase 643 (nl 0-160) U/L
- AST 45 (nl 10-40) U/L
- ALT 65 (nl 7-56) U/L
- ALK 120 (nl 20-140) U/L
- TBili 1.1 mg/dL (nl 0.3-1.3)
- CRP 23 (nl <0.5) mg/dL

2 of 5

BOARD REVIEW DAY 5 INFECTIOUS DISEASE BOARD REVIEW 2024

#64 **Plain film of the abdomen revealed an ileus.**

CT of the abdomen showed diffusely enlarged pancreas with evidence of phlegmonous changes.

3 of 5

BOARD REVIEW DAY 5 INFECTIOUS DISEASE BOARD REVIEW 2024

#64 **Which of the following is the most appropriate initial management?**

A) Upper endoscopy
B) Surgical exploration
C) Hydration and pain control
D) IV antibiotics to cover Gram-negative and anaerobic bacteria
E) ERCP or MRCP (endoscopic cholangiopancreatography or magnetic resonance cholangiopancreatography)

4 of 5

BOARD REVIEW DAY 5 INFECTIOUS DISEASE BOARD REVIEW 2024

#65 **A 68-year-old diabetic woman is admitted for pneumonia.**

- **A rapid RT-PCR test is positive for influenza A**
- **Sputum Gram-stain shows Gram-positive cocci in clusters**
- **The culture grows methicillin-resistant Staphylococcus aureus susceptible to vancomycin, daptomycin, linezolid, and trimethoprim-sulfamethoxazole (TMP/SMX)**

1 of 4

BOARD REVIEW DAY 5 INFECTIOUS DISEASE BOARD REVIEW 2024

#65 **She has been receiving vancomycin 1 gram once daily for the past 3 days based on a calculated creatinine clearance of 45 ml/min and has a trough concentration of 22 µg/ml.**

The primary physician is concerned because a vancomycin susceptibility result has returned with MIC = 2 µg/ml and has asked you to recommend an alternative agent.

2 of 4

BOARD REVIEW DAY 5 INFECTIOUS DISEASE BOARD REVIEW 2024

#65 **Which one of the following alternative regimens would you recommend?**

A) Daptomycin 6 mg/kg IV once daily
B) Linezolid 600 mg PO twice daily
C) Telavancin 7.5 mg/kg IV once daily
D) TMP-SMX 10 mg/kg (TMP component) per day in 2 divided doses

3 of 4

51

Lots of Protozoa

Dr. Edward Mitre

51 – Lots of Protozoa

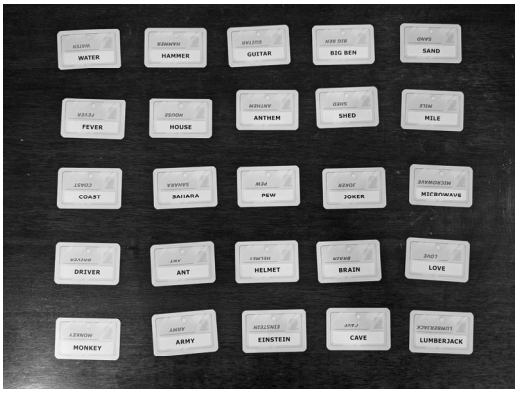
Speaker: Edward Mitre, MD

Lots of Protozoa

Edward Mitre, MD
Rockville, MD

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

  - None



Protozoa

Protozoa - Extraintestinal	Protozoa - Intestinal
Apicomplexa Plasmodium (Babesia) (Toxoplasma)	**Apicomplexa** Cryptosporidium Cyclospora Cystoisospora
Flagellates Leishmania Trypanosomes (Trichomonas)	**Flagellates** Giardia Dientamoeba
Amoebae Naegleria Acanthamoeba Balamuthia	**Amoebae** Entamoeba
	Ciliates Balantidium

Maybe Not Protozoa **Kingdom Fungi:** Microsporidiosis agents
Domain SAR: Blastocystis

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Maybe Not Protozoa **Kingdom Fungi:** Microsporidiosis agents
Domain SAR: Blastocystis

Question 1: A 54 yo woman presents with fever, chills, and oliguria one week after travel to Malaysia.

Vitals: **39.0º** C, HR 96/min, RR 24/min, **BP 86/50**

Labs: Hct 31%, platelets 14,000/µl, Cr of 3.2 mg/dL.

Peripheral blood smear has intraerythrocytic forms that are morphologically consistent with *Plasmodium malariae*.

The most likely infectious agent causing the patient's illness is:

A. Plasmodium malariae
B. Plasmodium knowlesi
C. Plasmodium vivax
D. Plasmodium falciparum
E. Babesia microti

P. knowlesi

morphologically similar to *P. malariae*

usually a parasite of long-tailed macaques

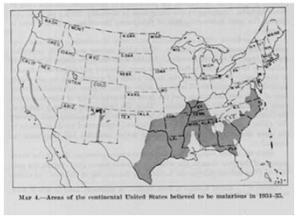
increasingly recognized in Myanmar, Philippines, Indonesia, and Thailand

causes high parasitemia

highly morbid and can be lethal

MALARIA

one of the most important pathogens in the history of the world



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

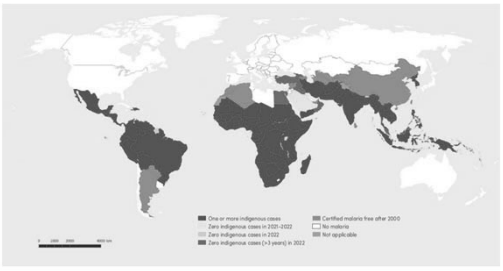
In 1775 the Continental Congress purchased quinine for George Washington's troops

Disease Burden - WHO 2023 World Malaria Report

249 million cases

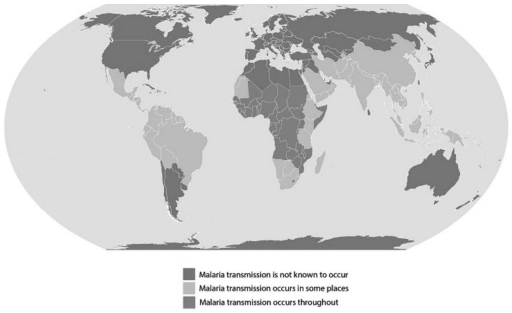
608,000 deaths

U.S. ~ 2000 cases reported each year



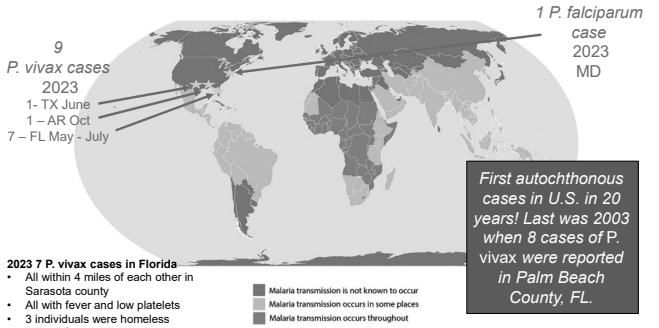
WHO: World Health Organization.
*Malaysia has a significant number of indigenous malaria cases caused by *Plasmodium knowlesi* infection.
†Countries with zero indigenous cases for at least 3 consecutive years are considered to have eliminated malaria. In 2022, Malaysia reported zero indigenous cases caused by human *Plasmodium* species for the fifth consecutive year and Cabo Verde reported zero indigenous cases for the fourth year. Belize was certified malaria free in 2021, following 4 years of zero malaria cases.

MALARIA EPIDEMIOLOGY – CDC map from a few years ago…what's missing?



https://www.cdc.gov/malaria/about/distribution.html

2023 U.S. Malaria Cases



First autochthonous cases in U.S. in 20 years! Last was 2003 when 8 cases of P. vivax were reported in Palm Beach County, FL.

2023 7 P. vivax cases in Florida
- All within 4 miles of each other in Sarasota county
- All with fever and low platelets
- 3 individuals were homeless
- April 20th there had been an imported P. vivax case
- CDC testing of 407 Anopheles mosquitoes → 3 A. crucians were PCR+

https://www.cdc.gov/mmwr/volumes/72/wr/mm7236a1.htm

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

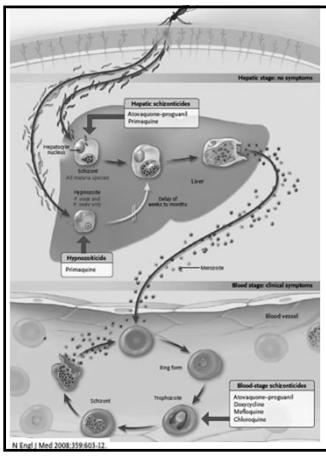
infected individuals can rapidly progress from appearing well to being critically ill

---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	



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)

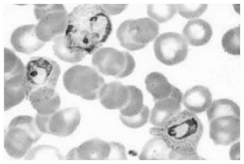
} Often seen in children of endemic countries. Adults more often get multiorgan failure.

- 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%.

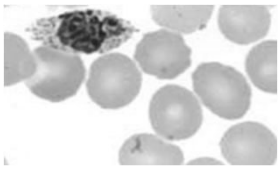
NOTE: in the absence of end organ damage, parasitemia ≥ 5% is often used as the cut-off to treat for severe malaria in the U.S.

P. vivax or ovale



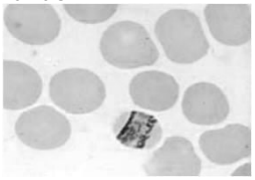
- intracellular Schüffner's dots
- enlarged infected cells

P. ovale



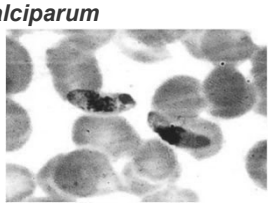
- elongated or oval
- 6-12 merozoites (vs 12-24 for vivax)

P. malariae



- band form
  (also seen in *P. knowlesi*)

P. falciparum



- Banana shaped gametocyte

Malaria: Diagnosis

Rapid diagnostic antigen tests
→ sensitivity > 90% for P. falciparum
(about 85% for P. vivax, lower for P. knowlesi and P. ovale)

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
→ Retest suspected patients that initially test negative

*Increasing false negative cases occurring worldwide due to mutations in HRP2

Question 2: A 33-year-old woman is traveling to Uganda to do field studies in anthropology. She is two months pregnant. Which of the following do you prescribe for malaria prophylaxis?

