IDBR INFECTIOUS DISEASE BOARD REVIEW AUGUST 20–24 2022

GW Office of Continuing Education in the Health Professions

27th Annual

COMPREHENSIVE REVIEW *for* INFECTIOUS DISEASE BOARD PREPARATION

VOLUME 2

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

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

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Agenda Day 1: Saturday, August 20, 2022

#	Start		End	Presentation	Faculty
AM Moderator: Henry Masur, MD					
1	8:30 AM EDT	-	9:00 AM EDT	Introduction	John Bennett, MD and Henry Masur, MD
2	9:00 AM	-	9:15 AM	How to Prepare for the Certification, Recertification, or Check-in Exam	Helen Boucher, MD
QP1	**9:15 AM**	**-**	**9:45 AM**	**Daily Question Preview: Day 1**	**Henry Masur, MD**
3	9:45 AM	-	10:45 AM	Core Concepts: Microbiology: What You Need to Know for the Exam	Robin Patel, MD
4	10:45 AM	-	11:00 AM	Microbiology Questions That Could Be on the Exam	Robin Patel, MD
FC1	**11:00 AM**	**-**	**11:30 AM**	**Faculty Q&A**	**Drs. Masur (Moderator), Bennett, Boucher, and Patel**
5	11:30 AM	-	12:15 PM	Core Concepts: Antibacterial Drugs I Gram Positive Organisms	Helen Boucher, MD
6	12:15 PM	-	12:30 PM	Antibacterial Drugs I: Key Points and Questions That Could be on the Exam	Helen Boucher, MD
	12:30 PM	-	1:15 PM	Lunch Break	
BR1	**1:15 PM**	**-**	**2:15 PM**	**Board Review Day 1**	**Drs. Masur (Moderator), Boucher, Gandhi, Gilbert, Kotton, Patel, and Winthrop**
PM Moderator: David Gilbert, MD					
7	2:15 PM	-	3:00 PM	Core Concepts: Antibacterial Drugs II Gram Negative Organisms	David Gilbert, MD
8	3:00 PM	-	3:15 PM	Antibacterial Drugs II: Key Points and Questions That Could Be on The Exam	David Gilbert, MD
9	3:15 PM	-	4:00 PM	Core Concepts: Antifungal Drugs	John Bennett, MD
10	4:00 PM	-	4:30 PM	CMV, EBV, HHV6 and HHV8 in Immunocompetent and Immunocompromised Patients	Camille Kotton, MD
FC2	**4:30 PM**	**-**	**5:00 PM**	**Faculty Q&A**	**Drs. Gilbert (Moderator), Bennett, Boucher, Kotton and Pavia**
11	5:00 PM	-	5:30 PM	Nontuberculous Mycobacteria in Normal and Abnormal Hosts	Kevin Winthrop, MD
12	5:30 PM	-	6:15 PM	Photo Opportunity I: Photos and Questions to Test Your Board Preparation	Rajesh Gandhi, MD
13	6:15 PM	-	7:00 PM	Skin and Soft Tissue Infections	Helen Boucher, MD
FC3	**7:00 PM**	**-**	**7:30 PM**	**End of the Day Meet the Professor (Live Registrants Only)**	**Drs. Gilbert, Boucher, Gandhi, Pavia, Patel, and Winthrop**

Agenda Day 2: Sunday, August 21, 2022

AM Moderator: Jack Bennett, MD					
#	Start		End	Presentation	Faculty
QP2	8:30 AM EDT	-	9:00 AM EDT	Daily Question Preview Day 2	Jack Bennett, MD
14	9:00 AM	-	10:00 AM	Clinical Immunology and Host Defense	Steven Holland, MD
15	10:00 AM	-	10:30 AM	Gastrointestinal Disease: Etiologic Agents	Herbert Dupont, MD
16	10:30 AM	-	11:00 AM	Gastrointestinal Disease: Clinical Syndromes	Herbert Dupont, MD
17	11:00 AM	-	11:45 AM	Fungal Diseases in Normal and Abnormal Hosts	Jack Bennett, MD
	11:45 AM	-	12:30 PM	Lunch Break	
BR2	12:30 PM	-	1:30 PM	Board Review Day 2	Drs. Bennett (Moderator), Aronoff, Chambers, Dupont, Klompas and Masur
PM Moderator: David Gilbert, MD					
18	1:30 PM	-	2:00 PM	Nocardia, Actinomycosis , Rhodococcus, and Melioidosis	David Aronoff, MD
19	2:00 PM	-	3:00 PM	Endocarditis of Native and Prosthetic Devices, and Infections of Pacers and Ventricular Assist Devices	Henry Chambers, MD
20	3:00 PM	-	3:45 PM	Zoonoses	David Aronoff, MD
FC4	3:45 PM	-	4:15 PM	Faculty Q&A	Drs. Gilbert (Moderator), Aronoff, Chambers, Dupont and Klompas
21	4:15 PM	-	5:00 PM	Staphylococcal Disease	Henry Chambers, MD
22	5:00 PM	-	5:30 PM	Helicobacter and Clostridioides Difficile	David Aronoff, MD
23	5:30 PM	-	6:30 PM	Hospital Epidemiology	Michael Klompas, MD
FC5	**6:30 PM**	**-**	**7:00 PM**	**End of the Day Meet the Professor (Live Registrants Only)**	**Drs. Aronoff, Chambers, Klompas and Dupont**

Agenda Day 3: Monday, August 22, 2022

#	Start		End	Presentation	Faculty
AM Moderator: Richard Whitley, MD					
QP3	**8:30 AM EDT**	**-**	**9:00 AM EDT**	**Daily Question Preview Day 3**	**Richard Whitley, MD**
24	9:00 AM	-	9:30 AM	Sexually Transmitted Infections: Genital Ulcers Diseases (GUD)	Khalil Ghanem, MD
25	9:30 AM	-	10:15 AM	Infections of Upper and Lower Urinary Tract	Barbara Trautner, MD
FC6	**10:15 AM**	**-**	**10: 45 AM**	**Faculty Q&A**	**Drs. Whitley (Moderator), Ghanem, and Trautner**
26	10:45 AM	-	11:45 AM	Sexually Transmitted Infections: Other Diseases and Syndromes	Khalil Ghanem, MD
27	11:45 AM	-	12:15 PM	HSV and VZV in Immuno-competent and Immunocompromised Hosts	Richard Whitley, MD
	12:15 PM	-	1:00 PM	Lunch Break	
BR3	**1:00 PM**	**-**	**2:00 PM**	**Board Review Day 3**	**Drs. Whitley (Moderator), Bell, Dhanireddy, Ghanem, Thomas, Trautner, and Tunkel**
PM Moderator: John Bennett, MD					
28	2:00 PM	-	2:45 PM	Syndromes in the ICU that ID Physicians Should Know	Taison Bell, MD
29	2:45 PM	-	3:30 PM	Immunizations: Domestic, Travel, and Occupational	Shireesha Dhanireddy, MD
30	3:30 PM	-	4:00 PM	Acute Hepatitis	David Thomas, MD
31	4:00 PM	-	4:45 PM	Viral and bacterial meningitis	Allan Tunkel, MD
32	4:45 PM	-	5:45 PM	Chronic Hepatitis	David Thomas, MD
33	5:45 PM	-	6:30 PM	Brain Abscess, Cavernous Sinus Thrombosis, and Subdural and Epidural Empyema	Alan Tunkel, MD
FC7	**6:30 PM**	**-**	**7:00 PM**	**End of the Day Meet the Professor (Live Registrants Only)**	**Drs. Bennett, Dhanireddy, Ghanem, Thomas, Trautner, Whitley**

Agenda Day 4: Tuesday, August 23, 2022

AM Moderator: Roy Gulick, MD					
#	**Start**		**End**	**Presentation**	**Faculty**
QP4	**8:30 AM EDT**	**-**	**9:00 AM EDT**	**Daily Question Preview Day 4**	**Roy Gulick, MD**
34	9:00-AM	-	9:30 AM	Clinical Manifestations of Human Retroviral Diseases and Slow Viruses	Frank Maldarelli, MD
35	9:30 AM	-	10:15 AM	HIV Associated Opportunistic Infections I	Henry Masur, MD
36	10:15 AM	-	10:30 AM	HIV Diagnosis	Frank Maldarelli, MD
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	-	1:00 PM	Lunch Break	
BR4	**1:00 PM**	**-**	**2:00 PM**	**Board Review Day 4**	**Drs. Gulick (Moderator), Bennett, Bloch, Dorman, Maldarelli, Pavia, and Saag**
PM Moderator: Andy Pavia, MD					
40	2:00 PM	-	2:45 PM	Syndromes that Masquerade as Infections	Karen Bloch, MD
41	2:45 PM	-	3:30 PM	Tuberculosis in Immunocompetent and Immunosuppressed Hosts	Susan Dorman, MD
42	3:30 PM	-	4:15 PM	Non-AIDS-Defining Complications of HIV/AIDS	Michael Saag, MD
FC8	**4:15 PM**	**-**	**4:45 PM**	**Faculty Q&A**	**Drs. Gulick (Moderator), Block, Dorman, Dupont, Maldarelli, and Saag**
43	4:45 PM	-	5:45 PM	Respiratory Viral Infections Including Influenza, Immunocompetent, and Immunocompromised Patients	Andy Pavia, MD
44	5:45 PM	-	6:00 PM	Pharyngitis Syndromes Including Group A Strep Pharyngitis	Karen Bloch, MD
45	6:00 PM	-	6:30 PM	Core Concepts: Antiviral Drugs	Andy Pavia, MD
FC9	**6:30 PM**	**-**	**7:00 PM**	**End of the Day Meet the Professor (Live Registrants Only)**	**Drs. Bloch, Gulick, Dorman, Maldarelli, Pavia and Saag**

Agenda Day 5: Wednesday, August 24, 2022

AM Moderator: Kieren Marr, MD					
#	**Start**		**End**	**Presentation**	**Faculty**
46	8:00 AM	-	9:00 AM	Infections in the Neutropenic Cancer Patient and Hematopoietic Stem Cell Recipients	Kieren Marr, MD
47	9:00 AM	-	9:45 AM	Photo Opportunities: Images You Should Know for the Exams	Jack Bennett, MD
FC10	**9:45 AM**	**-**	**10:00 AM**	**Faculty Q&A**	**Drs. Marr (Moderator) and Bennett**
48	10:00 PM	-	10:30 PM	Pneumonia: Some Cases that Could be on the Exam	Paul Auwaerter, MD
49	10:30 AM	-	11:130 AM	Lots of Protozoa	Edward Mitre, MD
	11:30 AM	-	12:00 PM	Lunch Break	
PM Moderator: Paul Auwaerter, MD					
BR5	**12:00 PM**	**-**	**12:45 PM**	**Board Review Day 5**	**Drs. Auwaerter (Moderator), Bennett, Marr, Masur, Nelson Mitre, and Rose**
50	12:45 PM	-	1:30 PM	Bone and Joint Infections	Sandra Nelson MD
51	1:30 PM	-	2:15 PM	Ticks, Mites, Lice, and the Diseases They Transmit	Paul Auwaerter, MD
52	2:15 PM	-	3:00 PM	Worms and More Worms	Edward Mitre, MD
FC11	**3:00 PM**	**-**	**3:15 PM**	**Faculty Q&A**	**Drs. Auwaerter (Moderator) Mitre, Nelson**
53	3:15 PM	-	3:45 PM	Lyme Disease	Paul Auwaerter, MD
54	3:45 PM	-	4:00 PM	Penicillin Allergies	Sandra Nelson, MD
55	4:00 PM	-	4:45 PM	Kitchen Sink: Syndromes Not Covered Elsewhere	Stacey Rose, MD

Online Only Lectures

#	Duration	Title	Faculty
OL - 1	45 Mins	Encephalitis including West Nile and Rabies	Allan Tunkel, MD
OL – 2	45 Mins	Management of AIDS-Related Opportunistic Infections II	Henry Masur, MD
OL – 3	45 Mins	Epididymitis, Orchitis, and Prostatitis	Barbara Trautner, MD
OL - 4	56 Mins	Management of AIDS-Related Opportunistic Infections III	Henry Masur, MD
OL - 5	40 Mins	ID Bootcamp: HIV	Roy Gulick, MD
OL - 6	50 Mins	ID Bootcamp: Transplant	Camille Kotton, MD
OL - 7	33 Mins	Other Antibacterial Drugs (Macrolides, TMP, SMX, etc)	David Gilbert, MD
OL – 8	25 Mins	Statistics	Khalil Ghanem, MD
OL – 9	60 Mins	Infections in Solid Organ Transplant Recipients	Barbara Alexander, MD
OL – 10	30 Mins	Even More Worms	Edward Mitre, MD

Primers and Study Guides

#	Title	Faculty
P - 1	Antibacterial Resistance Primer	Robin Patel, MD
P - 2	Antiviral Resistance Primer	Richard Whitley, MD Andrew Pavia, MD
P - 3	HIV Drug Resistance Primer	Roy Gulick, MD
P - 4	Antifungal Resistance Primer	John Bennett, MD
P - 5	Differential Diagnosis of Diseases presenting as Skin Nodules, Ulcers, or Ulceronodular Skin Lesion	David Gilbert, MD
P - 6	Microbiology Primer	Robin Patel, MD
P - 7	Rickettsia Primer	Paul Auwaerter, MD John Bennett, MD W. Michael Scheld, MD
P - 8	ID Images You should Know	Henry Masur, MD

Board Review Question Sets

Title	# Questions
Question Set A	100
Question Set B	100
Question Set C	100
Question Set D	100
Photo Opportunities	100

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COURSE OVERVIEW

ABOUT THE COURSE

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

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

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

EDUCATIONAL OBJECTIVES

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

PROGRAM FACILITATORS

The George Washington University
Office of Continuing Education in the Health Professions 2300 Eye Street, NW, Suite 112C
Washington, DC 20037
Ph: 202.994.4285
Email: IDBR@gwu.edu

ACCREDITATION, CME & MOC CLAIM INFORMATION - PHYSICIANS

TYPES OF CREDIT

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

1. Attending the Live Course - 43 credits
2. Completing the Online Materials - 74 credits

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

LIVE COURSE

Accreditation

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

CME Credit for Physicians

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

Claiming MOC Points

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

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

Deadline for Claiming MOC Points

ABIM Board Certified physicians need to claim MOC points for this course **by December 31, 2022** in order **for the MOC points to count toward any MOC requirements that are due by the end of 2022.**

CEHP will continue to submit participant completion data for the course until **August 20, 2023**. **No ABIM MOC credit will be awarded for this activity after August 20, 2023**.