A. Doxycycline
B. Chloroquine
C. Mefloquine
D. Atovaquone/proguanil
E. No prophylaxis

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***

51 – Lots of Protozoa

Speaker: Edward Mitre, MD

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 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

4) Hypoglycemia and ARDS are complications that can occur during treatment of malaria. ARDS sometimes develops even as pt improving from malaria.

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 with primaquine or tafenoquine

→ 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 UP DOSING 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, can calculate total dose 6 mg/kg and then extend duration of 30 mg daily doses until total goal met
-> if G6PD deficient consider weekly chloroquine x 1 year

- **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/hcp/clinical-guidance/treatment-uncomplicated.html

* 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

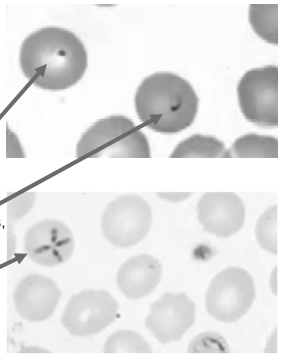
- Ixodes ticks in Northeast and upper midwest
→ co-infection with Lyme and Anaplasma
- Transfusion
(Ab screening tests approved by FDA in 2018)

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)

Amoebae
Naegleria
Acanthamoeba
Balamuthia

Protozoa - Intestinal

Apicomplexa
Cryptosporidium
Cyclospora
Cystoisospora

Flagellates
Giardia
Dientamoeba

Amoebae
Entamoeba

Ciliates
Balantidium

Maybe Not Protozoa **Kingdom Fungi:** Microsporidiosis agents
Domain SAR: Blastocystis

Leishmaniasis

> obligate intracellular protozoan infection
> transmitted by sand flies (noiseless, active in evenings)

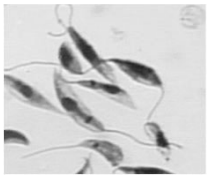
Lutzomyia
New world leishmaniasis

Phlebotomus
Old world leishmaniasis

Leishmania life cycle – Two stages

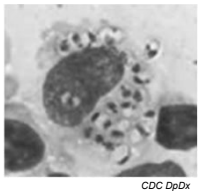
Promastigote

extracellular, in sand fly
2 µm wide x 20 µm long
- flagella
- large central nucleus
- band shaped kinetoplast



Amastigote

Intracellular (macrophages)
Round or oval
Wright-Giemsa:
- dark-purple nucleus
- small rod shaped kinetoplast



CDC DpDx

Question 3: A 42 yo man from Bolivia presents with nasal stuffiness and is found to have nasal septal perforation. Biopsy demonstrates intracellular amastigotes consistent with Leishmania.

Which is the most likely species?

A. L. mexicana
B. L. braziliensis
C. L. peruviana
D. L. infantum chagasi
E. L. major

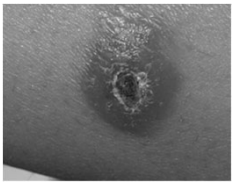
Leishmania taxonomy and disease simplified

	Cutaneous	Mucosal	Visceral
NEW WORLD			
L. mexicana complex	X		
L. braziliensis	X	X	
L. infantum chagasi			X
OLD WORLD			
L. tropica	X		
L. major	X		
L. donovani			X
L. infantum chagasi			X

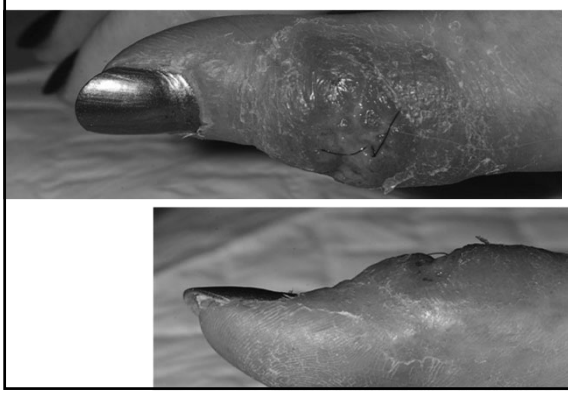
*note: ***L. braziliensis*** is in the Viannia subgenus. ***L. V. guyanensis*** and ***L. V. panamensis*** also cause mucosal disease. ***L. peruviana*** DOES NOT

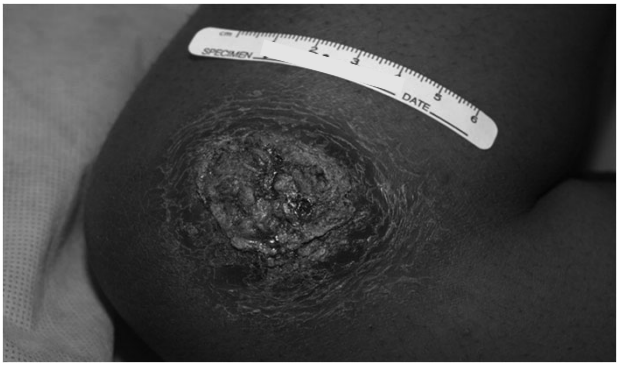
Cutaneous Leishmaniasis – Clinical Presentation

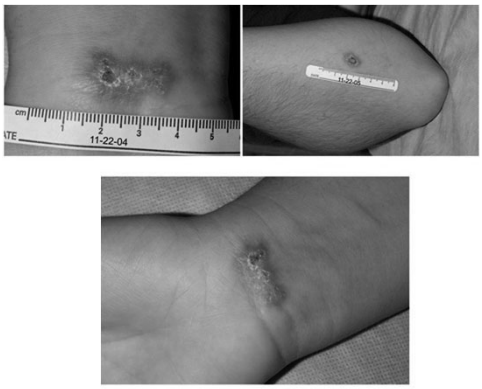
- **papule → nodule → ulcerative lesion → atrophic scar**
  - **ulcerative lesion may have:**
    - **induration,**
    - **scaliness**
    - **central depression**
    - **raised border**

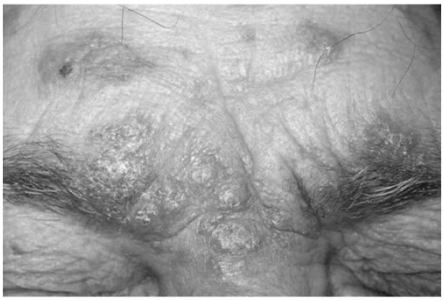


- **takes weeks to months to develop**
- **usually painless, unless superinfected**
- **most lesions will eventually resolve on their own**









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

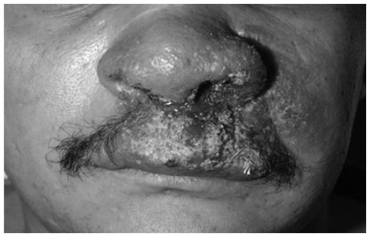
local: heat with radiotherapy (FDA approved), cryotherapy, intralesional therapy
systemic
oral: miltefosine for certain species, especially New World CL species
ketoconazole, fluconazole (off-label)
IV: liposomal amphotericin B (off-label)
pentavalent antimony *(meglumine antimoniate, ASTMH website has instructions for obtaining on IND from Sanofi)*

*****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 persistent disease that can reactivate
TNF blockade, HIV CD4 < 200

- wks/months of fevers, chills, hepatosplenomegaly
- pancytopenia & hypergammaglobulinemia

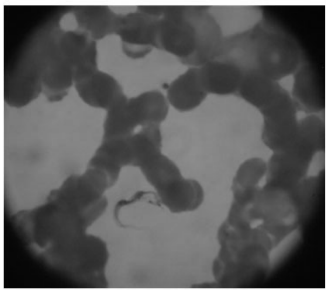
Diagnosis: PCR, culture, or histopathology for intracellular amastigotes
→ bone marrow aspirate preferred, can also check LN, spleen, or buffy coat antibody to rK39 recombinant Ag (dipstick test)

Treatment: liposomal ampho B (FDA approved)
miltefosine (oral) FDA approved for *L. donovani*
(combination treatment for L. donovani in people living with HIV in SE Asia)

51 – Lots of Protozoa

Speaker: Edward Mitre, MD

Question 4: A 41 yo woman presented to a local emergency department with a one day history of fever associated with swelling and redness in her groin four days after returning from safari in Tanzania. Peripheral blood smear is obtained.



What is the most likely diagnosis?

A. Leishmania donovani
B. Plasmodium vivax
C. Trypanosoma brucei
D. Wuchereria bancrofti
E. Leptospira interrogans

African Trypanosomiasis (sleeping sickness)

Vector = tse tse fly (Glossina sp)

Trypanosoma brucei gambiense (W. Africa)
- humans as reservoirs
- progression over many months

Trypanosoma brucei rhodesiense (E. Africa)
- cattle and game park animals as reservoirs
- progression over weeks

DISEASE
within 5 days: chancre at Tse Tse fly bite
regional lymphadenopathy

for weeks: fever, hepatosplenomegaly, lymphadenopathy, faint rash, headache

late: mental status changes, terminal somnolent state

African Trypanosomiasis – Lab findings

Non-specific lab findings
- anemia
- thrombocytopenia
- elevated IgM
- hypergammaglobulinemia

Diagnostic lab findings
- detection of parasite in lymph node, circulating blood, or CSF

-->do FNA of lymph node while massaging node, then push out the aspirate onto a slide and immediately inspect under 400x power. Trypanosomes can be seen moving for 15-20minutes, usually at edge of the coverslip

- a card agglutination test that detects T.b.gambiense sp. antibodies.
  -->V. sensitive (94-98%), but poor specificity
  --> can get false +s in pts with Schisto, filaria, toxo, malaria

African Trypanosomiasis - Life Cycle

Q. Why are Trypanosoma brucei infections associated with persistently elevated IgM levels?

African 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

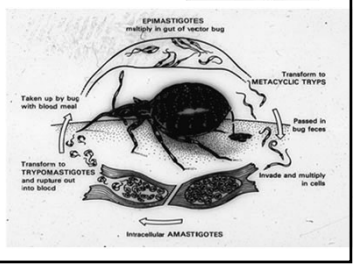
July 16, 2021: Oral fexinidazole FDA approved for T. gambiense

Notes: 1) Melarsoprol associated with ~5% death rate due to reactive encephalopathy.
2) This is reduced by co-administration of corticosteroids.

51 – Lots of Protozoa
Speaker: Edward Mitre, MD

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



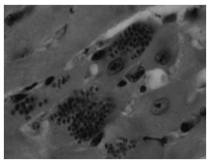
- oral ingestion of food and drinks contaminated with reduviid bugs or the feces of those bugs is a major route of infection
  (acai and sugar cane juice)

Chagas – Clinical Disease

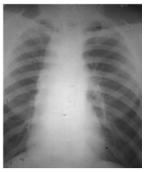
Acute (starts 1 week after infection, can persist for 8 weeks)
- fever
- local lymphadenopathy
- unilateral, painless periorbital edema

Indeterminate stage
- serology positive, no evidence of disease

Chronic

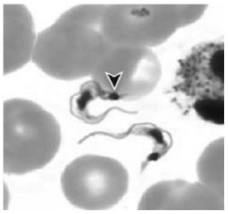


dilated cardiomyopathy, R>L
(CHF, syncope, arrythmia)



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

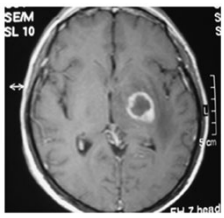
Treatment

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

Apicomplexa
- Plasmodium
- Babesia
- (Toxoplasma)

Flagellates
- Leishmania
- Trypanosomes
- (Trichomonas)

Amoebae
- Naegleria
- Acanthamoeba
- Balamuthia

Protozoa - Intestinal

Apicomplexa
- Cryptosporidium
- Cyclospora
- Cystoisospora

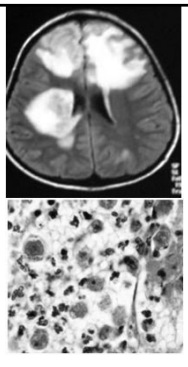
Flagellates
- Giardia
- Dientamoeba

Amoebae
- Entamoeba

Ciliates
- Balantidium

Maybe Not Protozoa **Kingdom Fungi:** Microsporidiosis agents
Domain SAR: Blastocystis

Free-living amoebae



Naegleria fowleri
- warm freshwater exposure
- enters through olfactory neuroepithelium
- fulminant meningoencephalitis
- immunocompetent children/young adults

Acanthamoeba
- found in soil and water
- enter through lower respiratory tract or broken skin
- subacute granulomatous encephalitis
- immunocompromised hosts
- chronic granulomatous keratitis (contact lens, LASIK)

Balamuthia mandrillaris
- likely enters through lower respiratory tract or broken skin
- transmission by solid organ transplantation has been reported
- subacute granulomatous encephalitis
- normal and immunocompromised hosts

Outcome → often fatal (amphotericin B, azoles, pentamidine, others tried)

51 – Lots of Protozoa

Speaker: Edward Mitre, MD

Protozoa

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Maybe Not Protozoa **Kingdom Fungi:** Microsporidiosis agents
Domain SAR: 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

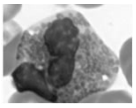
Intestinal Apicomplexa: clinical clues

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!

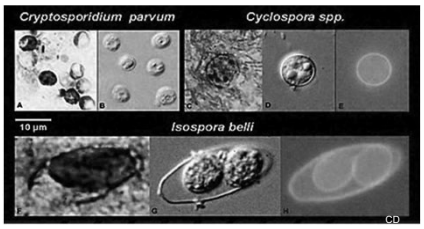
- abrupt onset with nausea, vomiting, and fever early
- anorexia, weight loss, fatigue late in course
- food associated outbreaks: raspberries, lettuce, herbs
- esp. Nepal, Peru, Guatemala

Cystoisospora belli
- no animal reservoirs known
- watery diarrhea
- may be associated with a peripheral eosinophilia!
  (the ONLY intestinal protozoa that does this)



Intestinal Apicomplexa 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

51 – 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

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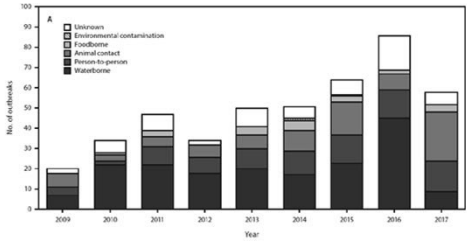


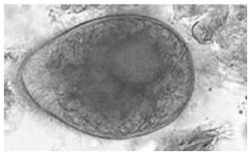
"The number of reported outbreaks has increased an average of approximately 13% per year."

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?

A. Balantidium coli
B. Entamoeba histolytica
C. Giardia lamblia
D. Dientamoeba fragilis
E. Endolimax nana

Balantidium coli

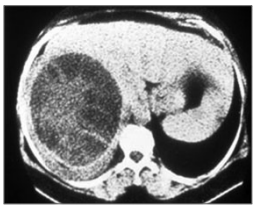


CDC DpDx

- the only ciliated pathogen of humans!
- largest protozoan pathogen of humans!
  (about 70 µm wide and up to 200 µm long)
- found worldwide, especially Central and S. America, S.E. Asia, and Papua New Guinea
- associated with eating food/water contaminated with pig feces
- Symptoms: most people asymptomatic
  can cause colitis with abdominal pain, weight loss, +/- diarrhea
  (especially in malnourished and immunocompromised)
- Treatment: tetracycline (!) or metronidazole

Entamoeba histolytica

- strictly human pathogen
- fecal/oral (contaminated food/water)
- cysts = infective stage
- trophozoites = active form, tissue-destructive



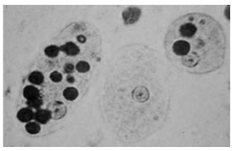
clinical presentations
- asymptomatic
- traveler's diarrhea
- colitis
  sharp abdominal pain
  bloody diarrhea
  fever
  flask-shaped ulcerations
  > onset can occurs weeks to months after travel
- ameboma
- liver and brain abscesses, esp in young men, usually 2-5 months after travel

Entamoeba histolytica

Diagnosis

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%)



E. histolytica trophozoites with ingested RBCs.

Stool antigen testing > 85% sensitive for intestinal disease

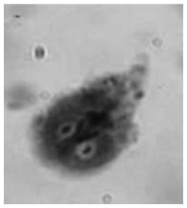
Serology 95% sensitive for liver abscess, 85% sensitive for intestinal infection

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

51 – Lots of Protozoa

Speaker: Edward Mitre, MD

Giardia duodenalis - *described by Antony van Leeuwenhoek in 1681!*



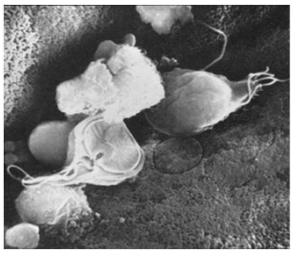
Flagellated protozoan
- fecal/oral via ingestion of cyst form in food/water
- cyst is chlorine resistant
- cysts from humans (beavers, muskrats)

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"

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)

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- Acanthamoeba
- Balamuthia

Protozoa - Intestinal

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- Cryptosporidium
- Cyclospora
- Cystoisospora

Flagellates
- Giardia
- Dientamoeba

Amoebae
- Entamoeba

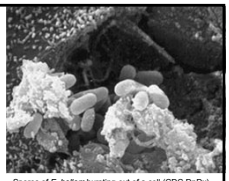
Ciliates
- Balantidium

Maybe Not Protozoa

Kingdom Fungi: Microsporidiosis agents
Domain SAR: Blastocystis

Microsporidia – obligate intracellular fungi!

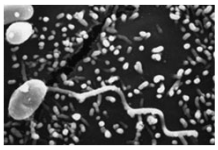
- Produce extracellular, 1-2 micron, infective spores
- Spores have a coiled organelle called a polar tubule
- After ingestion, the spore germinates and the polar tubule is used to inject sporoplasm into a host cell



Spores of *E. hellem* bursting out of a cell (CDC DpDx)

Enterocytozoon bieneusi
- watery diarrhea
- biliary disease (cholangitis, acalculous cholecystitis)

Encephalitozoon intestinalis
- watery diarrhea
- biliary disease
- disseminated disease (liver, kidney, lung, sinuses)



Polar tubule inserted into a eukaryotic cell (CDC DpDx)

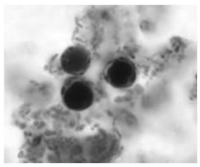
Encephalitozoon cuniculi, hellem
- can cause disseminated disease of multiple organs, plus eye

Many species (including *Vittaforma corneae*): punctate keratoconjunctivitis (contact lens use, after eye surgery, bathing in hot springs)

DIAGNOSIS: modified trichrome stain, Calcofluor white, IFA
TREATMENT: albendazole (not effective for *E. bieneusi*)

Blastocystis

What is it?



Blastocystis cyst-like forms , trichrome (CDC DpDx)

Currently classified as a protozoa.