OVERVIEW AND INSTRUCTIONS FOR CLAIMING CME CREDIT AND MOC POINTS

LIVE MATERIALS

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

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

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

ONLINE MATERIALS

Credit

The George Washington University School of Medicine and Health Sciences designates this enduring material for a maximum of 74 *AMA PRA Category 1 Credit(s)™.* Physicians should claim only the credit commensurate with the extent of their participation in the activity.

MOC Points

Successful completion of this CME activity enables the participant to earn up to 74 MOC points in the American Board of Internal Medicine's (ABIM) Maintenance of Certification (MOC) program.

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

Claiming Credit and MOC

Participants can earn up to 74 hours of CME credit and MOC points by completing the below online activities associated with the course.

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

Deadlines for Claiming MOC Points

ABIM Board Certified physicians need to claim MOC points for this course **by December 31, 2022** in order **for the MOC points to count toward any MOC requirements that are due by the end of 2022.**

CEHP will continue to submit participant completion data for the course until **August 20, 2023. No ABIM MOC credit will be awarded for this activity after August 20, 2023**.

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: 53**	**MOC Points: 53**
• There are four (4) sets of 100 board prep questions. • There are one (1) set of 100 photo opportunity questions. • You will see the correct answer and rationale after submitting each question. • You can only go in the forward direction when answering questions. • You cannot go backwards, but you can retake each set of questions as many times as you like.		
Online Primers and Study Guides	**CME Hours: 12**	**MOC Points: 12**
• There are eight (8) study guides and primers that present core material for you to review. • This PDF reviews information that summarizes important topics in photos, tables and short summaries.		

GUIDE TO ONLINE MATERIALS ACCESS

Initial Notification

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

Current Access

Instructions for accessing the Online Materials

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

- Course Page: https://cme.smhs.gwu.edu/idbr22/homepage

Important Links

Please note that you must be logged in to access.

- **Main Course Link:** https://cme.smhs.gwu.edu/idbr22/homepage
- **To Edit Your User Profile:** https://cme.smhs.gwu.edu/user/login?destination=my/edit/profile
- **To View/Download Your CME Certificate After Completing the Course:** https://cme.smhs.gwu.edu/user/login?destination=my/activities
- **To Access Your Receipt of Payment:** https://cme.smhs.gwu.edu/user/login?destination=my/orders

FACULTY LISTING

COURSE DIRECTORS

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

CO-DIRECTORS

Paul G. Auwaerter, MD
Johns Hopkins University
Baltimore, Maryland

David N. Gilbert, MD
Oregon Health and Science University
Portland, Oregon

Roy M. Gulick, MD, MPH
Weill Cornell Medical College
New York, New York

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

Andrew T. Pavia, MD
University of Utah
Salt Lake City, Utah

Richard J. Whitley, MD
University of Alabama at Birmingham
Birmingham, Alabama

FACULTY

Barbara D. Alexander, MD, MHS
Duke University
Durham, North Carolina

David M. Aronoff, MD, FIDSA
Indiana University School of Medicine
Indianapolis, Indiana

Taison Bell, MD
University of Virginia
Charlottesville, Virginia

Karen Bloch, MD
Vanderbilt University Medical Center
Nashville, Tennessee

Helen Boucher, MD
Tufts University School of Medicine
Boston, Massachusetts

Henry F. Chambers, MD
University of California San Francisco
San Francisco, California

Shireesha Dhanireddy, MD
University of Washington
Seattle, Washington

Susan Dorman, MD
Medical University of South Carolina
Charleston, South Carolina

Herbert L. DuPont, MD
The University of Texas-Houston Medical School
Houston, Texas

Rajesh T. Gandhi, MD
Harvard Medical School
Boston, Massachusetts

Khalil G. Ghanem, MD, PhD
Johns Hopkins University
Baltimore, Maryland

Steven M. Holland, MD*
Bethesda, Maryland

Michael Klompas, MD
Harvard Pilgrim Health Care Institute
Boston, Massachusetts

Camille Kotton, MD
Harvard Medical School
Boston, Massachusetts

Frank Maldarelli, MD, PhD*
Bethesda, Marylan

Edward Mitre, MD*
Bethesda, Maryland

Sandra Nelson, MD
Massachusetts General Hospital
Boston, Massachusetts

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

Robin Patel, MD
Mayo Clinic
Rochester, Minnesota

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

David L. Thomas, MD, MPH
Johns Hopkins University
Baltimore, Maryland

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

Allan R. Tunkel, MD, PhD
Brown University
Providence, Rhode Island

Kevin Winthrop, MD, MPH
Oregon Health & Science University
Portland, Oregon

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

FACULTY DISCLOSURES AND RESOLUTIONS

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

FACULTY (SPEAKERS)

- David Aronoff, MD
- Taison Bell, MD
- Karen C. Bloch, MD, MPH, FIDSA, FACP
- Shireesha Dhanireddy, MD
- Susan Dorman, MD
- Herbert L. Dupont, MD
- Khalil G. Ghanem, MD
- Roy M. Gulick, MD, MPH
- Steven M. Holland, MD
- Frank Maldarelli, MD
- Edward Mitre, MD
- Sandra Nelson, MD
- Stacey R. Rose, MD, FACP
- Michael Saag, MD
- Allan R. Tunkel, MD, PhD, MACP

PLANNERS

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

Both planners also resolved financial disclosures

STAFF

- Leticia Hall
- Naomi Loughlin
- Sheena P. King

The following faculty members (speakers) disclosed commercial relationships:

FACULTY MEMBER (Speaker)	FINANCIAL DISCLOSURE(S)
Paul G. Auwaerter, MD	• Consulting: EMD Serono, Humanigen, Pfizer • Ownership Interest: Johnson & Johnson, Wellstat • Research: Pfizer
Barbara D. Alexander, MD, MHS	• Consulting: Scynexis, Astellas, HealthTrackRx • Research Grant (Institution): Leadiant • Clinical Trials (Site PI/Study PI): Astellas, Cidara, Scynexis, Shire, F2G • Royalties (Chapter Author): UpToDate
Helen Boucher, MD	• Editor: ID Clinics of North America, Antimicrobial Agents and Chemotherapy, Sanford Guide • Treasurer: Infectious Diseases Society of America • Member: ID Board, American Board of Internal Medicine • Voting Member: Presidential Advisory Council on Combating Antibiotic Resistant Bacteria (PACCARB)
Henry F. Chambers, MD	• Equity: Moderna, Merck • Data Monitoring Committee: Merck
Rajesh Gandhi, MD	• Scientific Advisory Board: Merck
David Gilbert, MD	• Consulting: Biomerieux • Grantee: Biofire (diagnostics)
Michael Klompas, MD	• Grant Funding: Centers for Disease Control and Prevention, Agency for Healthcare Research and Quality, Mass Department of Public Health • Royalties: UpToDate
Camille Kotton, MD	• Consulting: Biotest (CMV immunoglobulins), Hookipa (CMV Vaccine trial), Merck (CMV), Oxford Immunotec (CMV), Takeda (CMV) • Scientific Advisory Board: Biotest, Oxford Immunotec (CMV), Takeda (CMV)

Kieren A. Marr, MD	• Consulting: Cidara Therapeutics • Employment: Sfunga Therapeutics • Ownership Interests: Pearl Diagnostics, Sfunga Therapeutics
Robin Patel, MD	• Contracted Research: ContraFect, TenNor Therapeutics Limited, BioFire • Consulting: Curetis, Specific Technologies, Next Gen Diagnostics, PathoQuest, Selux Diagnostics, 1928 Diagnostics, PhAST, Torus Biosystems, Day Zero Diagnostics, Mammoth Biosciences, CARB-X, Qvella, Netflix • Patent: Bordetella pertussis/parapertussis PCR; a device/method for sonication; an anti-biofilm substance • Mayo Clinic and Dr. Patel have a relationship with Adaptive Phage Therapeutics and Pathogenomix
Andrew T. Pavia, MD	• Commercial Interests: Antimicrobial Therapy Inc, WebMD, Merck and Company
David L. Thomas, MD, MPH	• Data and Safety Monitoring Board: Merck • Advisory Board: Merck, Excision Bio
Barbara W. Trautner, MD	• Consulting: Genentech (Covid-related research)
Richard J. Whitley, MD	• Member of the Board of Directors and the Health Policy Advisory Board: Gilead Sciences • Chairperson: NIAID Covid-19 Vaccine DSMB, Merck Letermovir DMC and GSK IDMC (Zoster) • Scientific Advisory Board: Treovir, LLC • Member of the Board of Directors: Evrys Bio, Virios Therapeutics
Kevin L. Winthrop, MD	• Research: Insmed • Consulting: Insmed, Spero, Red Hills, Paratek, AN2

Agenda Day 4: Tuesday, August 23, 2022

#	Start		End	Presentation	Faculty
AM Moderator: Roy Gulick, MD					
QP4	**8:30 AM EDT**	**-**	**9:00 AM EDT**	**Daily Question Preview Day 4**	**Roy Gulick, MD**
34	9:00-AM	-	9:30 AM	Clinical Manifestations of Human Retroviral Diseases and Slow Viruses	Frank Maldarelli, MD
35	9:30 AM	-	10:15 AM	HIV Associated Opportunistic Infections I	Henry Masur, MD
36	10:15 AM	-	10:30 AM	HIV Diagnosis	Frank Maldarelli, MD
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	-	1:00 PM	Lunch Break	
BR4	**1:00 PM**	**-**	**2:00 PM**	**Board Review Day 4**	**Drs. Gulick (Moderator), Bennett, Bloch, Dorman, Maldarelli, Pavia, and Saag**
PM Moderator: Andy Pavia, MD					
40	2:00 PM	-	2:45 PM	Syndromes that Masquerade as Infections	Karen Bloch, MD
41	2:45 PM	-	3:30 PM	Tuberculosis in Immunocompetent and Immunosuppressed Hosts	Susan Dorman, MD
42	3:30 PM	-	4:15 PM	Non-AIDS-Defining Complications of HIV/AIDS	Michael Saag, MD
FC8	**4:15 PM**	**-**	**4:45 PM**	**Faculty Q&A**	**Drs. Gulick (Moderator), Block, Dorman, Dupont, Maldarelli, and Saag**
43	4:45 PM	-	5:45 PM	Respiratory Viral Infections Including Influenza, Immunocompetent, and Immunocompromised Patients	Andy Pavia, MD
44	5:45 PM	-	6:00 PM	Pharyngitis Syndromes Including Group A Strep Pharyngitis	Karen Bloch, MD
45	6:00 PM	-	6:30 PM	Core Concepts: Antiviral Drugs	Andy Pavia, MD
FC9	**6:30 PM**	**-**	**7:00 PM**	**End of the Day Meet the Professor (Live Registrants Only)**	**Drs. Bloch, Gulick, Dorman, Maldarelli, Pavia and Saag**

QP4

Daily Question Preview 4

Dr. Roy Gulick (Moderator)

QP4 – Daily Question Preview: Day 4

Moderator: Roy Gulick, MD

IDBR INFECTIOUS DISEASE BOARD REVIEW AUGUST 20-24 2022

Daily Question Preview: Day 4

Moderator: Roy Gulick, MD

7/31/2022

PREVIEW QUESTION

4.1 An asymptomatic patient with a new diagnosis of HIV (CD4 = 10 cells/uL and HIV Viral Load 300,000 copies/uL is started on antiretroviral therapy (dolutegravir plus tenofovir alafenamide/emtricitabine).

His labs are unremarkable as is his chest xray.

His serum toxoplasma IgG is positive.

He asks whether you want to add prophylaxis for pneumocystis pneumonia but warns you that twice when he has taken sulfonamides he has developed hives and laryngeal edema.

PREVIEW QUESTION

4.1 What would you recommend regarding PCP and Toxo prophylaxis?

A) No chemoprophylaxis: his viral load should fall quickly, and his CD4 will rise quickly in response to this first exposure to antiretroviral therapy

B) Trimethoprim sulfamethoxazole plus solu-medrol dose pak

C) Dapsone

D) Aerosol pentamidine plus pyrimethamine

E) Atovaquone

PREVIEW QUESTION

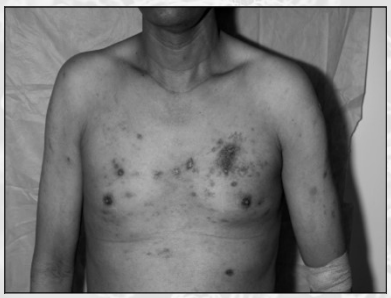
4.2 The patient whose photo is shown is HIV positive (CD4=10 cells/uL, VL=2 mil copies) and has noted these lesions developing on his trunk, face and extremities over the past 8 months.

He has had low grade fevers for several months.

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

PREVIEW QUESTION

4.2



PREVIEW QUESTION

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

A) HHV-6

B) CMV

C) Cryptococcus neoformans

D) Bartonella

E) Rhodococcus

QP4 – Daily Question Preview: Day 4

Moderator: Roy Gulick, MD

PREVIEW QUESTION

4.3 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.

PREVIEW QUESTION

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

Which of these regimens do you recommend?

A) IM cabotegravir/rilpivirine

B) tenofovir alafenamide/emtricitabine/rilpivirine

C) abacavir/lamivudine + efavirenz

D) dolutegravir/lamivudine

E) tenofovir alafenamide/emtricitabine/bictegravir

PREVIEW QUESTION

4.5 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.

PREVIEW QUESTION

4.5 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) Etravirine

E) Emtricitabine

PREVIEW QUESTION

4.6 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.

PREVIEW QUESTION

4.6 The genotype shows an M184V and K65R mutations.

Which nRTI drugs would you include?

A) ZDV

B) TDF

C) ddI

D) ABC

QP4 – Daily Question Preview: Day 4

Moderator: Roy Gulick, MD

PREVIEW QUESTION

4.7 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.

PREVIEW QUESTION

4.7 Which statement is correct?

A) ART should not be offered.

B) ART would decrease his symptoms.

C) ART has long-term virologic benefits in this setting.

D) ART has long-term clinical benefits in this setting.

PREVIEW QUESTION

4.8 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

PREVIEW QUESTION

4.9 38 y/o M physician, previously healthy, with periodic travel to South Africa for medical research work.

Reports a positive TST six years ago, and admits poor adherence with a course of isoniazid preventive therapy at that time.

Now with 5 weeks of fever, chills, night sweats, 10-lb wt loss, productive cough. CXR shows RUL cavitary lesion.

Sputum GeneXpert MTB/RIF test result is "MTB detected" and "Rifampin resistance not detected" (culture results pending).

HIV test is negative, liver chemistries are normal.

PREVIEW QUESTION

4.9 What is the best course of action?

A) Prescribe 9 months of isoniazid for presumed latent TB infection

B) Do nothing pending culture results

C) Start TB treatment with rifampin, isoniazid, PZA, ethambutol

D) Start TB treatment with rifampin, isoniazid, PZA

E) Start TB treatment with a regimen for multidrug-resistant TB

PREVIEW QUESTION

4.10 24 y/o M from Zambia, in U.S. for community college, recently tested HIV-positive with CD4 400, not yet on ART.

He has a prominent anterior cervical lymph node but is otherwise well-appearing with normal BMI, normal liver and renal chemistries, and mild anemia.

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

QP4 – Daily Question Preview: Day 4

Moderator: Roy Gulick, MD

PREVIEW QUESTION

4.10 What is the best course of action with respect to the timing of TB therapy and HIV therapy?

A) Start ART immediately, defer TB tx

B) Start TB tx immediately, defer ART until after completion of 6 months of TB tx

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

D) Start both TB tx AND ART immediately

PREVIEW QUESTION

4.11 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.

PREVIEW QUESTION

4.11 Which if 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

PREVIEW QUESTION

4.12 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, bupropion, norco, prilosec, trazodone, pravachol ibuprofen

PREVIEW QUESTION

4.12 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.
- 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

PREVIEW QUESTION

4.12 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

QP4 – Daily Question Preview: Day 4

Moderator: Roy Gulick, MD

PREVIEW QUESTION

4.13 A 45-year-old international agricultural researcher presents in June in the US with fever, cough, diarrhea, myalgia, sore throat, and dyspnea. He is hypotensive and hypoxemic.

CBC shows mild leukopenia, chemistry panel and LFT's are normal.

Three days prior to the onset of his illness he was inspecting poultry operations Jiangsu Province, China.

PREVIEW QUESTION

4.13 Assuming the he acquired his severe respiratory illness from the poultry he was inspecting, the most likely diagnosis would be:

A) H1N1 influenza

B) H3N2 influenza

C) Leptospirosis

D) H7N9 influenza

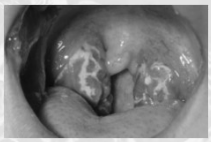
E) Blastomycosis

PREVIEW QUESTION

4.14 38yo female with 1 day of sore throat and fever.

Childhood history of anaphylaxis to penicillin.

Physical exam
- T=102.3
- HEENT-tonsillar purulence
- Neck-Tender bilateral anterior LAN



Labs:
- Rapid strep antigen test negative

PREVIEW QUESTION

4.14 What is the most appropriate antimicrobial treatment?

A) Cephalexin

B) None

C) Doxycycline

D) Clindamycin

E) Levofloxacin

PREVIEW QUESTION

4.15 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.

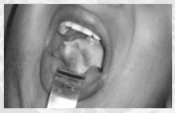
PREVIEW QUESTION

4.15 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.

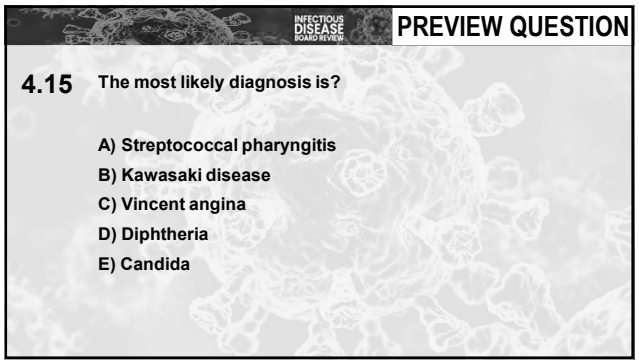


An S3 gallop is heard.

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

QP4 – Daily Question Preview: Day 4

Moderator: Roy Gulick, MD



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 20-24 2022

Clinical Manifestations of Human Retroviral Diseases and Slow Viruses

Frank Maldarelli, MD, PhD *
Bethesda, Maryland

6/24/2022

INFECTIOUS DISEASE BOARD REVIEW AUGUST 20-24 2022

Disclosures of Financial Relationships with Relevant Commercial Interests

- **None**

Adults and Children Estimated to be Living with HIV 2020-2021

Total Infections: 37.7 million [30.2 million – 45.1 million]
28.2 million accessing antiretroviral therapy
HIV prevalence is increasing: 1.5 million new infections; 680,000 deaths in 2020

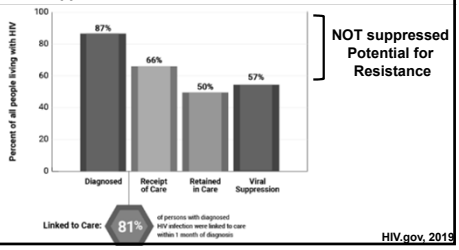
UNAIDS

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

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

CDC, 2020

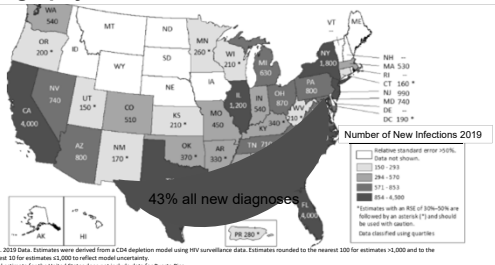
HIV Eradication Goals NOT Met
90 % Diagnosed: Close
90% Undergoing Antiretroviral Therapy: NOT Met
90% Viral RNA Suppressed: NOT Met



Linked to Care: 81% of persons with diagnosed HIV infection were linked to care within 1 month of diagnosis

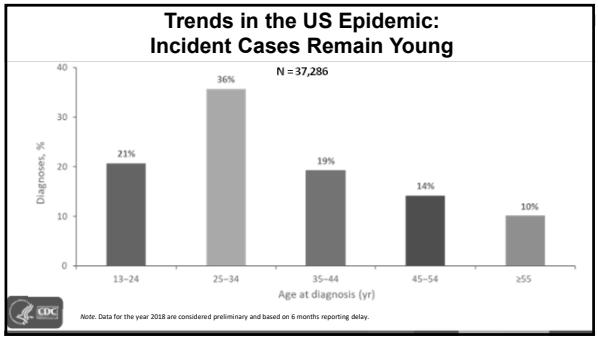
HIV.gov, 2019

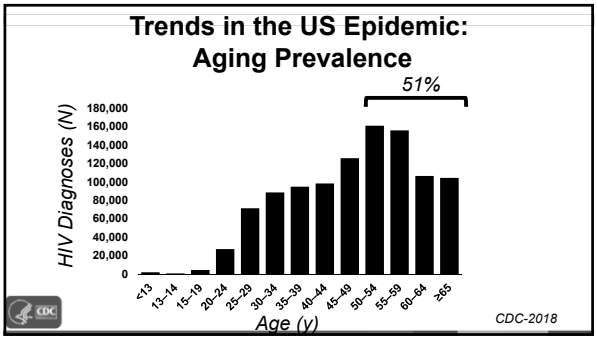
Trends in the US Epidemic:
Geography: Shift South and Out of Metro Areas

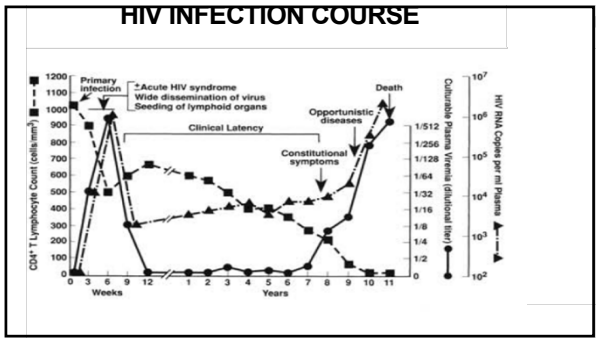


34 – Clinical Manifestations of Human Retroviral Diseases and Slow Viruses

Speaker: Frank Maldarelli, MD





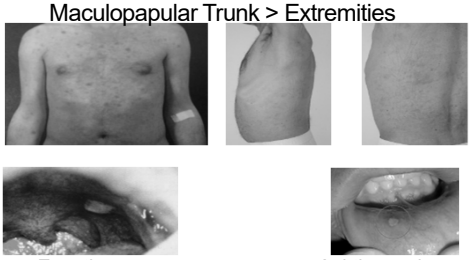


Acute HIV Syndrome

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 Diagnosis: Question #1

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

ELISA remains reactive. HIV-2 assay is negative.

Viral RNA on therapy is <40 c/ml.

34 – Clinical Manifestations of Human Retroviral Diseases and Slow Viruses

Speaker: Frank Maldarelli, MD

HIV Diagnosis: Question #1 continued

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

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

Early Antiretroviral Therapy

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

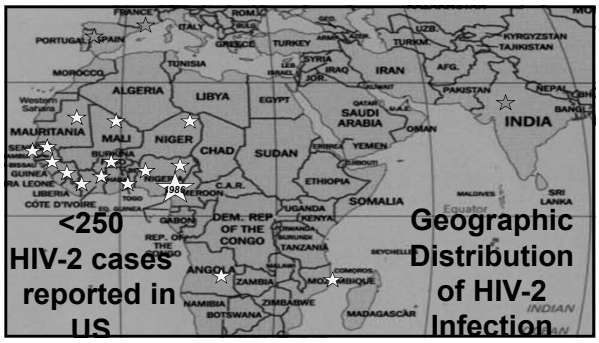
HIV Clinical Presentation: Question #2

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

CD4 cell count is 350 cells/µl.

Which of the following is correct?

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



HIV-1 and HIV-2

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

Question #3

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

34 – Clinical Manifestations of Human Retroviral Diseases and Slow Viruses

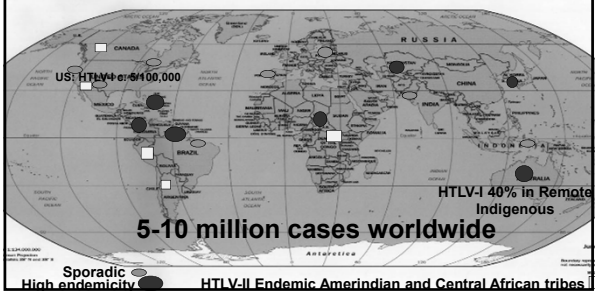
Speaker: Frank Maldarelli, MD

Question #4

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

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

HTLV DISTRIBUTION



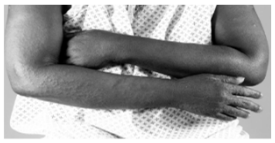
HTLV-I Transmission, Pathogenesis, Diagnostics

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

Question #5

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

WBC: 50,000, 90% lymphocytes



Which is most likely cause of her presentation?

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

HTLV-I Acute T cell Leukemia (ATL)

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

Question #6

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

WBC = 7500 cells/µl

CD4 T cell = 1000 cells/µl

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

CSF protein: 75 mg/dl

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Speaker: Frank Maldarelli, MD

Question #6 Continued

The etiologic agent associated with this illness is also associated with

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

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

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

HTLV-I TSP/HAM

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

Therapy of HTLV-I TSP/HAM

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

Question #7

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

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

Question #7

62 year old man from Jamaica with rheumatoid arthritis has not responded to several antirheumatic drugs including the methotrexate that he is currently taking. He is now being considered for treatment with rituximab. He is hepatitis B positive (surface antibody positive, surface antigen negative) and HTLV-I positive (antibody and PCR), but has never had complications from HTLV. He will continue to receive Tenofovir + FTC to prevent HBV reactivation, and you are consulted regarding the use of antiretrovirals in HTLV in this circumstance. HTLV-I drug resistance. Which of the following is most correct:

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

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Speaker: Frank Maldarelli, MD

Question #8

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

Which of the following is most correct:

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

Pearls

HTLV-1 Infection

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

Associated Infections

- **Strongyloides hyperinfection**
- **Norwegian Scabies**
- **Pneumocystis**
- **MAC**

HTLV-II

Not a cause of disease
A distractor

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

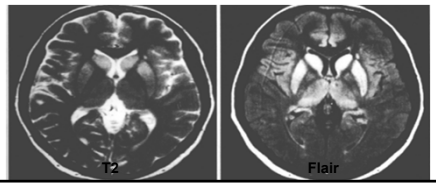
SLOW VIRUSES

Prion Disease Question #1

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

Acquisition of this illness was most likely due to:

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

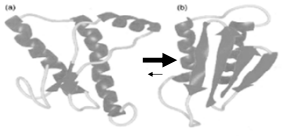


Prion Diseases: Transmissible Spongiform Encephalopathies

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

Prion Disease Pathogenesis
A. Initiation

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



NORMAL ABNORMAL

Transition to abnormal conformation is rare but essentially irreversible

Naturally occurring mutations favor interconversion

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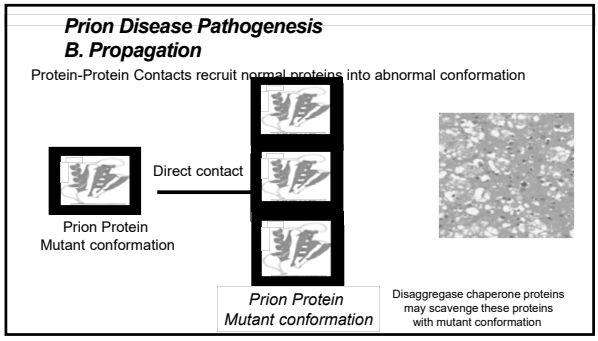


Spontaneous Creutzfeldt-Jacob Disease (sCJD) Epidemiology

- 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

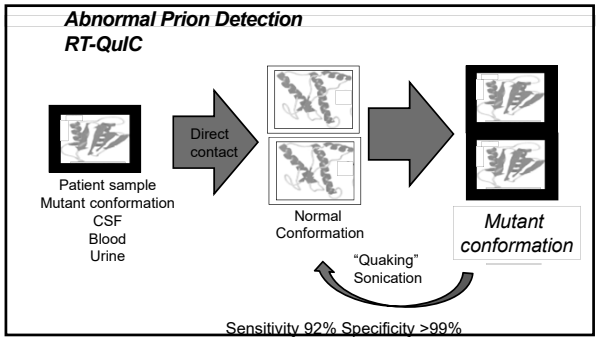
Dementia Comparison

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 Creutzfeld Jakob Disease: .