Forms are 5-40 microns wide.
Anaerobic. Eukaryotic.
- cystic, ameboid, granular, and vacuolar forms

Often the most common eukaryotic organism found in human stool samples

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)

51 – Lots of Protozoa

Speaker: Edward Mitre, MD

Protozoan infections that can reactivate in the severely immunocompromised

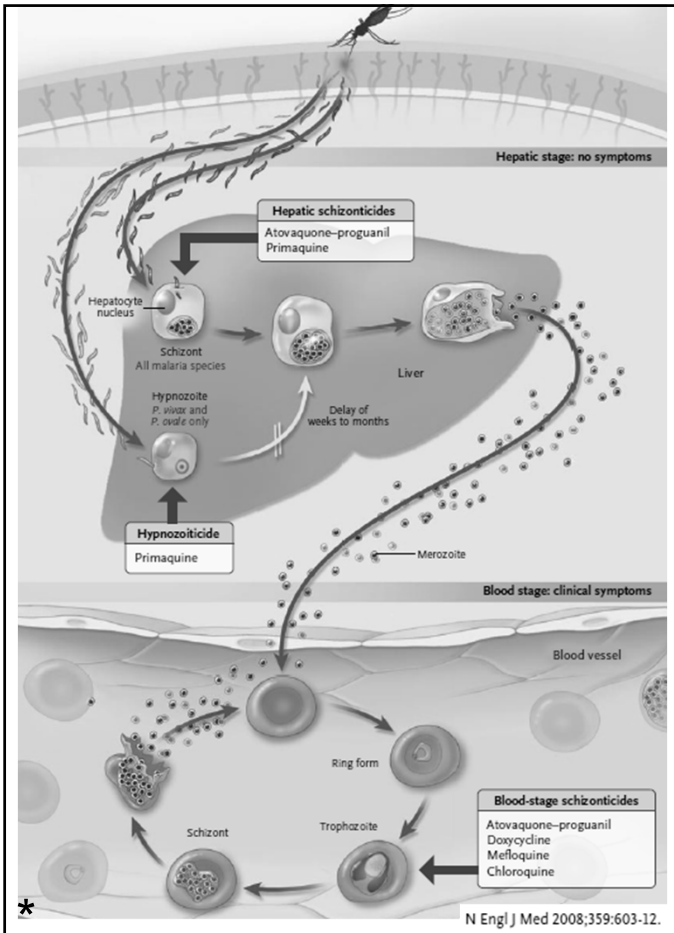
- Toxoplasmosis
  - encephalitis with mass lesions
  - pneumonitis
  - retinitis
- Leishmania
  - reactivation of visceral and cutaneous reported
  - visceral with fever, hepatosplenomegaly, pancytopenia
- Chagas
  - encephalitis with mass lesions
  - hepatosplenomegaly and fevers
  - myocarditis in 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

Good luck on the exam!

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

52

Worms That Could be on the Exam

Dr. Edward Mitre

52 – Worms That Could be on the Exam

Speaker: Edward Mitre, MD

IDBR INFECTIOUS DISEASE BOARD REVIEW AUGUST 17-21, 2024

Worms and More Worms

Edward Mitre, MD
Rockville, MD

IDBR INFECTIOUS DISEASE BOARD REVIEW AUGUST 17-21, 2024

- **Disclosures of Financial Relationships with Relevant Commercial Interests**
  - None

Question #1

28 yo F
- recurrent abdominal cramps for several months
- just returned to the U.S. after living in Tanzania for one year
- colonoscopy reveals small white papules
- biopsy reveals an egg with eosinophilic granulomatous inflammation

Most likely diagnosis?

A. *Entamoeba histolytica*
B. *Ascaris lumbricoides*
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
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- *Echinococcus multilocularis*

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- *Necator americanus*
- *Trichuris trichiura*
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- *Paracapillaria philippinensis*
- *Enterobius vermicularis*

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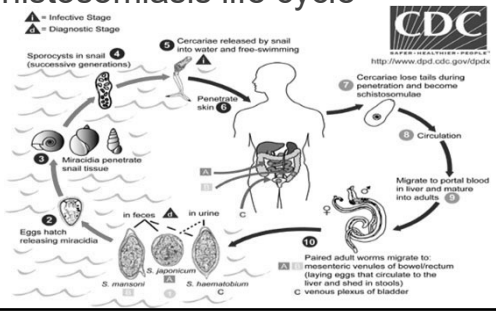
- *Toxocara canis/cati*
- *Baylisascaris procyonis*
- *Gnathostoma spinigerum*

Schistosomiasis life cycle



Acute Schistosomiasis

Cercarial dermatitis (Swimmer's itch)
- urticarial plaques and pruritic papules
- occurs upon reexposure to cercariae penetrating skin in a sensitized individual
- symptoms develop minutes to days after water exposure
- can occur with human or avian schistosomes

Katayama fever
- fever, myalgias, abdominal pain, headache, diarrhea, urticaria
- occurs in previously unexposed hosts.
- symptoms typically start 3 - 8 weeks after water exposure
- eosinophilia, elevated AST and alkaline phosphatase
- no reliable way to confirm diagnosis acutely as serology and stool O/P frequently negative

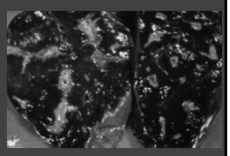
Chronic Schistosomiasis

Intestinal and hepatosplenic disease (**Sm**, Sj, Si, Smk, Sh/b)
- granulomatous colitis
- portal hypertension

Genitourinary disease (**Sh**, Sh/b)
- granulomatous cystitis
- bladder fibrosis and cancer
- obstructive uropathy

Pulmonary Disease (Sm, Sh, Sj)

CNS disease (any, most often Sj)
- eggs to spinal cord or brain
- in spinal cord: often causes transverse myelitis
- in brain (less common): one or more intracerebral inflammatory lesion(s)



Major Schistosoma species
- *S. mansoni (Sm)*
- *S. japonicum (Sj)*
- *S. intercalatum (Si)*
- *S. mekongi (Smk)*
- *S. haematobium (Sh)*
- *S. haematobium/S. bovis hybrid (Sh/b)**

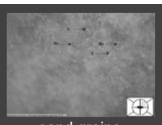
**primarily in W. Africa, with endemicity in Corsica, France since 2013*

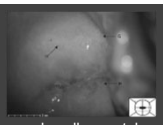
Schistosoma genital disease

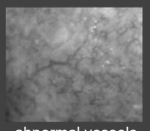
primarily due to *S. haematobium*

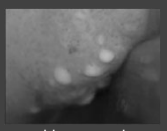
women
- vaginal and cervical lesions)
- pelvic pain
- dysmenorrhea
- dyspareunia
- post-coital bleeding
- endometritis/salpingitis

men
- epididymitis
- prostatitis


sand grains


sandy yellow patches

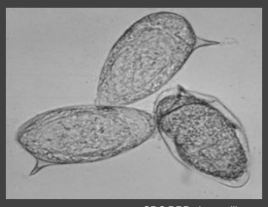

abnormal vessels


rubbery papules

WHO Female Genital Schistosomiasis Pocket Atlas

Schistosome eggs

S. mansoni
(lateral spine)


CDC DPDx image library

S. haematobium
(terminal spine)


CDC DPDx image library

Question #2

A person that ingests food contaminated with Taenia solium eggs is at risk of which of the following?

A. HTLV-1 infection
B. bladder cancer
C. vitamin B12 deficiency
D. seizures
E. anemia

Major Helminth Pathogens

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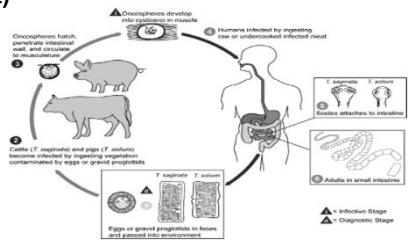
- *Loa loa*
- *Trichinella spiralis*
- *Angiostrongylus cantonensis*
- *Anisakis simplex*
- *Toxocara canis/cati*
- *Baylisascaris procyonis*
- *Gnathostoma spinigerum*

Taenia lifecyle for tapeworm infection in humans

prey (larval cyst) — **predator (tapeworm)**



52 – Worms That Could be on the Exam

Speaker: Edward Mitre, MD

INTESTINAL TAPEWORMS

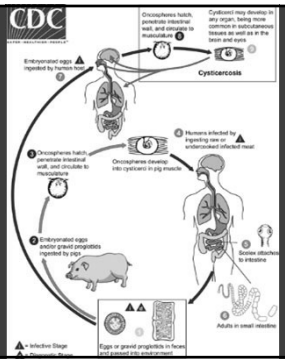
Taenia solium
tapeworm is acquired by eating larvae in pork
adult tapeworm causes few symptoms

Taenia saginatum
acquired by eating larvae in undercooked beef
causes few symptoms
can grow to 10 m

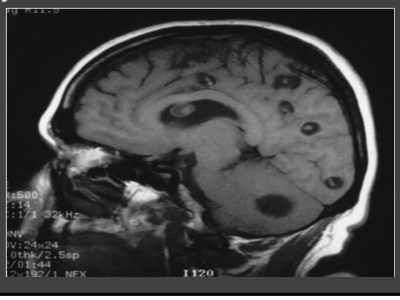
Diphyllobothrium latum *(can grow > 10 m)*
acquired by ingesting fish with larvae
***B12 deficiency in up to 40% of patients**

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.



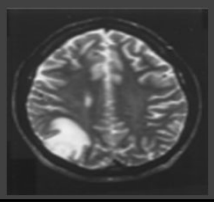
Neurocysticercosis



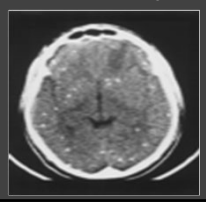
Neurocysticercosis

Clinical manifestations
- seizures
- hydrocephalus
- headaches
- focal neurologic deficits

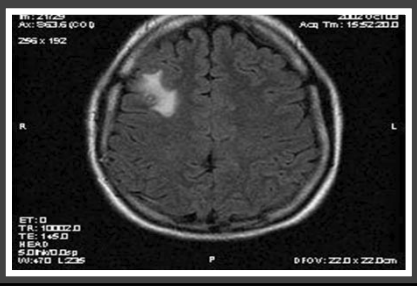
Perilesional edema
- Typically around dying cyst
- often seen with new seizure or terrible headache



Multiple intracerebral calcifications
- sometimes a clinical clue
- non-contrast head CT scan



Neurocysticercosis – single lesion disease is diagnostic challenge



Neurocysticercosis

Diagnosis:

Definitive = tissue biopsy
multiple cystic lesions each with scolex on imaging
retinal cysticercus seen on fundoscopic exam

Presumptive = suggestive lesions on imaging

Cysticercosis serology → supportive (sensitive if high burden of disease)

Treatment: *Medical therapy decreases risk of future seizures, but has immediate risk of increasing seizures/brain inflammation*

If hydrocephalus or diffuse cerebral edema, treat with steroids and/or surgery, not anti-parasitic therapy

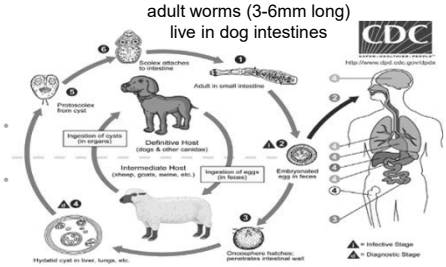
If no increased ICP: 1-2 viable cysts →albendazole for 1-2 viable cysts
> 2 viable cysts →albendazole + praziquantel

AND corticosteroids started before anti-parasitic therapy

****2017 IDSA Guidelines for Diagnosis and Treatment of Cysticercosis****

Echinococcus granulosus

adult worms (3-6mm long)
live in dog intestines



humans = accidental hosts

infected by ingestion of eggs in dog feces

Echinococcus granulosus

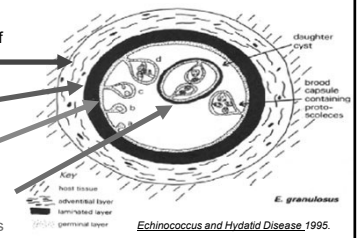
hydatic cyst = "watery vessel"

surrounding inflammatory response of fibrosis and chronic inflammation

outer acellular laminated layer

inner, nucleated germinal layer (PLURIPOTENTIAL TISSUE!)

internal cystic fluid and daughter cysts



Echinococcus and Hydatid Disease 1995.