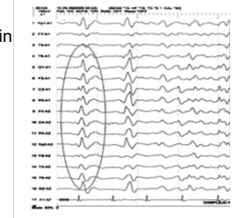
A. 14-3-3 protein: Positive
B. RT-QuIC: Positive
C. T-tau protein: 3000 pg/ml (normal 0-1150 pg/mL)
D. Aβ42: 1250 pg/mL (normal >1026 pg/mL)



Spontaneous Creutzfeldt-Jacob Disease

Typical Clinical Presentation

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



Herran, BMC Neurology 2018

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Speaker: Frank Maldarelli, MD

Prion Disease Question #2

A 40 year old man presents with dementia progressing over the last year. He was born in rural Indonesia, lived in London from 1985 – 2010, then moved to Philadelphia.

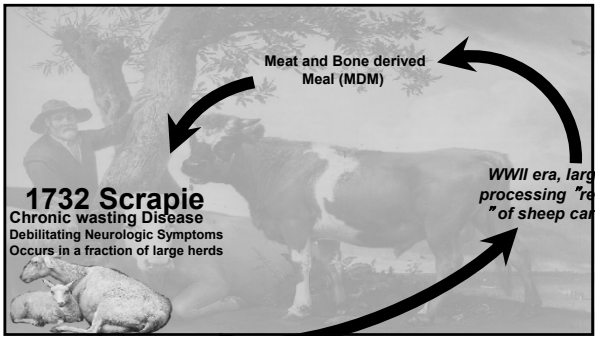
Which of the following diseases is most likely the cause of his symptoms:

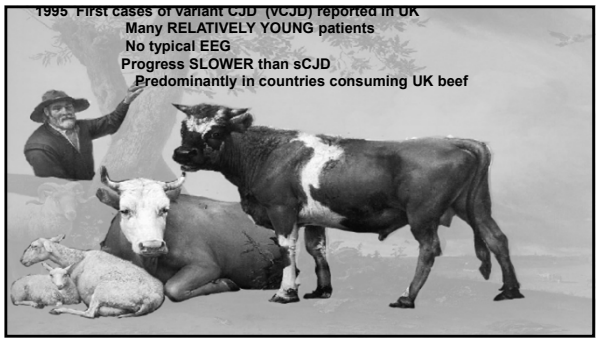
A. Kuru

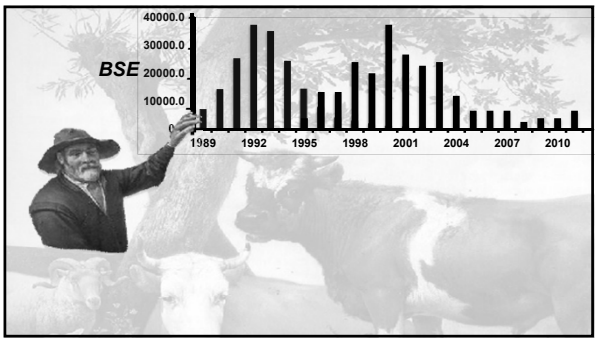
B. variant Creutzfeldt-Jacob Disease

C. Familial Creutzfeldt-Jacob Disease

D. Rabies







Question #4 vCJD Geographic Distribution

Residence in which of the following countries after 1980 represents the highest risk for acquiring variant CJD (vCJD):

A. France

B. Borneo

C. United States

D. Australia

E. Argentina

Numbers of vCJD Cases Worldwide

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

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

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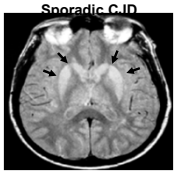
vCJD vs. sCJD

	sCJD	vCJD
Source	Spontaneous event	Ingested beef
Distribution	Worldwide	Linked to Beef originating largely in UK
Median Age (y)	68	28
Progression	SHORTER	LONGER
EEG	Typically abnormal	NOT Typically abnormal
MRI Basal ganglia	"Double Hockey Stick"	"Pulvinar sign"
Pathology	Abnormal Prion Protein deposits	"Florid Plaques"

sCJD

Sporadic CJD

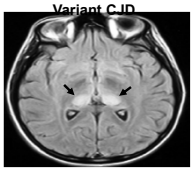


T2 axial proton weighted Putamen and caudate head "Double hockey stick sign"

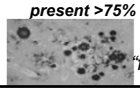
"Abnormal Prion accumulation"

vCJD

Variant CJD



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



"florid plaques"

Prion Diseases Question #5

A 49 year old man recently emigrated from Japan presents with rapidly progressing dementia.

He underwent a meningioma resection with dura mater graft in Japan 35 years ago.

He is an avid deer hunter and consumes venison.

What is the most likely cause of his dementia:

A. Iatrogenic CJD from the dura mater graft

B. CJD from eating deer.

C. HTLV-I

D. Spontaneous CJD

Iatrogenic CJD ~450 cases

Definite Causes

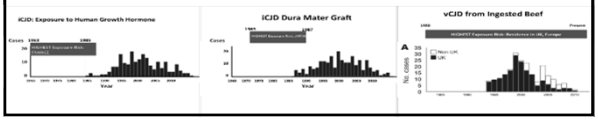
- **Pituitary extracts**
  - **Human Growth Hormone**
  - **Delay may be >30 y**
  - **(Role in AD as well?)**
- **Dura mater grafts**
  - **Mostly Lyodura brand**
- **Transplants**
  - **Corneal**
  - **Pericardium**
  - **Liver**
- **Instrumentation/Laboratory accident**
  - **NeurosurgeonsImplantable Neurosurgical-implanted EEG, stereotactic procedures**
  - **Pathologist**
  - **Scientists (Emilie Jaumain, FR)**

No Link

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

Transmissible Spongiform Encephalopathy:Time and Place

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



Zoonotic Transmission CJD

Documented Risk

- Ingestion of Beef
  - Geographically limited
  - Emphasis on UK, France

No Documented Risk

- Mink:
  - Transmissible Mink Encephalopathy
- Elk, Mule deer:
  - Chronic Wasting Disease
- Sheep, goats
  - Scrapie
- Cat:
  - Feline Spongiform Encephalopathy

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Speaker: Frank Maldarelli, MD

CJD and Blood Supply

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

CJD and Recommendations

•Patient

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

•Family members

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

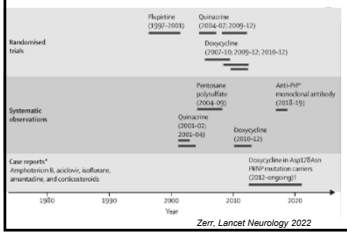
Transmissible Spongiform Encephalopathy

Infection Control Issues

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

Transmissible Spongiform Encephalopathy

Multiple trials 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

Kuru "shivering,trembling"

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

Resources

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

35

HIV-Associated Opportunistic Infections I

Dr. Henry Masur

IDBR INFECTIOUS DISEASE BOARD REVIEW AUGUST 20-24 2022

Management of AIDS-Related Opportunistic Infections I

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

7/24/2022

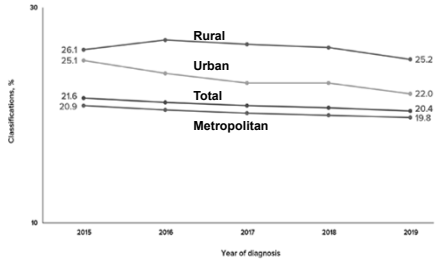
INFECTIOUS DISEASE BOARD REVIEW AUGUST 20-24 2022

Disclosures of Financial Relationships with Relevant Commercial Interests

- None

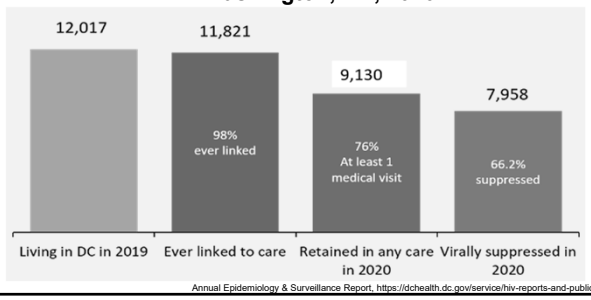
AIDS at Time of Diagnosis 2015-2019, United States

20-25% PWH Continue to Present Late in Disease



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

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



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

Causes of Death in Persons With HIV

	DAD Study (1999-2011) N=3909 deaths		London (2016) N=206 deaths	
AIDS-related	[illegible]	[illegible]	[illegible]	[illegible]
Liver-related	515	**(13%)**	12	**(6%)**
CVD-related	[illegible]	[illegible]	[illegible]	[illegible]
Non-AIDS cancer	590	**(15%)**	40	**(29%)**
Drug-related	[illegible]	[illegible]	[illegible]	[illegible]
Bacterial infection	259	**(7%)**	14	**(7%)**

Smith et al Lancet 2014; 384: 241–48
Croxford, HIV Medicine, 2019

Question #1

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

What would you recommend regarding PCP and Toxo prophylaxis?

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

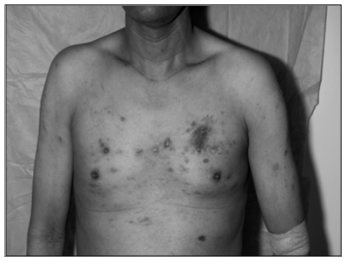
Question #2

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

He has had low grade fevers for several months.

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

Question #2

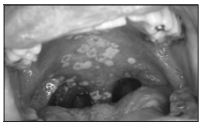


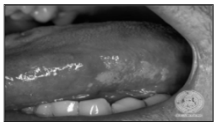
Question #2

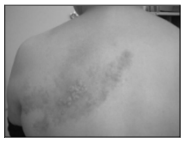
The most likely cause of these skin lesions, if they are not Kaposi sarcoma, is:

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

Clinical Indicators of Immunosuppression







Cardinal AIDS-Defining Illnesses

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

Is COVID-19 an HIV Related Opportunistic Infection?

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

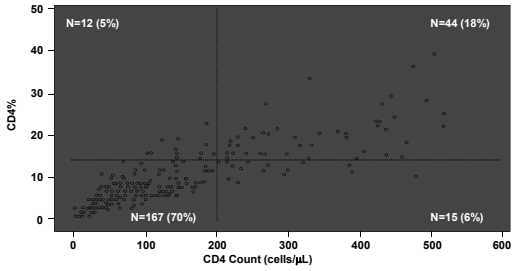
PS: Monkeypox could be presented in terms of prior US cases linked to travel or to the 2003 pet shop related outbreaks but…. the current outbreak in MSM will NOT show up on exam—too new and too many unresolved issues!!

Susceptibility to Opportunistic Infections Patients with HIV

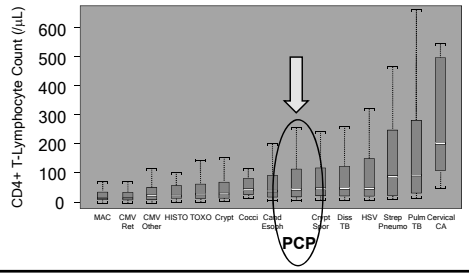
- **CD4 Count**
  - Current count is most important
  - Prior nadir count is much less important
- **Viral Load**
  - Independent risk factor for OIs

At What CD4 Counts Do Opportunistic Infections Occur?

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



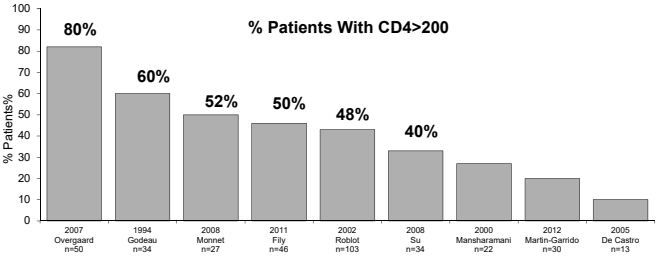
CD4+ Lymphocyte Counts Are Excellent Predictor of the Occurrence of Opportunistic Infections for HIV/AIDS



CD4 Counts in Non-HIV Patients

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

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



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

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

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

Antiretroviral Therapy

When to Start ART Following Opportunistic Infection

You Have Seen This Question!!

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

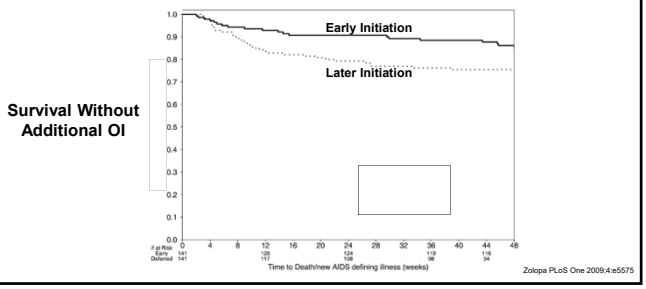
When should she start ART?