Echinococcus granulosus - presentation

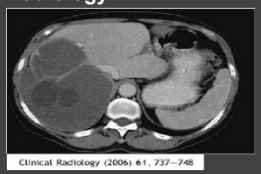
Most cysts (65%) in the liver
25% in the lung, usually in the right lower lobe
Rest occur practically everywhere else in the body

Common presentations
- allergic symptoms/anaphylaxis due to cyst rupture after trauma
- cholangitis and biliary obstruction due to rupture into biliary tree
- peritonitis b/c intraperitoneal rupture
- pneumonia symptoms due to rupture into the bronchial tree

Uncommon presentations
- bone fracture due to bone cysts
- mechanical rupture of heart with pericardial tampanode
- hematuria or flank pain due to renal cysts

Echinococcus granulosus - diagnosis

Radiology



Clinical Radiology (2006) 61, 737–748

Microscopy

Serology
- IgG ELISA about 85% sensitive for liver cysts of E. granulosus
- only 50% sensitive in cases of single pulmonary cyst

Echinococcus granulosus – treatment

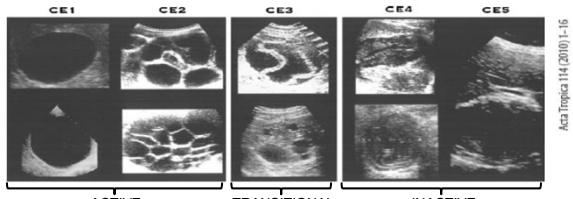
Risks of cyst rupture
1. Anaphylaxis may occur
2. Spilled protoscoleces can reestablish infection

Typically treat with albendazole for a few days
before surgery or PAIR (usually 3-4 days before and 1-3 months after)

52 – Worms That Could be on the Exam

Speaker: Edward Mitre, MD

Cystic Echinococcus Treatment – depends on cyst stage



ACTIVE		TRANSITIONAL	INACTIVE
Unilocular Simply cyst Cyst wall visible	Multivesicular Multiseptated cysts	Anechoic content Detached membrane Solid matrix	Heterogenous, hypoechoic or hyperechoic No daughter cysts CE5 with thick calfied wall
---ALB +/- PAIR or Surgery---	---SURGERY---	---SURGERY--- ---PAIR if no solid matrix---	---NO TREATMENT--

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- *Toxocara canis/cati*
- *Baylisascaris procyonis*
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Intestinal Helminths - Lifecycles

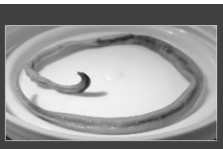
Three intestinal nematodes transit through the lungs and can cause Loeffler's syndrome
- → transient cough, wheeze, shortness of breath, shifting pulmonary infiltrates, eosinophilia
- → usually starts within a week after exposure and typically lasts for about two weeks

- Ascaris
- Hookworms
- Strongyloides

Ascaris (ingestion of eggs, larvae released in intestinal tract)
GUT → PORTAL CIRCULATION → LUNGS → GUT

Strongyloides and Hookworms (skin penetration by larvae)
SKIN → SYSTEMIC CIRCULATION → LUNGS → GUT

Ascaris lumbricoides

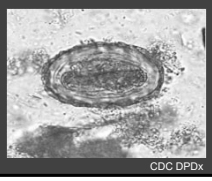


up to 40 cm long and 6 mm wide!

Symptoms
- abdominal distention, pain, & intestinal obstruction with large worm burdens
- cholangitis and/or pancreatitis b/c aberrant migration

Diagnosis
- stool o/p exam
- note: will not find eggs until 2-3 months after pulmonary symptoms occur

Treatment
- albendazole or mebendazole



CDC DPDx

HOOKWORMS

Ancylostoma duodenale and Necator americanus
(also Ancylostoma ceylanicum - zoonotic from dogs/cats in Asia)

Rockefeller Foundation Archive Center

- abdominal pain
- MAJOR cause of ANEMIA and protein loss (b/c plasma loss)
- Loeffler's syndrome
- ground itch (if previously sensitized, dermatitis at entry site)

If worms migrate laterally → **cutaneous larva 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

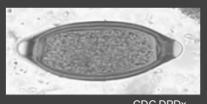
Trichuris trichiura (whipworm)

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

52 – Worms That Could be on the Exam

Speaker: Edward Mitre, MD

Question #3

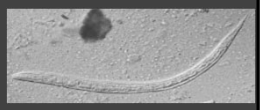
A 25 yo F from rural Peru presents with shortness of breath, bilateral interstitial infiltrates, fever, loose stools, hypotension, and *E. coli* bacteremia. She has received 1 month of high dose corticosteroids and cyclophosphamide for a recent diagnosis of lupus nephritis.

Which of the following anthelmintic agents should be included in her empiric treatment regimen?

A. *Albendazole*
B. *Ivermectin*
C. *Praziquantel*
D. *Pyrantel pamoate*
E. *Diethylcarbamazine*

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*

Filariae: tissue-invasive, thread-like nematodes, transmitted by arthropod vectors

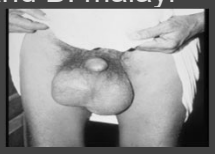
	Adults	Microfilariae
Wuchereria bancrofti *Brugia malayi* (lymphatic filariasis) --mosquitoes--	lymphatics	blood (night)
Loa loa (eyeworm) --Chrysops flies--	SQ tissues (moving)	blood (day)
Onchocerciasis (river blindness) --blackflies--	SQ tissues (nodules)	skin

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

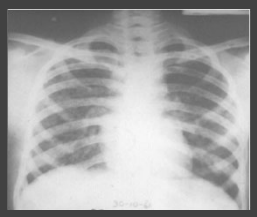




- Asymptomatic microfilaremia
- Lymphangitis
  - retrograde (filarial lymphangitis)
  - bacterial skin/soft tissue infections (dermatolymphangioadenitis)
- Lymphatic dysfunction
  - Lymphedema, elephantiasis, hydrocele, chyluria

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")

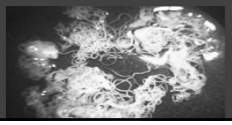
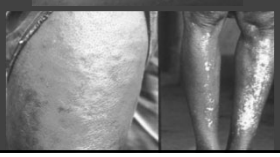
Presumptive diagnosis
- Compatible clinical picture + positive antifilarial antibodies

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

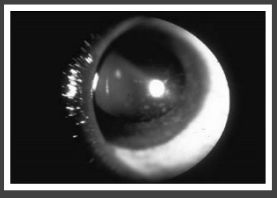
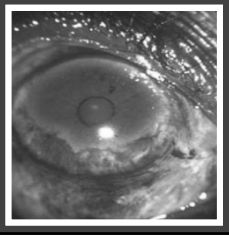
Skin: nodules, pruritus, rash, depigmentation, lichenification



Manifestations of Onchocerciasis

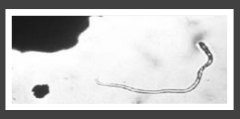
- Eye: punctate keratitis, sclerosing keratitis, chorioretinitis

52 – Worms That Could be on the Exam

Speaker: Edward Mitre, MD

Onchocerciasis



Diagnosis
- Serology
  - anti-filarial
  - onchocerca-specific
- Parasitologic: skin snips, nodulectomy

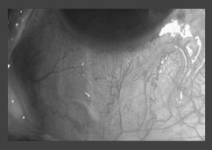
Treatment

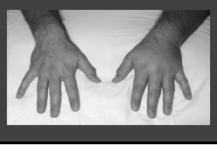
Ivermectin

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)

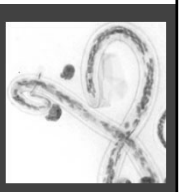
Loiasis: clinical manifestations





- Eyeworm
- Asymptomatic microfilaremia
- Non-specific symptoms
  (fatigue, urticaria, arthralgias, myalgias)
- Calabar swellings
  (transient, migratory, subcutaneous swellings)
- End organ complications (rare)
  (endomyocardial fibrosis, encephalopathy, renal failure)

Loiasis: Diagnosis



CDC DpDx

Definitive diagnosis
- Identification of adult worm in subconjunctiva
- Detection of Loa microfilariae in **noon blood**

Presumptive diagnosis

Compatible clinical picture + positive antifilarial antibodies

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

Good Luck!

Ed Mitre
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53

Penicillin Allergies

Dr. Sandra Nelson

53 – Penicillin Allergies

Speaker: Sandra Nelson, MD

Penicillin Allergies

Sandra B. Nelson, MD
Assistant Professor of Medicine
Harvard Medical School

7/1/2024

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

  - None

Case #1

A 73-year-old woman undergoing chemotherapy for cholangiocarcinoma is hospitalized for bacteremia and sepsis due to *Enterococcus faecalis*. She is currently receiving IV vancomycin but has had progressive renal injury. 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.

3

Case #1: Vote

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. Continue vancomycin; there is no safe path for transition to ampicillin.

4

Penicillin (PCN) Allergy: Premise

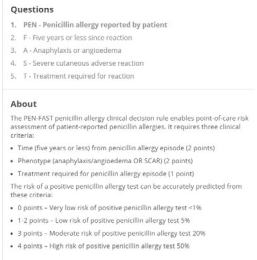
- 10% of the US population have reported penicillin allergy
- Majority with history of PCN allergy can safely receive penicillins (with appropriate evaluation and testing)
  - Reactions do not always recur
  - True allergies often wane with time
  - Some reactions are not allergic

- PCN allergy is associated with important morbidity
  - Higher risk of MRSA and VRE, *C difficile* colitis, surgical site infection
  - Greater associated antimicrobial costs and toxicities

5

Likelihood of true penicillin allergy

- Highest with:
  - Five or fewer years since the reaction
  - Anaphylaxis or angioedema
  - Severe cutaneous adverse reaction
  - Treatment required for reaction



Questions

1. PEN - Penicillin allergy reported by patient
2. F - Five years or less since reaction
3. A - Anaphylaxis or angioedema
4. S - Severe cutaneous adverse reaction
5. T - Treatment required for reaction

About

The PEN-FAST penicillin allergy clinical decision rule enables point-of-care risk assessment of patient-reported penicillin allergies. It requires three clinical criteria:

- Time (five years or less) from penicillin allergy episode (2 points)
- Phenotype (anaphylaxis/angioedema OR SCAR) (2 points)
- Treatment required for penicillin allergy episode (1 point)

The risk of a positive penicillin allergy test can be accurately predicted from these criteria:

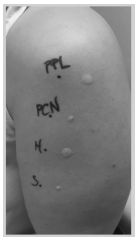
- 0 points – Very low risk of positive penicillin allergy test <1%
- 1-2 points – Low risk of positive penicillin allergy test 5%
- 3 points – Moderate risk of positive penicillin allergy test 20%
- 4 points – High risk of positive penicillin allergy test 50%

PEN-FAST Decision Tool: https://qxmd.com/calculate/calculator_752/pen-fast-penicillin-allergy-risk-tool

6

Options for Approaching PCN Allergy

1. Monitored oral challenge
   - Use with low-risk reactions (e.g. remote rash, pruritus)
2. Penicillin skin testing
   - Procedure: epicutaneous and intradermal administration of PPL (penicilloyl polylysine, Pre-Pen) and penicillin G
   - Use with history of or suspected IgE mediated reaction
   - Consider for unknown history when other high-risk features
   - If negative, followed by test dose of implicated or desired drug



Shenoy JAMA 2019;321:188

7

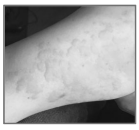
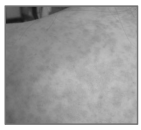
Options for Approaching PCN Allergy

3. Graded challenge (also called test dose procedure)
   - Procedure: 1/4th to 1/10th dose, followed by full dose 30-60 minutes later
   - Can be used as a first step if suspicion for immediate reaction is low
   - Also used after negative PCN skin testing
4. Desensitization
   - Administration of increasing doses 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

8

Deciphering Cutaneous Reactions

- IgE Mediated Reactions (hives)
  - Occur within minutes to hours, resolve within 24 hours
  - Often recurs with repeat exposure
- Benign T-cell mediated
  - Morbilliform or maculopapular
  - May have associated eosinophilia
  - Usual onset days to weeks
  - Persists longer than 24 hours and resolves over days to weeks
  - May not recur with subsequent exposure

Shenoy JAMA 2019;321:188

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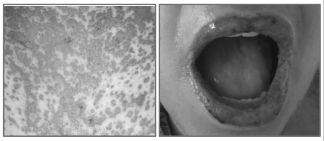
Deciphering Cutaneous Reactions

- Severe cutaneous reactions
  - DRESS, AGEP and SJS/TEN
  - Usual onset days to weeks
  - Blistering, mucosal involvement, severe skin desquamation, organ involvement
- Vague or unknown skin reaction
  - Evaluate risk of severe cutaneous reaction
  - Assume possibly IgE mediated




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

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Putting it all together: penicillin skin reactions

IgE Mediated (Urticaria)	Penicillin Skin testing If positive: desensitization or alternative therapy If negative: test dose amoxicillin
Benign Skin Rash	If a penicillin: amoxicillin oral challenge Any cephalosporin safe
Severe Cutaneous Adverse Reaction SJS/TEN, DRESS, AGEP	Avoid beta-lactams

11

What about non-cutaneous reactions?

IgE Mediated Angioedema and Anaphylaxis	Penicillin Skin testing If positive: desensitization or alternative therapy If negative: test dose amoxicillin
Antibody mediated (*Hemolytic anemia, neutropenia, thrombocytopenia*) Immune-complex (*vasculitis, serum sickness*) Cell-mediated (*Interstitial nephritis, drug-induced liver injury*)	No available testing In general, when severe avoid beta-lactams

12

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.

13

Case #2: Vote

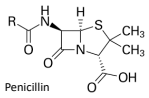
What do you do counsel?

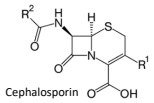
A. Administer clindamycin
B. Administer cefazolin
C. Administer cefazolin after intraoperative test dose
D. Administer ceftriaxone
E. Administer vancomycin

14

PCN Allergy and use of cephalosporins

- Significant cross reactivity rare
  - higher with earlier generation cephalosporins
- For IgE mediated PCN allergy:
  - use structurally dissimilar (3rd/4th gen) cephalosporin without prior testing
  - use structurally similar (1st/2nd gen) after PCN skin testing and amoxicillin challenge
- Mild delayed drug rash:
  - any cephalosporin OK
- Avoid if severe reaction to PCN





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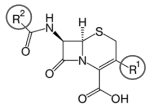
Cephalosporin Allergy



- 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

16

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

17

Thank you and good luck!

"The penicillin looks good."

18

54

Kitchen Sink: Syndromes Not Covered Elsewhere

Dr. Stacey Rose

54 – Kitchen Sink: Syndromes Not Covered Elsewhere

Speaker: Stacey Rose, MD

Kitchen Sink: Syndromes Not Covered Elsewhere

Stacey R. Rose, MD, FACP, FIDSA
Associate Professor of Medicine, Infectious Diseases
Associate Director, Center for Professionalism
Baylor College of Medicine

7/1/2024

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

  - None

Session plan

- Case-based discussions of topics not extensively covered in other sessions
- Highlight points likely to be assessed on ID Boards (rather than comprehensive overview)

3

Question 1

- A 51 year-old male with past medical history significant for insulin dependent diabetes presents with a six-month history of progressive athralgias, abdominal pain, diarrhea, weight loss, and low-grade fevers.
- Work up thus far:

Negative blood cultures x 2
Negative Rheumatoid factor
Normal metabolic panels
Mild normocytic anemia

4

Question 1

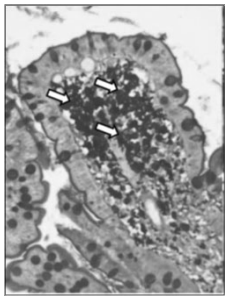
- Which of the following tests will most likely yield the diagnosis?

a) Anti-streptolysin O Antibody
b) Anti-nuclear Antibody
c) Stool ova and parasite
d) Duodenal biopsy

5

Whipple's disease

- Caused by *Trophyrema whipplei* (gram variable bacterium, difficult to cultivate)
- More common in middle aged, Caucasian men
- Diagnosis often delayed due to indolent clinical presentation
- Most commonly diagnosed via duodenal biopsy, stained with PAS
- PCR increasingly used



Periodic acid-Schiff-diastase (PAS-D)-stained duodenal biopsy specimens with PAS-D-positive granules in the foamy macrophages (arrows).

Dolmans RAV, Boel CHE, Lacle MM, Kusters JG. 2017. Clinical manifestations, treatment, and diagnosis of Tropheryma whipplei infections. Clin Microbiol Rev 30:529–555.

6

Whipple's: clinical presentations

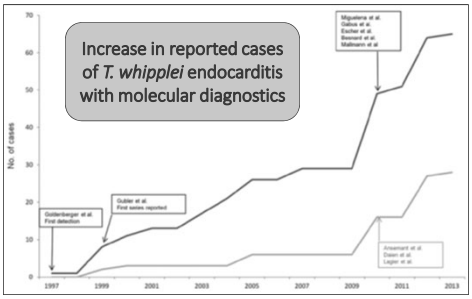
TABLE 1 Clinical manifestations of *Tropheryma whipplei* infection[a]

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 diagnosed



- Consider in patients with arthralgias plus "culture negative" endocarditis
- *T. whipplei* PCR from blood added to Duke's criteria (2023) for diagnosis of endocarditis

Total published cases
Cases from this article

Fenollar F, Cellard 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 trimethoprim-sulfamethoxazole (~1 year)

OR

- Doxycycline plus hydroxychloroquine (12-18 mos)

Symptoms improve, but relapse is common without prolonged treatment / suppression

Clinical manifestations, treatment, and diagnosis of Tropheryma whipplei infections. Clin Microbiol Rev 2017.
Whipple's disease and Tropheryma whipplei infections: from bench to bedside. Lancet Infect Dis. 2022
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 infected tissue or blood
- Prolonged treatment needed to prevent relapse

Whipple's disease

Take home points

10

Question 2

- A 20 year-old female school teacher presents with a 1-week history of fever and pain / swelling in knees, elbows and wrists. She notes that the pain moves 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 and Anti-DNase B titers; pregnancy and HIV tests (4th generation Ag/Ab) are negative.

11

Question 2

Which of the following is the best explanation for her symptoms?

a. Acute HIV infection
b. Mononucleosis due to Epstein Barr Virus
c. Acute rheumatic fever
d. Lemierre's syndrome

12

54 – Kitchen Sink: Syndromes Not Covered Elsewhere

Speaker: Stacey Rose, MD

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.