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

When to Start ART Following Opportunistic Infection

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

ART Initiation Following HIV Related Opportunistic Infections
Early Favors Survival



Zolopa PLoS One 2009;4:e5575

When to Start ART Following Opportunistic Infection

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

Primary and Secondary OI Prophylaxis

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

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

***Some experts would give Histo primary prophylaxis with itraconazole in high risk situations if CD4<150**

Prophylaxis NOT Routinely Recommended in US

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

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

Discontinue Prophylaxis/Chronic Maintenance

Board might consider this a "look up"

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

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

Primary Coccidiomycosis Prophylaxis 2022 OI Guideline

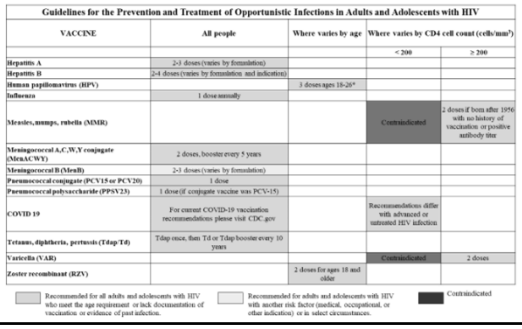
Testing

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

Primary Prophylaxis

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

OI Guidelines Vaccination Recommendations

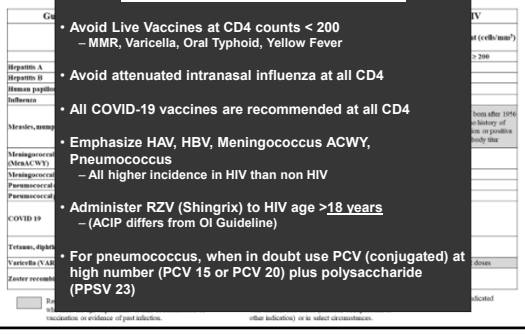


Guidelines for the Prevention and Treatment of Opportunistic Infections in Adults and Adolescents with HIV

VACCINE	All people	Where varies by age	Where varies by CD4 cell count (cells/mm³)	
			< 200	≥ 200
Hepatitis A	2-3 doses (varies by formulation)			
Hepatitis B	2-4 doses (varies by formulation and indication)			
Human papillomavirus (HPV)		3 doses ages 18-26*		
Influenza	1 dose annually			
Measles, mumps, rubella (MMR)			Contraindicated	2 doses if born after 1976 with no history of vaccination or positive antibody titer
Meningococcal A,C,W,Y conjugate (MenACWY)	2 doses, booster every 5 years			
Meningococcal B (MenB)	2-3 doses (varies by formulation)			
Pneumococcal conjugate (PCV15 or PCV20)	1 dose			
Pneumococcal polysaccharide (PPSV23)	1 dose if conjugate vaccine was PCV<15)			
COVID 19	For current COVID-19 vaccination recommendations please visit CDC.gov		Recommendations differ with advanced or untreated HIV infection	
Tetanus, diphtheria, pertussis (Tdap/Td)	Tdap once, then Td or Tdap booster every 10 years			
Varicella (VAR)			Contraindicated	2 doses
Zoster recombinant (RZV)		2 doses for ages 18 and older		

Recommended for all adults and adolescents with HIV who meet the age requirement or lack documentation of vaccination or evidence of past infection. Recommended for adults and adolescents with HIV with another risk factor (medical, occupational, or other indication) or in select circumstances. Contraindicated

OI Gu…tions



This Is All Oversimplified, But for the Exam

- **Avoid Live Vaccines at CD4 counts < 200**
  - **MMR, Varicella, Oral Typhoid, Yellow Fever**
- **Avoid attenuated intranasal influenza at all CD4**
- **All COVID-19 vaccines are recommended at all CD4**
- **Emphasize HAV, HBV, Meningococcus ACWY, Pneumococcus**
  - **All higher incidence in HIV than non HIV**
- **Administer RZV (Shingrix) to HIV age >18 years**
  - **(ACIP differs from OI Guideline)**
- **For pneumococcus, when in doubt use PCV (conjugated) at high number (PCV 15 or PCV 20) plus polysaccharide (PPSV 23)**

Pneumococcal Vaccine for Persons With HIV

Bottom Line: Give Polyvalent Pneumococcal Conjugate PCV15 or 20 and Then See Details

- Administer either 15-valent pneumococcal conjugate vaccine (PCV15) or 20-valent (PCV20)
- If PCV15 is used, a dose of 23-valent pneumococcal polysaccharide vaccine (PPSV23) should be administered at least 8 weeks later.
- For PWH who previously started or completed a pneumococcal vaccination series, there is no need to restart the series.
  - PWH who previously received only the 13-valent pneumococcal conjugate vaccine (PCV13) should receive PPSV23 at least 8 weeks later
- PWH who have received PCV13 and PPSV23 should receive a booster PPSV23 at least 5 years after the first dose.
- If they were <65 at the time of the second dose, they should receive a third and final dose at or after age 65, at least 5 years after the second PPSV23 dose
- PWH who have only received PPSV23 may receive a PCV (either PCV20 or PCV15) ≥1 year after their last PPSV23 dose.
- When PCV15 is used in those with history of PPSV23 receipt, it need not be followed by another dose of PPSV23.

Who Should be Vaccinated for HBV

- **People without chronic HBV infection and without immunity to HBV infection (anti-HBs <10 mIU/mL)**
  - ACIP and NIH OI Guidelines Differ
    - Whether to Use Single or Double Dose for 3 dose series
  - The specific regimens are too granular and changing to likely be on exam
  - NIH/IDSA and CDC have different perspectives re rechecking antibody
    - 1-2 months post vaccine and then
    - Annually and boost responders if annual level <10mIU/ml

HBV Non-Responders

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

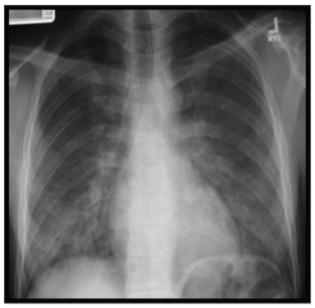
HBV Immunization for Persons with Isolated Anti HBc

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

Post Exposure to HBV for PWH

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

HIV Associated Pulmonary Disease



Etiology of HIV Associated Pulmonary Disorders

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

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

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

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

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

Approach to Diagnosis and Therapy of Pneumonia in PWH

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

Pneumococcal Disease in Persons with HIV Infection

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

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

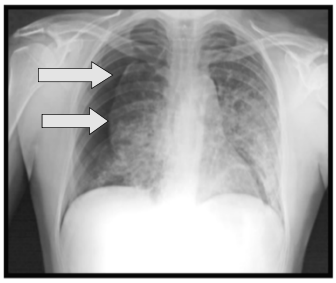
Strategies to Reduce Incidence of Pneumonia for Patients with HIV

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

Question #3

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

HIV Patient with Shortness of Breath



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The patient lives in Chicago, works in an office and has never left the Midwest and no unusual exposures.
The most likely INFECTIOUS cause of this pneumothorax is:

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

Pneumocystis Jirovecii **(Formerly *P. carinii*)**

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

Host Susceptibility to PCP

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

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

No Feature is Present 100% of Initial Presentations

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

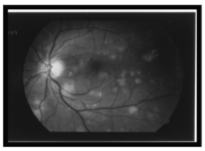
Walzer, Ann Intern Med 1974

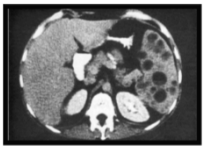
PCP is More Subacute in Persons With HIV Than Other Immunosuppressed Persons

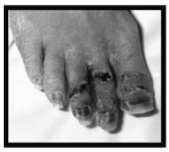
Sign or Symptom	HIV (n=48)	Non-HIV (n=38)
Symptom		
Fever	81%	87%
Cough	81%	71%
Shortness of breath	68%	66%
Duration of symptoms,	28 days	5 days
Temp> 38°C	76%	92%
PaO_2	69 mm Hg	52 mm Hg
A-a gradient	41 mm Hg	59 mm Hg
% with normal ABG	5-20%	

Kovacs et al. Ann Intern Med 1984

Uncommon Manifestations of PCP

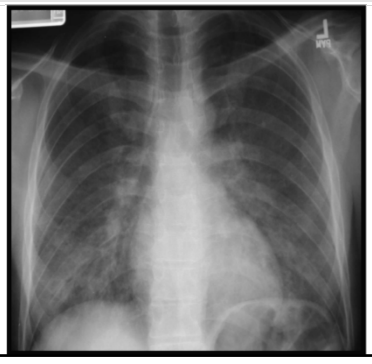




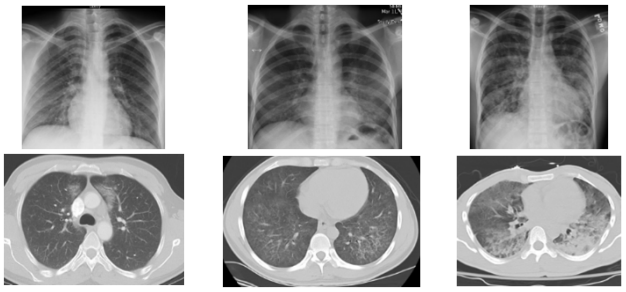


Imaging of PCP

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



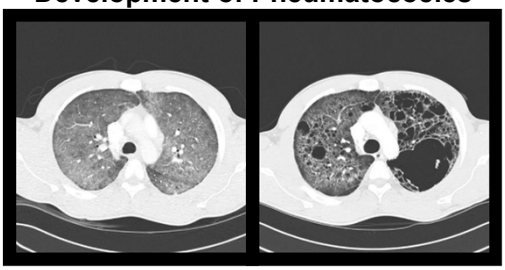
HIV Related PCP



Asymptomatic
Incidental Finding

⇩

Development of Pneumatocoeles



May 23 June 13

Radiologic Patterns Associated with Documented Pneumocystis Pneumonia

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

Radiologic Patterns Associated with Documented Pneumocystis Pneumonia

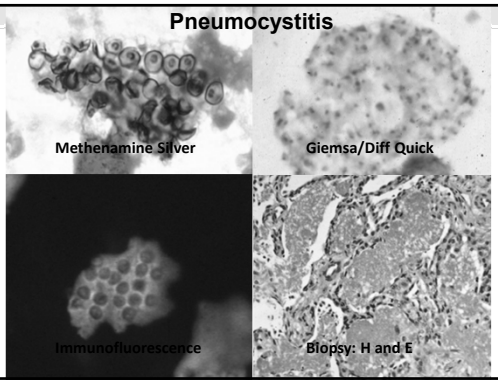
- **Other Patterns Recognized**
  - **(Other concomitant infectious or neoplastic disease processes?)**
  - **Lobar infiltrates**
  - **Upper lobe infiltrates**
  - **Pneumothorax**
  - **Solitary nodules**
  - **Cavitating lesions**
  - **Infiltrates with effusions**
  - **Asymmetric or unilateral processes**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

Diagnosis of Pneumocystis Pneumonia

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

1957 ↓ 2022

Pneumocystitis



PCR
For Diagnosis of Pneumocystis in Bronchoalveolar Lavage

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

PCR
For Diagnosis of Pneumocystis in Bronchoalveolar Lavage

- **High**
  - No
- **High**
  - Po
  - Cy

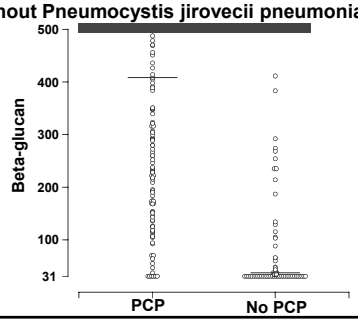
Negative BAL PCR rules out PCP

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

Is There A Serologic Test for PCP?
No!

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

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



Sax PE. *Clin Infect Dis* 2011

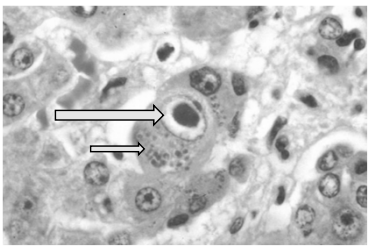
Question #4

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

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

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

CMV Cytology



Eosinophilic Intranuclear Inclusion and Coarse Basophilic Cytoplasmic Inclusions

CMV Almost Never Causes Pneumonia In HIV Infected Pts

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

Question #5

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

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

Pulse oximetry shows an O2 saturation of 85%

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

The ABG lab reports methemoglobinemia = 25%

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

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

Answer #5

Methemoglobinemia = Methemoglobin>3%

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

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

Answer #5

Methemoglobinemia = Methemoglobin>3%

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

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

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

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

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

Question #6

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

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

An EKG done by the code team is normal.

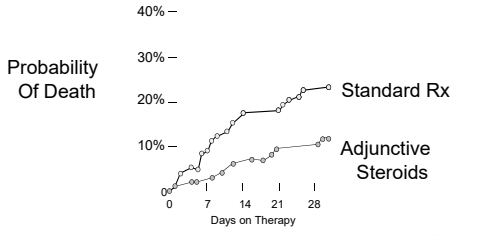
What Non cardiac toxicity of pentamidine would be most likely

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

Therapy for Pneumocystis Pneumonia

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

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



(Bozette, NEJM 5/90)

A Question That Could Be on Boards

- What drugs should only be given after screening for Glucose-6-Phosphate Dehydrogenase
- Drugs
  - Primaquine
  - Dapsone
  - And…..fluoroquinolones, Nitrofurantoin, Nalidixic acid, tafenoquine

A Question That Could Be on Boards

- What drugs should only be given after screening for Glucose-6-Phosphate Dehydrogenase
  - G6PD is common and nationality is increasingly difficult to define as a predictor
  - Males have more severe hemolysis since this is X linked
- Presentation
  - Hemolysis, jaundice, back and abdominal pain 2-4 days post drug exposure
  - Smear shows hemolytic pattern and "Heinz bodies"
  - Hemoglobinuria, high retic count
- Drugs
  - Primaquine
  - Dapsone
  - And…..fluoroquinolones, Nitrofurantoin, Nalidixic acid, tafenoquine
- Screening
  - Qualitative assay is used in urgent situations before drug administration
    - Testing after hemolysis can be misleading
  - Other management issues are too complicated for ID boards

How to Manage Patients Who Are Failing TMP-SMX

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

Reasons to Deteriorate During Treatment for PCP

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

Reasons to Deteriorate During Treatment for PCP

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

Patients Failing TMP-SMX Not Testable!