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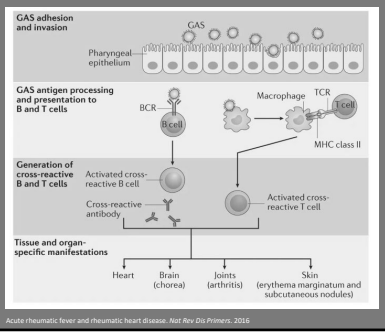
Acute Rheumatic Fever



- Rare in US (0.5 per 100K per year), but 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**)

Acute rheumatic fever and rheumatic heart disease. *Nat Rev Dis Primers.* 2016

14

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) or anti-DNase B (ADB)**

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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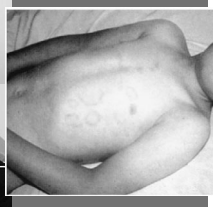
Revision of the Jones Criteria for the diagnosis of acute rheumatic fever in the era of Doppler echocardiography: a scientific statement from the American Heart Association. *Circulation.* 2015

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

20

Question 3

- A 34 year-old male with a history of injection drug use presents to the emergency room with two days of blurry vision and difficulty swallowing. He is also beginning to feel weak in his arm muscles.
- On examination, vital signs are normal, but the patient is noted to have ptosis and sluggish pupillary responses as well as slurred speech.

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Question 3

- Which of the following treatments are recommended?

A. Plasmapheresis
B. Naloxone
C. Tetanus antitoxin
D. Botulinum antitoxin

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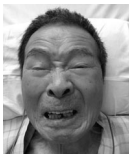
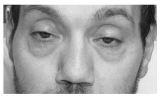
Explanation



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

Botulism

https://phil.cdc.gov/details.aspx?pid=2107

- Caused by **Clostridium botulinum* (gram positive, strict anaerobe with subterminal spore; found in soil)
- Symptoms due to TOXINS which prevent release of acetylcholine in neuromuscular junction
- Leads to flaccid paralysis of motor and autonomic nerves, beginning with the cranial nerves (*descending* weakness)
- DX: culture or detection of toxin

**other neurotoxin producing species of Clostridium: C. butyricum, or C. baratii*

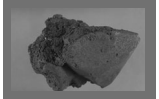
24

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.*

25

RED FLAGS: symmetric CN palsies and descending / symmetric flaccid paralysis should raise suspicion for botulism

Adverse Effects Linked to Counterfeit or Mishandled Botulinum Toxin Injections

Print

HAN HEALTH ALERT NETWORK

This is an official CDC HEALTH ADVISORY

Distributed via the CDC Health Alert Network
April 23 2024, 11:00 AM ET
CDCHAN-00507

https://emergency.cdc.gov/han/2024/han00507.asp

26

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: ***symmetric, descending flaccid paralysis***, starting with ***cranial nerves*** (ptosis, blurred vision, slurred speech)
- Diagnosis: clinical; confirmed by culture or detection of toxin
- Treatment: ***antitoxin*** & supportive care; wound debridement

Botulism

Take home points

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Question 4

- 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.
- PCR respiratory panel was positive for *Bordatella pertussis*.
- 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 4

https://www.youtube.com/watch?v=31tnXPlhA7w (NEJMvideo)

- 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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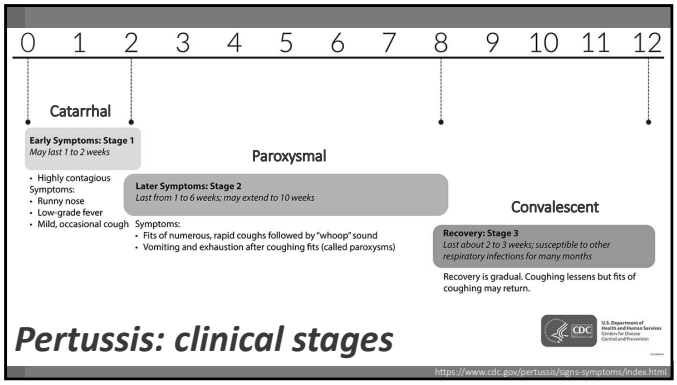
54 – Kitchen Sink: Syndromes Not Covered Elsewhere

Speaker: Stacey Rose, MD



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://wwwn.cdc.gov/nndss/conditions/pertussis/case-definition/2020/; https://www.cdc.gov/pertussis/clinical/diagnostic-testing/diagnosis-per-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

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)

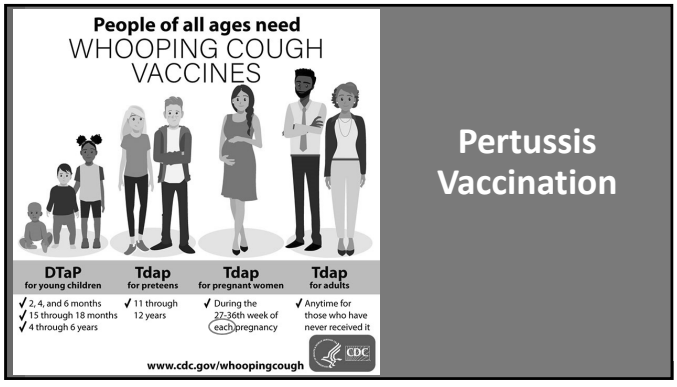
https://www.cdc.gov/pertussis/
Decker MD, Edwards KM. Pertussis (Whooping Cough). *J Infect Dis*. 2021.

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



Pertussis in the news

ECDC warns of surge in pertussis cases in Europe

News brief | May 8, 2024

https://www.cidrap.umn.edu/pertussis/ecdc-warns-surge-pertussis-cases-europe

Constrained U.S. Td supply, 2024

Production of one tetanus and diphtheria (Td) vaccine, TdVax™, has been discontinued. As a result, CDC anticipates that the supply of Td vaccine in the U.S. market will be constrained during 2024. CDC has developed guidance to help vaccination providers.

https://www.cdc.gov/vaccines/vpd/dtap-tdap-td/hcp/recommendations.html

Guidance: use TdaP in lieu of Td where available

- 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

Bordetella pertussis

Take home points

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Question 5

- 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 5

- 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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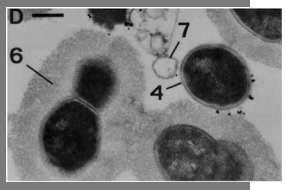
Splenectomy and infection risk



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)*
- *Bordetella holmesii*
- *Salmonella typhi*

Rubin LG, Schaffner W. Clinical practice. Care of the asplenic patient. N Engl J Med. 2014

40

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

41

- 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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54 – Kitchen Sink: Syndromes Not Covered Elsewhere

Speaker: Stacey Rose, MD

Question 6

- 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, with no evidence of periappendiceal abscess.
- The patient wants to avoid surgery if at all possible.

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Question 6

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 <u>disadvantage</u> 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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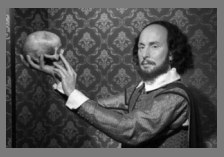
Appendicitis: to cut or not to cut…



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

45

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

For the ID boards:
know when to recommend surgery

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

46

- Non-operative management of acute appendicitis may be considered if ***<u>uncomplicated</u>***
  - <u>Features which should prompt immediate surgery</u>: perforation; abscess; suspected tumor; peritonitis; systemic illness
- Up to 50% will require subsequent appendectomy
- *ID board potential* – recognize when an operation is NEEDED

Appendicitis

Take home points

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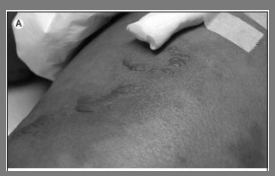
Question 7



- 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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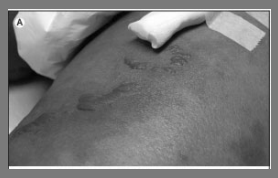
54 – Kitchen Sink: Syndromes Not Covered Elsewhere

Speaker: Stacey Rose, MD

Question 7



- The patient's clinical syndrome was most likely caused by which of the following exposures?

A. Rat bite
B. Tick bite
C. Consumption of raw oysters
D. Consumption of raw egg

Lancet Infect Dis. 2008 Jun;8(6):399.

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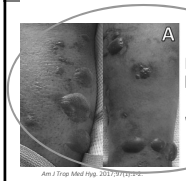
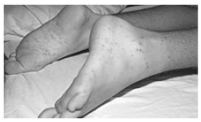
Explanation



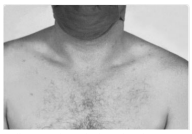
Hemorrhagic bullae from *Vibrio vulnificus*

Am J Trop Med Hyg. 2017;97(1):9-2.



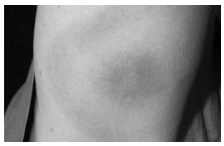
Petechial rash from *Streptobacillus moniliformis* (rat bite fever); fever, rash, migratory arthritis

CMAJ. 2006 Aug 15;175(4):354.



Rose spots from *Salmonella typhi*

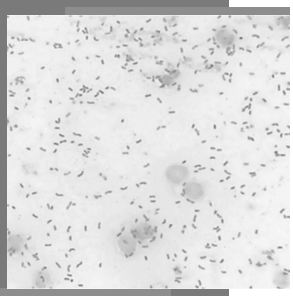
https://www.cdc.gov/vaccines/vpd/typhoid/public/photos.html



Erythema migrans due to *Borrelia burgdorferi* (tick borne)

https://www.cdc.gov/lyme/signs_symptoms/rashes.html

50



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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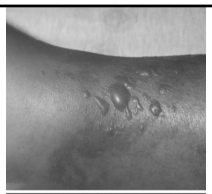
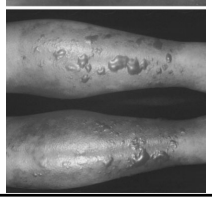
Clinical presentation and treatment





Principles and Practice of Infectious Diseases, 9th ed.

- 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)

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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 8

- A 38 year-old female travels to Bangladesh for a friend's (outdoor) wedding.
- She has never traveled to this region. In preparation for the trip, she received Typhoid vaccine and was started on malaria prophylaxis with doxycycline.
- Five days after returning home, she develops fever, headache and diffuse muscle and joint pain.
- Over the next few days, a rash develops – beginning on the dorsum of her hands and feet with spread to her arms, legs and torso.
- She presents to urgent care for evaluation.

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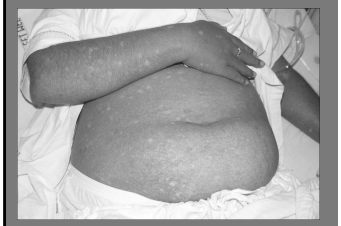
Question 8



Indian J Dermatol. 2010;55(1):79-85.

- Physical exam is notable for fever (101.2 degrees Fahrenheit) and a diffuse, morbilliform rash.
- CBC is as follows:
  - WBC 3.26 x 10^9 / L (normal)
  - Hgb 12.9 g/dL (normal)
  - Platelets 113,000 / mcL (low)
- A comprehensive metabolic profile is normal including renal and liver function tests.

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Question 8

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

A. *Dengue* real-time PCR
B. Blood culture
C. *Lyme* enzyme immunoassay (EIA)
D. *Malaria* rapid diagnostic test (RDT)

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Question 8 - explained

Fever, headache, body pain, rash and low platelets in a returning traveler

- ✓ **Dengue** – characteristic symptoms and epidemiology; PCR or NS1 antigen test recommended within first 7 days
- ✗ **Blood culture** – presumably looking for Typhoid fever, but rash is not characteristic and no gastrointestinal symptoms
- ✗ **Lyme** – wrong epidemiology (no known exposure to ticks) and rash not typical for Lyme; low platelets does not fit
- ✗ **Malaria** – RDT would be diagnostic, BUT no anemia and rash not typical with malaria; also was taking prophylaxis

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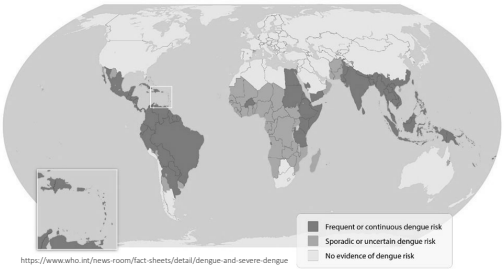
Dengue is common worldwide…and rising



https://www.who.int/news-room/fact-sheets/detail/dengue-and-severe-dengue

- Tropical and subtropical climates, outbreaks in urban and semi-urban areas
- 100-400 million infections each year worldwide

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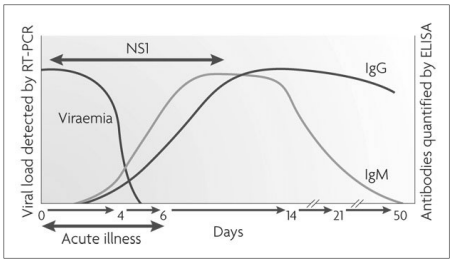
Dengue: diagnostic testing



Guzman, M. G. et al. Dengue: A continuing global threat. Nature Reviews Microbiology 8, S7–S16 (2010).
https://www.cdc.gov/dengue/hcp/diagnosis-testing/index.html

- Early in disease course: **nucleic acid testing (PCR)** or **NS1 antigen**
- **IgM** is more sensitive after 7 days
- **IgG** not helpful in acute phase

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Severe Dengue

- Symptomatic infection typically improves after 1-2 weeks
- May progress to severe Dengue; risk increased if prior infection (with another serovar)
- Signs of severe dengue:
  - Vomiting
  - Tachypnea
  - Mucosal bleeding (gums; epistaxis)
  - Blood in vomit or stool
  - Hypotension / shock

https://www.who.int/news-room/fact-sheets/detail/dengue-and-severe-dengue
https://www.cdc.gov/dengue/hcp/clinical-signs/index.html

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54 – Kitchen Sink: Syndromes Not Covered Elsewhere

Speaker: Stacey Rose, MD

Aedes aegypti mosquito, image from https://www.cdc.gov/mosquitoes/gallery/aedes/index.html

Mosquito-borne illnesses in a returning traveler

For the boards, know:
-typical epidemiology
-clinical presentation
-vector

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Key features of mosquito-borne illnesses

	Epidemiology	Vector	Clinical features
Chikungunya	Africa, the Americas, Asia, Europe, islands in Indian and Pacific Oceans; prominent outbreak Caribbean 2013	***Aedes*** *aegypti* (*A. albopticus* in Europe)	Fever and **joint pain**; rash less common. Can have chronic sx's
Dengue	Americas, Africa, Caribbean, Middle East, Asia, Pacific Islands 4 serotypes; infection with a 2nd serotype → severe illness	***Aedes*** *aegypti* (or *A. albopticus*)	Fever, **headache**, rash, **muscle and joint pain** Severe: hemorrhagic fever / shock
Zika	Prominent in Americas ~2017, then more widespread (Caribbean, Africa, India)	***Aedes*** *aegypti* **Also sexual transmission**	Often asx; fever; **rash** (starts on face); **conjunctivitis** If infected during pregnancy → fetal anomalies (microcephaly)

CDC; PPID 9th edition

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Diagnostic approach for mosquito-borne illnesses

	Within 7 d of symptom onset	> 7 d after symptom onset
Chikungunya	Nucleic acid testing (RT-PCR)	IgM
Dengue	Nucleic acid testing (RT-PCR) or NS1 (non structural protein 1) immunoassay	IgM
Zika	Nucleic acid testing (RT-PCR)	IgM

- Testing available through health department or CDC
- IgM for *Zika* and *Dengue* cross-react; if PCR negative, positive IgM should prompt PRNT to differentiate
- IgG not helpful as remains positive lifelong

https://www.cdc.gov/dengue/healthcare-providers/diagnosis.html
https://www.cdc.gov/chikungunya/hc/diagnostic.html
Dengue infection. *Nat Rev Dis Primers*. (2016). https://doi.org/10.1038/nrdp.2016.55

PRNT = plaque reduction neutralization test

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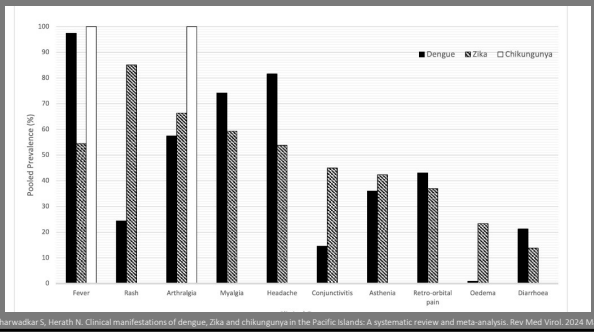
Comparing sx's of Dengue, Zika, Chikungunya



Kharwadkar S, Herath N. Clinical manifestations of dengue, Zika and chikungunya in the Pacific Islands: A systematic review and meta-analysis. Rev Med Virol. 2024 Mar.

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https://cdc.gov/malaria/about/distribution.html

Malaria

- **Epidemiology**: worldwide, tropics and subtropics
- **Vector**: *Anopheles* mosquito
- **Symptoms**: Fever, headache, N/V, diarrhea; severe: anemia, jaundice, splenomegaly, neurologic
- *Species-specific* features

https://www.cdc.gov/malaria/diagnosis_treatment/diagnostic_tools.html

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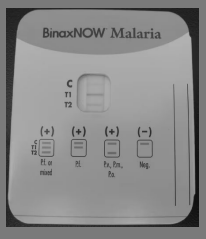
Malaria



- **Epidemiology**: worldwide, tropics and subtropics
- **Vector**: *Anopheles* mosquito
- **Symptoms**: Fever, headache, N/V, diarrhea; severe: anemia, jaundice, splenomegaly, neurologic
- *Species-specific* features
- Microscopy (blood smear); RDT if microscopy not available

https://www.cdc.gov/malaria/diagnosis_treatment/diagnostic_tools.html

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54 – Kitchen Sink: Syndromes Not Covered Elsewhere

Speaker: Stacey Rose, MD

Important Updates on Locally Acquired Malaria Cases Identified in Florida, Texas, and Maryland

HAN HEALTH ALERT NETWORK

This is an official CDC HEALTH UPDATE

Distributed via the CDC Health Alert Network
August 28, 2023, 2:15 PM ET
CDCHAN-00496

Summary

The Centers for Disease Control and Prevention (CDC) is issuing this Health Alert Network (HAN) Health Update to share new information with clinicians, public health authorities, and the public about locally acquired malaria cases identified in the United States. On August 18, 2023, a single case of locally acquired malaria was reported in Maryland in the National Capital Region. This case was caused by the *Plasmodium falciparum (P. falciparum)* species and is unrelated to the cases involving local transmission of *Plasmodium vivax (P. vivax)* malaria in Florida and Texas described in the HAN Health Advisory 494 issued on June 26, 2023. As an update to that report, to date, Florida has identified seven cases and Texas has identified one case of locally acquired *P. vivax* malaria, but there have been no reports of local transmission of malaria in Florida or Texas since mid-July 2023.

https://emergency.cdc.gov/han/2023/han00496.asp#print

Mosquito borne illnesses have overlapping features; look for keywords

- Dengue, Zika, Chikungunya all spread via *Aedes* mosquitos
  - *Dengue*: headache, rash, "bone-break" pain, low platelets; infxn w/ 2nd serotype → severe dengue
  - *Zika*: may be asx; rash / conjunctivitis common; birth defects
  - *Chikungunya*: prominent joint pain; may become chronic
- Diagnosis:
  - PCR if < 7 d (plus NS1 antigen for *Dengue*)
  - IgM if > 7 d but *Dengue / Zika* cross-react
- Malaria: *Anopheles* mosquito; fever, anemia, species-specific presentations (*P. falciparum* - severe; *P. vivax / ovale - relapsing)*
  - Diagnosis: blood smear or rapid detection test (RDT)

Mosquito-borne illness in a returning traveler

Take home points

Kitchen Sink summary

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:

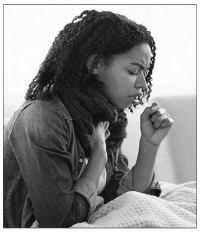
- Kids / young adults with migratory polyarthritis, carditis, chorea, subcutaneous nodules, erythema marginatum following GAS pharyngitis
- Monthly IM penicillin prophylaxis for 10 years or to age 40 if carditis + residual valvular disease

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



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

Kitchen Sink summary - 3

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

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)

54 – Kitchen Sink: Syndromes Not Covered Elsewhere

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