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

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

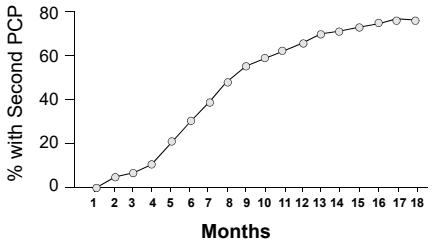
Toxicities of TMP-SMX and Pyrimethamine-Sulfadiazine

Drug	Toxicities
TMP-SMX	↓WBC, ↓plat, ↑LFT, ↑Creat, ↑Amylase, rash, fever, pruritus, "Sepsis" syndrome-distributive shock Hyperkalemia (TMP) Cross reactivity: dapsone (± 50%)
Pyrimethamine-Sulfadiazine	Similar to TMP-SMX Folinic acid necessary (not folate) to prevent cytopenias

Toxicity and Other Considerations Regarding Antipneumocystis Therapy

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

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



Fischl/ACTG 002, 10/88

Indications for Primary and Secondary PCP Prophylaxis

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

Whether prophylaxis is needed at CD4 100-200 with suppressed viral load is too controversial for exam

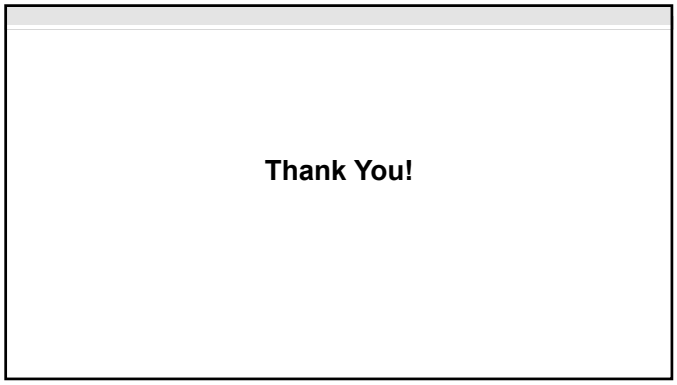
Non HIV---When Is PCP Prophylaxis Indicated

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

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

Primary or Secondary Prophylaxis Agents for Pneumocystis Pneumonia

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



36

HIV Diagnosis

Dr. Frank Maldarelli

36 – HIV Diagnosis

Speaker: Frank Maldarelli, MD

IDBR INFECTIOUS DISEASE BOARD REVIEW AUGUST 20-24 2022

HIV Diagnosis

Frank Maldarelli, MD, PhD *
Bethesda, Maryland

6/24/2022

INFECTIOUS DISEASE BOARD REVIEW AUGUST 20-24 2022

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

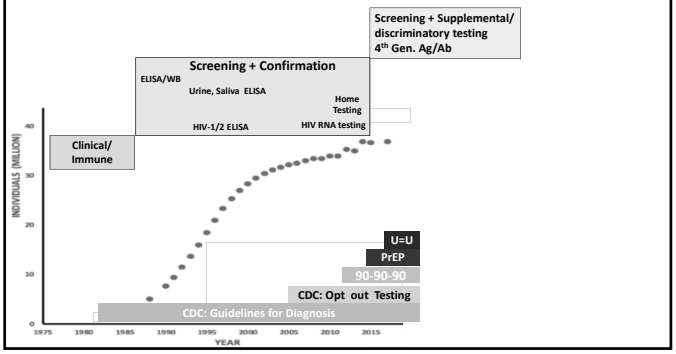
C. This person is infected with an HIV variant that is not detected by the supplemental test

D. This person is not HIV-infected

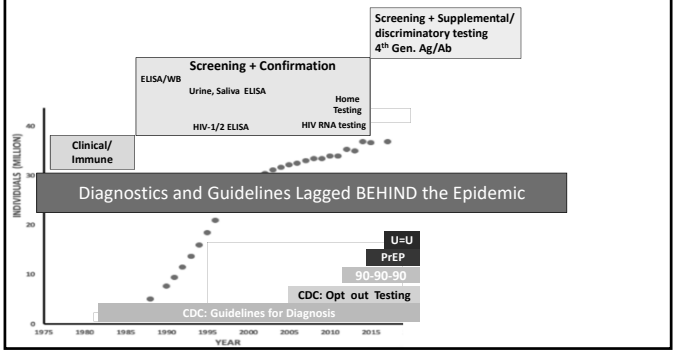
HIV Diagnosis: New Modalities and New Terminology Old Limitations Persist

- 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



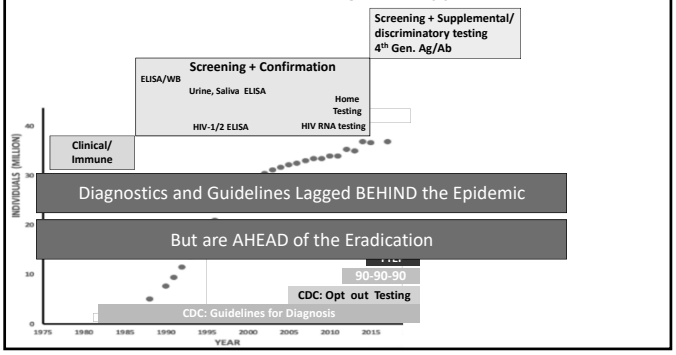
Evolution of the HIV Diagnostic Approach



36 – HIV Diagnosis

Speaker: Frank Maldarelli, MD

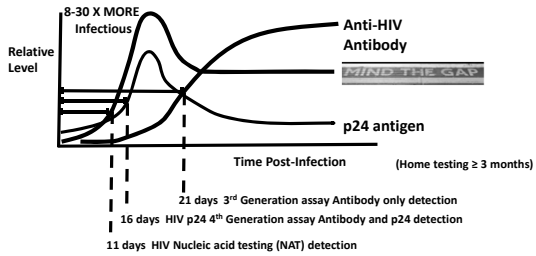
Evolution of the HIV Diagnostic Approach



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



CDC 2014

Detecting HIV Infection TWO STEPS

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

Diagnosis of Early HIV Infection

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

Evaluation for HIV Infection during PrEP

- **Every three months**
- **Includes detailed history and physical examination**
- **Ag/Ab (4th generation) testing preferred**
- **Viral RNA**
  - **Qualitative assay – FDA approved**
  - **Quantitative assay**
    - **>3000 copies/ml plasma cutoff**

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 Testing During Pregnancy

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

Question#4
A 65 yo American male has had unprotected sex with men for many years. The HIV-1/2 ELISA is reactive and supplemental testing is positive for HIV-1. Viral RNA level is <50 copies/ml and CD4 count is 700 cells/µl. He has never been on antiretroviral therapy and has no history of travel outside the US. Which of the following is most likely:

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

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

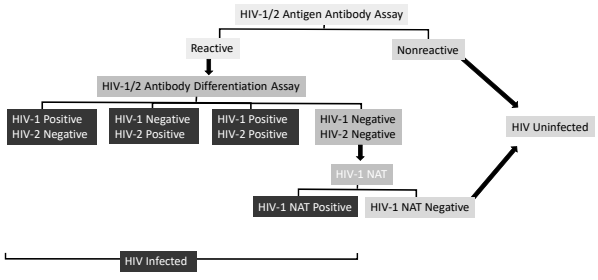
D. The patient is not infected with HIV-1 or -2, all tests are false positive.

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

HIV-1 Long Term Non-Progressors

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

HIV Diagnostic Algorithm



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

HIV Testing and False Positives

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

HIV Testing

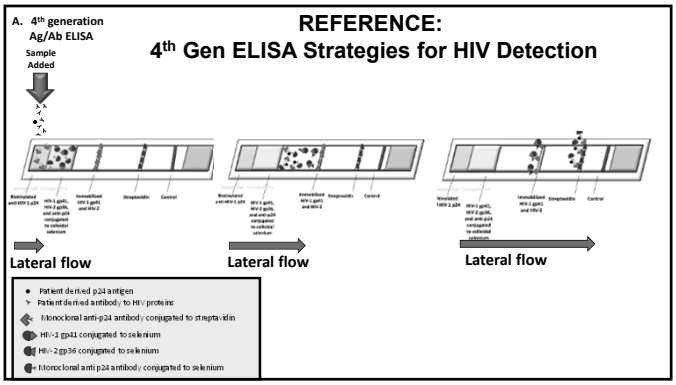
- **Opt-out testing is Recommended by IDSA and CDC**
  - **Patients are informed that an HIV test will be conducted unless they explicitly decline to be tested.**
  - **Written consent in this setting is incorporated into intake**
  - **Counseling is available**
- **Opt-in: NOT Recommended by IDSA and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

Pearls for Board Exam

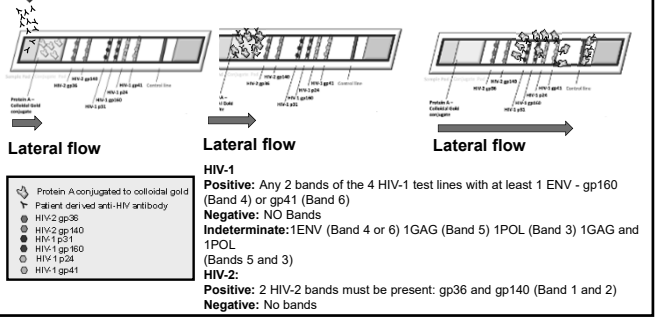
- **HIV Testing is Comprehensive**
  - **Non-B Subtypes are all detectable**
  - **HIV-2 has an approved diagnosis**
  - **Long term Non-Progressor**
    - **ELISA reactive / Supplemental Positive**
- **Resources:**
  - **https://www.cdc.gov/hiv/guidelines/testing.html**
  - **Fmaldarelli3@gmail.com**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

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

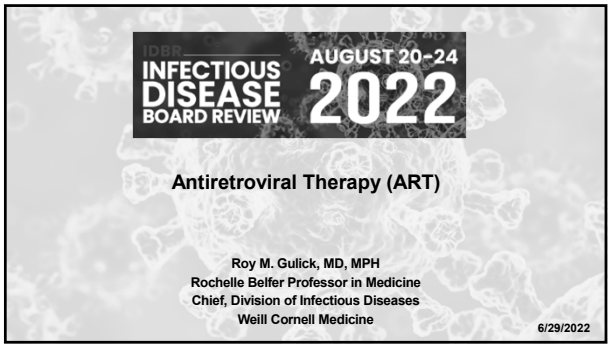
37

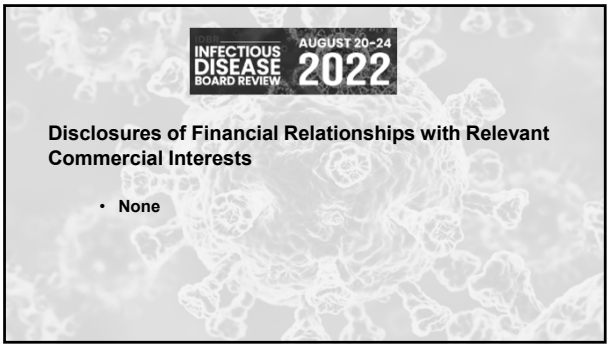
Antiretroviral Therapy

Dr. Roy Gulick

37 – Antiretroviral Therapy

Speaker: Roy Gulick, MD





ID Boards – Medical Content: 15% HIV

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

ID Boards – Medical Content: 15% HIV

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

Antiretroviral Therapy (ART)

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

WHEN TO START?

Question #1

2022 PREVIEW QUESTION

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

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

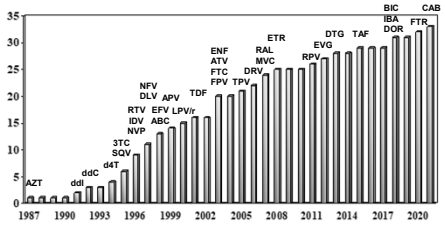
When to Start?: Chronic Infection

	AIDS/ symptoms	Asymptomatic			
		CD4 <200	CD4 200-350	CD4 350-500	CD4 >500
US DHHS 2022 www.clinicalinfo.hiv.gov	recommended				
IAS-USA 2020 Saag JAMA 2020;324:1651-1669	recommended				

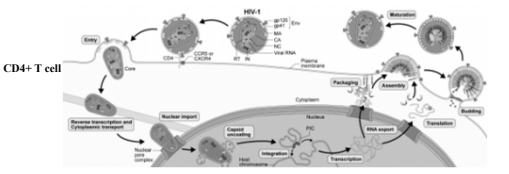
Goal of Antiretroviral Therapy

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

Antiretroviral Drug Approval: 1987 - 2022

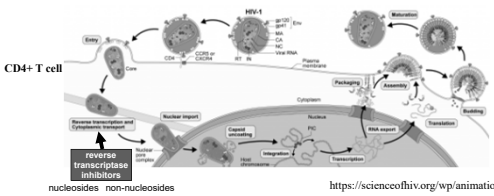


Life Cycle of HIV



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

Life Cycle of HIV



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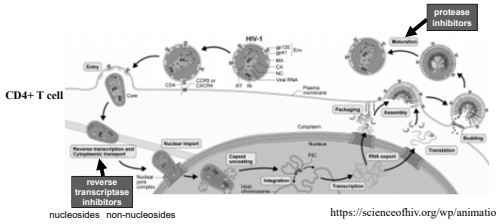

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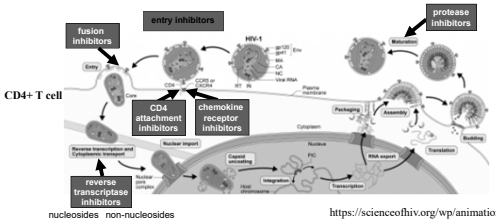

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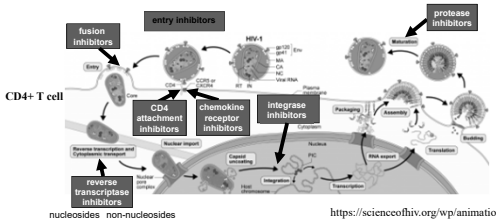

https://scienceofhiv.org/wp/animations/

Approved ART: 2022*

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

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

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

*ddI, ddC, d4T, DLV, and APV discontinued from market; FPV will be discontinued 1/24

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

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

WHAT TO START?

Question #2

2022 PREVIEW QUESTION

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

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

First ART Regimen: Individual Factors

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

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

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

U.S. DHHS Guidelines 6/20/22 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)

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Alternative Regimens (Certain Situations) (2)

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

U.S. DHHS Guidelines 6/20/22 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 6/20/22 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 6/20/22

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 6/20/22

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 6/20/22

Choice of Integrase Inhibitors

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

Based on DHHS Guidelines 6/20/22

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

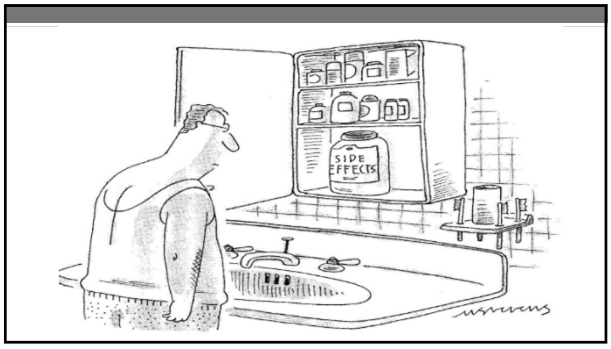
Selected Drug Interactions (2)

- 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 6/20/22



ART: Side Effects (1)

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

ART Side Effects (2)

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

ART Side Effects (3)

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

ART Switch

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

DHHS Guidelines 6/20/22

Why Does Treatment Fail Patients?

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

Question #3

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

What do you recommend?

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

When to change therapy?

Virologic failure

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

Immunologic failure

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

DHHS Guidelines 6/20/22

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

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

Design a regimen with 2 fully active agents (one with a high barrier to resistance: boosted darunavir, dolutegravir, [bictegravir])

DHHS Guidelines 6/20/22

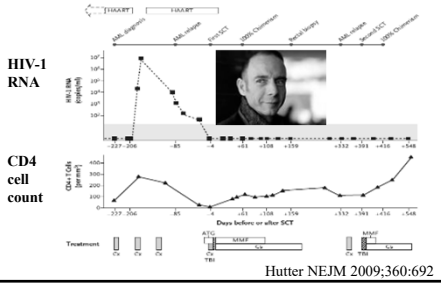
TREATMENT = PREVENTION

Treatment = Prevention

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

CURE

HIV Cure (N=3)



Hutter NEJM 2009;360:692

Cure #2 Gupta Nature 2019;568: 244-248.

Cure #3 Bryson CROI 2022 Abstract #65

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).
- **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

IDBR INFECTIOUS DISEASE BOARD REVIEW AUGUST 20-24 2022

HIV Drug Resistance

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

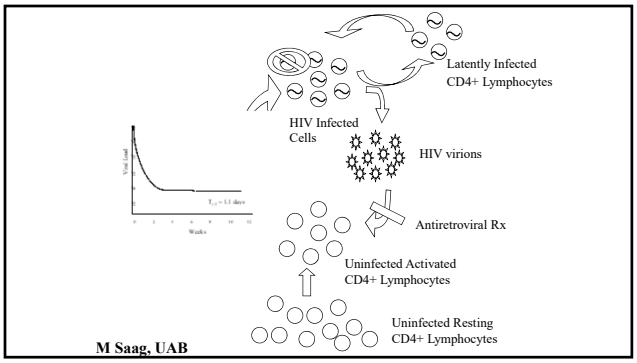
7/19/2022

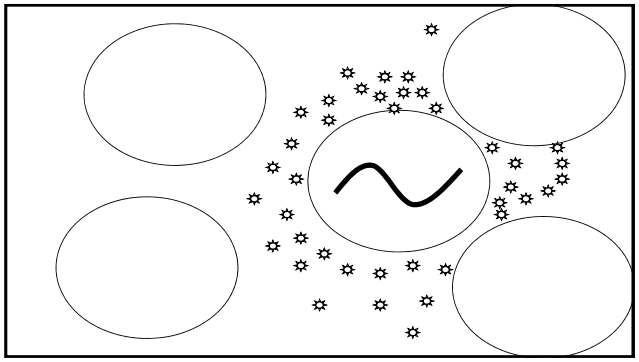
IDBR INFECTIOUS DISEASE BOARD REVIEW AUGUST 20-24 2022

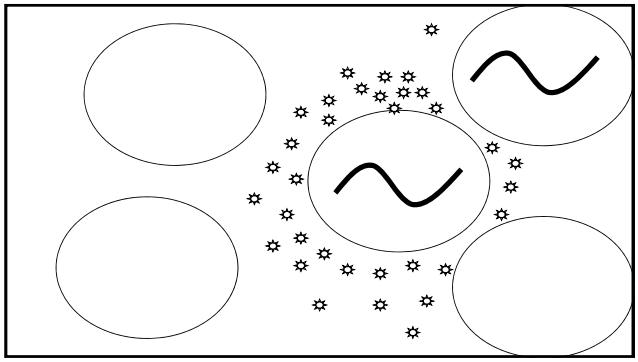
Disclosures of Financial Relationships with Relevant Commercial Interests

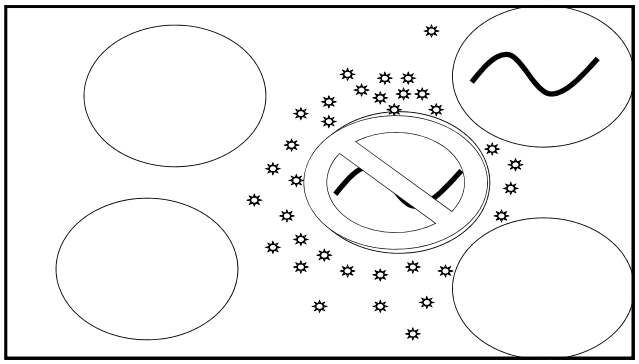
- **None**

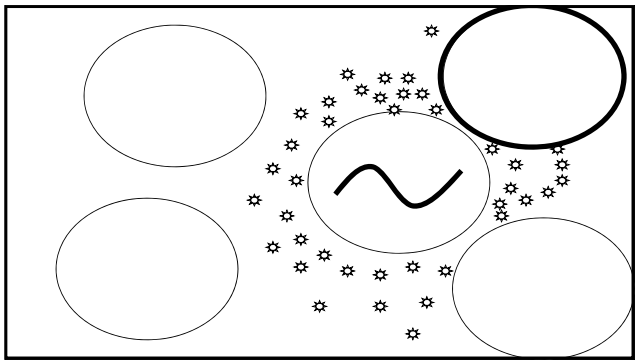
How does resistance happen?

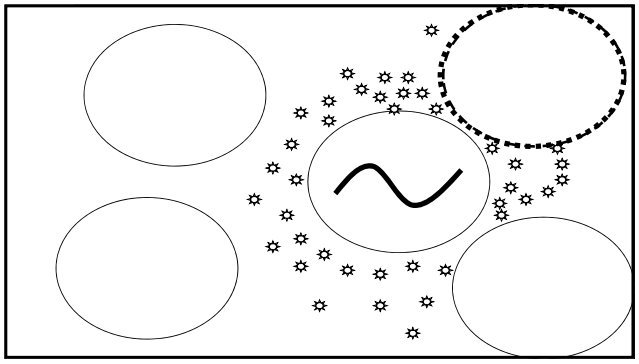


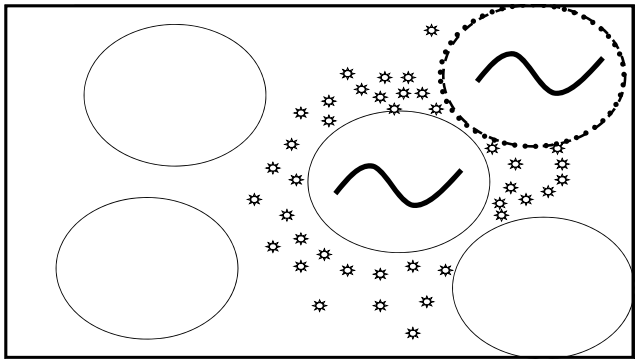








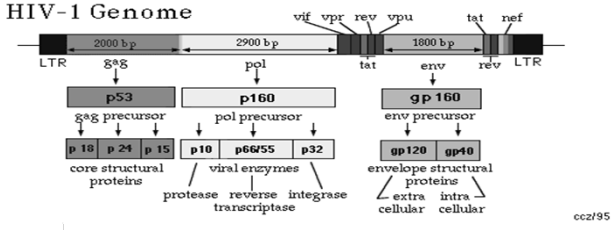




Resistance Testing

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

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

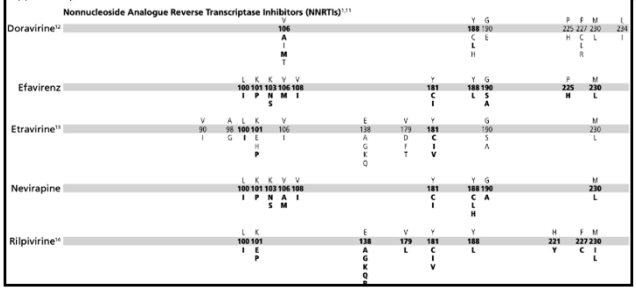
Wild-type amino acid (consensus)

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
Tyrosine	Y

Mutations Selected by NNRTIs



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

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

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

CASE 1

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

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Question #1

INFECTIOUS DISEASE BOARD REVIEW AUGUST 20-24 2022 PREVIEW QUESTION

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

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

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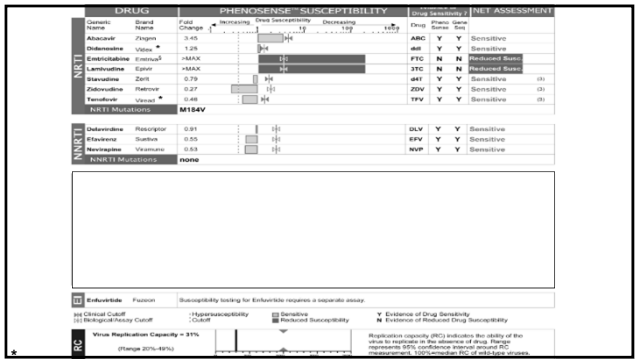


CASE 2

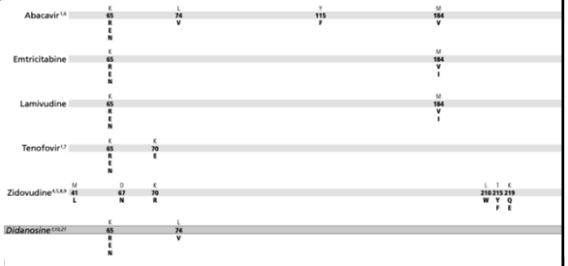
- 34 yo woman diagnosed with HIV 10 years ago
- Initially presented with PJP
- Initial Lab values
  - CD4 82 cells/uL
  - VL 106,000 c/mL
- Started on TDF / FTC / EFV (FDC)
- Did well for a while, then the regimen failed

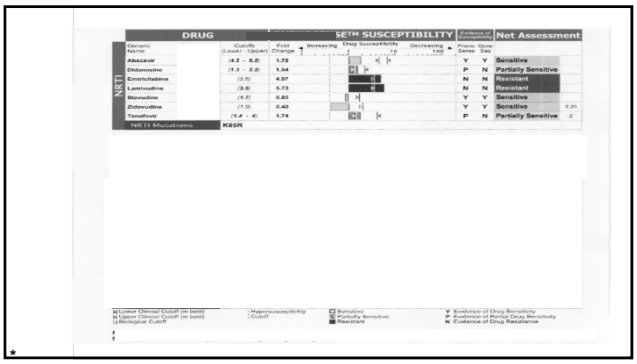
Question #2

INFECTIOUS DISEASE BOARD REVIEW AUGUST 20-24 2022 PREVIEW QUESTION

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.

HIV Resistance – Protease inhibitors (PI)

- In general, currently used protease inhibitors require multiple mutations for resistance (i.e. have a high genetic barrier).
  - Exception: I50L alone confers resistance to atazanavir (ATV).
- Patients experiencing failure on a 2 NRTI + boosted PI regimen most often have NO PI mutations.
- With significant prior protease inhibitor use, because of multiple mutations, a phenotype is preferred to a genotype.

CASE 3

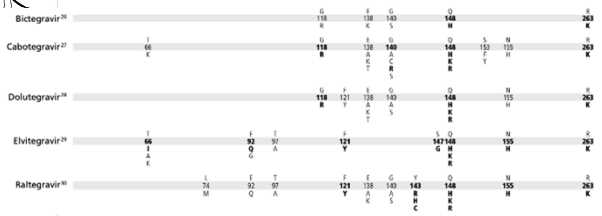
- 34 yo woman diagnosed with HIV three years ago
- Initially presented with PJP
- Initial Lab values
  - CD4 82 cells/uL
  - VL 106,000 c/mL
- She was treated with TDF / FTC / ELV/ Cobi (FDC)
- The regimen failed after 12 months

Question #3

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

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

InSTI Resistance Mutations



Question #4

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

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

CASE 4

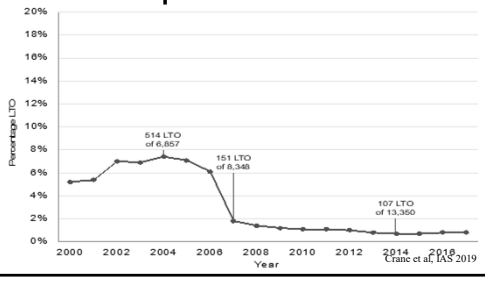
- 34 yo woman diagnosed with HIV 22 years ago
- Initially presented with PJP
- Initial Lab values
  - CD4 82 cells/uL
  - VL 106,000 c/mL
- Has been on multiple regimens over the years

Question #5

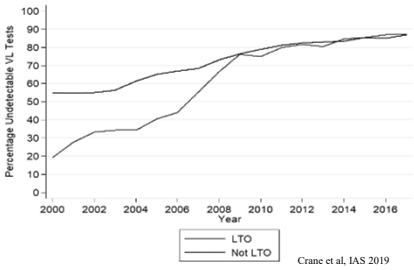
What is the likelihood she has high level resistance (< 2 active drugs available) ?

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

Prevalence of Patients with Limited Treatment Options

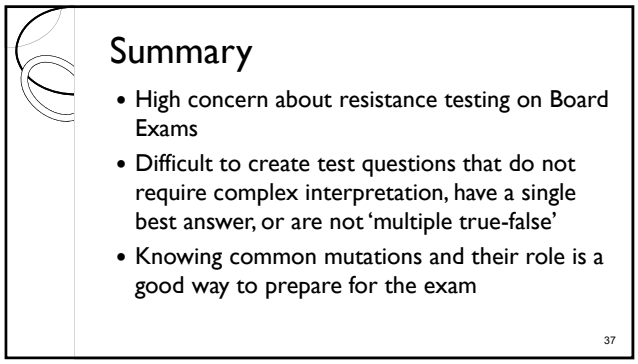


Virologic Success in Those with or without LTO



Common Mutations To Memorize

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



39

Antiretroviral Therapy for Special Populations

Dr. Roy Gulick

39 – Antiretroviral Therapy for Special Populations

Speaker: Roy Gulick, MD

IDBR INFECTIOUS DISEASE BOARD REVIEW AUGUST 20-24 2022

Antiretroviral Therapy (ART) for Special Populations

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

6/29/2022

INFECTIOUS DISEASE BOARD REVIEW AUGUST 20-24 2022

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

IDBR 2022 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.
- If ART is started, use standard regimens with goal of full virologic suppression.
- Obtain genotype prior to ART.
- If ART is started prior to genotype results, use **bictegravir, dolutegravir,** or **boosted darunavir,** together with tenofovir (TAF or TDF) + emtricitabine.
- Can modify regimen, if needed, when testing results return.

DHHS Guidelines 6/20/22

Question #2

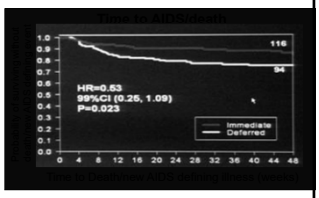
A 52-year-old woman is admitted for progressive SOB, is intubated, undergoes BAL and is found to have PCP. HIV Ab test is positive, CD4 103, HIV RNA 135,000 copies/ml. She is day 4 of IV trimethoprim-sulfa and corticosteroids and still intubated.

When should she start ART?

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

ACTG 5164: Immediate vs Delayed ART with an Acute OI

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



Zolopa PLoS One 2009;4:e5575

Acute Cryptococcal Meningitis

- Randomized clinical trial at Parirenyatwa Hospital in Harare, Zimbabwe
- Study population: 54 patients with CM treated with 800 mg fluconazole daily; median CD4 37
- Study Treatment: early ART (within 72 hours of diagnosis) or delayed ART (10 weeks after fluconazole)
- Results (through 3 years): 73% mortality rate overall
  - 88% (early ART) vs. 54% (late ART)
  - HR of death 2.85 (95% CI 1.1, 7.2)
- Conclusion: Early ART led to ↑ mortality

Makadzange CID 2010;50:1532

HIV-TB Co-infection

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

DHHS Guidelines 6/20/22

Question #3

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

Which ART regimen do you recommend?

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

HIV-TB Co-infection (2)

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

DHHS Guidelines 6/20/22

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

HIV-HBV Co-infection

- Some ART has activity against HBV
  - lamivudine (3TC), emtricitabine (FTC), tenofovir (TDF and TAF)
- Some HBV drugs have activity against HIV
  - entecavir (can select M184V) *McMahon NEJM 2007;356:2614*
- If treatment started, treat both optimally
  - 2 active agents for HBV
  - + 3rd drug for HIV (preferred = BIC or DTG)

DHHS Guidelines 6/20/22

HIV-HCV Co-Infection

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

DHHS Guidelines 6/20/22

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 prevention of MTCT for all pregnant women, as early as possible, regardless of CD4 or VL level
  - Perform drug-resistance testing if VL >500-1000 cps/ml and adjust regimen, based on results
  - ART does NOT increase the risk of birth defects
  - Start (or continue) standard ART as early as possible:
    - 2 NRTIs + 3rd drug (PI, II, or NNRTI)
    - NO 2-drug regimens
- Near delivery, if HIV RNA >1000 (or unknown), use intravenous zidovudine, and recommend Cesarean section at 38 weeks

DHHS Perinatal Guidelines 6/15/22 <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 HIV RNA >1000

DHHS Perinatal Guidelines 6/15/22 <www.clinicalinfo.hiv.gov>

ART in Pregnancy: NNRTI

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

DHHS Perinatal Guidelines 6/15/22 <www.clinicalinfo.hiv.gov>

ART in Pregnancy: PI

- Preferred:
  - atazanavir/ritonavir
  - darunavir/ritonavir (need to use bid)
- Not recommended:
  - cobicistat (↓ drug concentrations, limited experience)
  - lopinavir/ritonavir (side effects, need to use bid)

DHHS Perinatal Guidelines 6/15/22 <www.clinicalinfo.hiv.gov>

ART in Pregnancy: II

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

DHHS Perinatal Guidelines 6/15/22 <www.clinicalinfo.hiv.gov>

ART in Pregnancy: Other

- Not recommended:
  - 2-drug regimens (e.g. dolutegravir/lamivudine, dolutegravir/rilpivirine)
  - enfuvirtide (not for treatment-naïve)
  - fostemsavir (limited data)
  - maraviroc (tropism testing; not recommended in treatment-naïve)
- Insufficient data: ibalizumab

DHHS Perinatal Guidelines 6/15/22 <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+ source – recommended
- Presentation ≤72 hours with substantial risk exposure from source with unknown HIV status – case-by-case basis
- Presentation >72 hours or no substantial risk of exposure – not recommended

- Testing: rapid HIV (Ag)/Ab test or if results not available, start PEP
- Treatment: 4 weeks of
  - Preferred: **TDF/FTC + dolutegravir** (not in women in early pregnancy or sexually active and not on birth control) or **raltegravir**
  - Alternative: **TDF/FTC + darunavir/ritonavir**

PHS Guidelines update 5/23/18 <www.clinicalinfo.hiv.gov>

Question #7

23 year old 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 to reduce MTCT; modify ART recommendations based on safety and experience.
6. Post-exposure prophylaxis (PEP) – ART within 72 hours; give for 4 weeks; adjust for known drug resistance.
7. Pre-exposure prophylaxis (PrEP) – TDF/FTC (♂+♀), TAF/FTC (♂), 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!

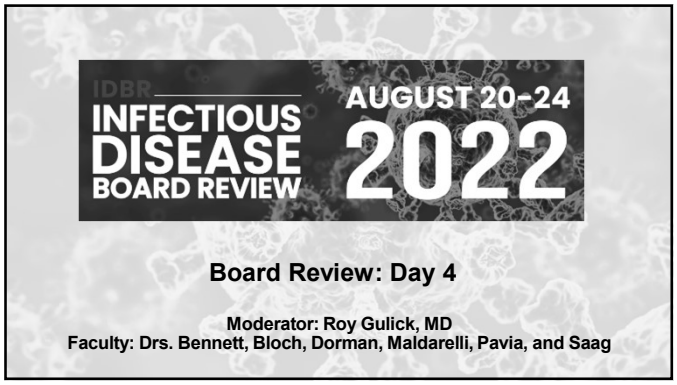
BR4

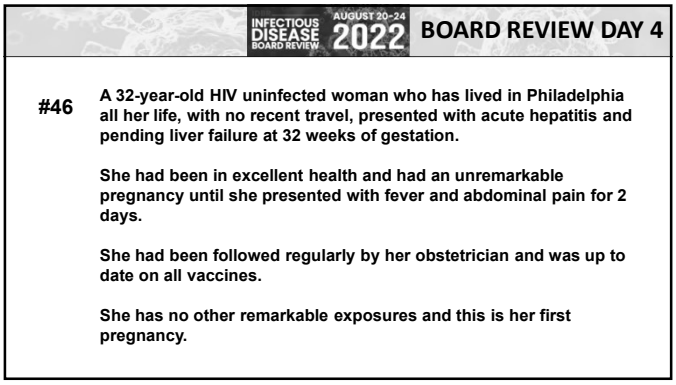
Board Review Session 4

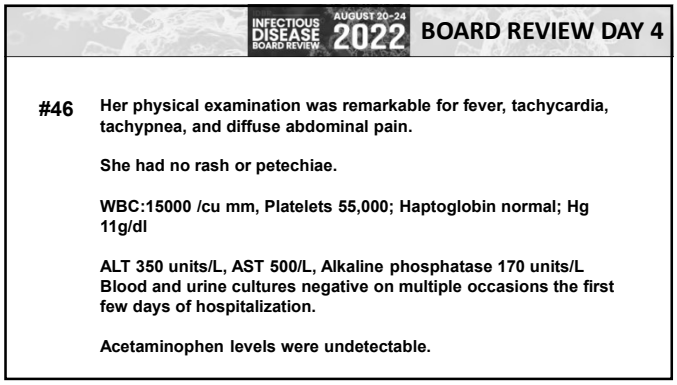
Drs. Gulick (Moderator), Bennett, Bloch, Dorman, Maldarelli, Pavia, and Saag

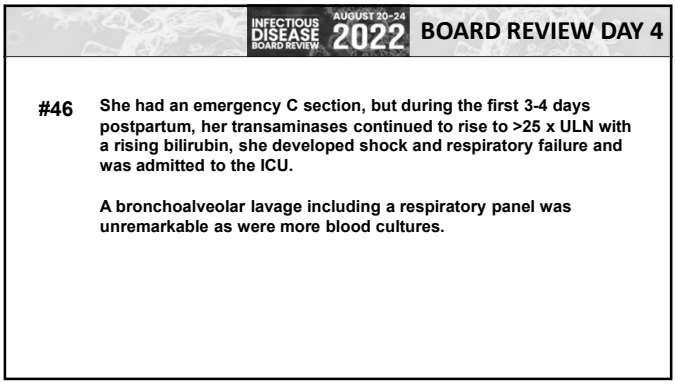
BR4 – Board Review: Day 4

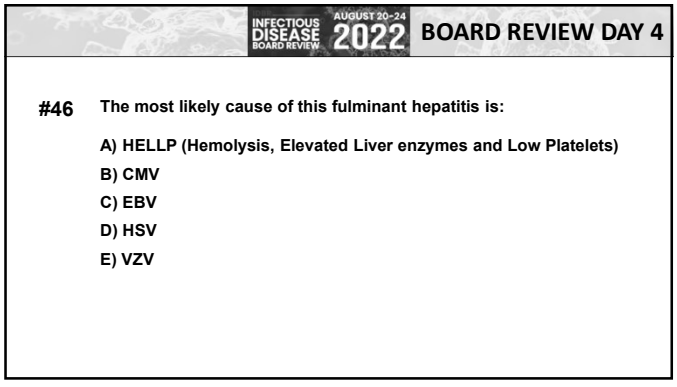
Moderator: Roy Gulick, MD

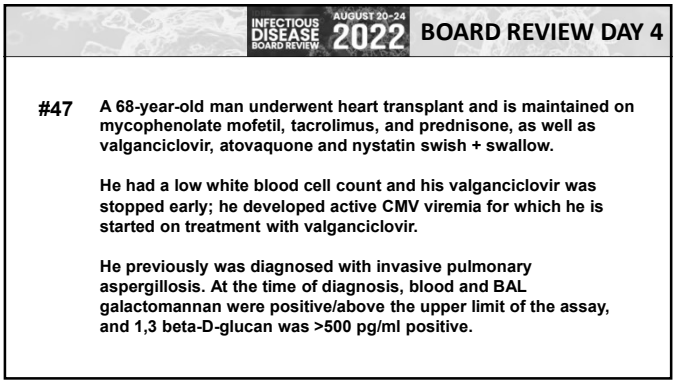












BR4 – Board Review: Day 4

Moderator: Roy Gulick, MD

INFECTIOUS DISEASE BOARD REVIEW AUGUST 20-24 2022 BOARD REVIEW DAY 4

#47 His pulmonary lesions improved and he became afebrile on voriconazole.

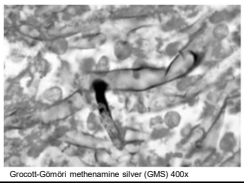
Three months later, while he was still on voriconazole, he became febrile and a large new pulmonary lesion appeared on CT in a different location. The earlier lesion had nearly resolved.

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

INFECTIOUS DISEASE BOARD REVIEW AUGUST 20-24 2022 BOARD REVIEW DAY 4

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

His is new lesion is shown below on chest CT. A biopsy is performed.



Grocott-Gömöri methenamine silver (GMS) 400x

INFECTIOUS DISEASE BOARD REVIEW AUGUST 20-24 2022 BOARD REVIEW DAY 4

#47 What is the most likely pathogen?

A) Cryptococcus neoformans
B) Aspergillus terreus
C) Scedosporium apiospermum
D) Cunninghamella bertholletiae
E) Fusarium solani

INFECTIOUS DISEASE BOARD REVIEW AUGUST 20-24 2022 BOARD REVIEW DAY 4

#48 A 24-year-old-man who moved from Cambodia is found to have HIV infection.

Initial lab work-up reveals HIV RNA 12,560, CD4 cell count 327/mm^3, and HLA -B5701 negative and he is started on abacavir, lamivudine and dolutegravir which he is tolerating well.

Further work-up reveals an interferon gamma release assay (IGRA) is positive.

He is asymptomatic and has a negative CXR.

INFECTIOUS DISEASE BOARD REVIEW AUGUST 20-24 2022 BOARD REVIEW DAY 4

#48 How would you manage the positive IGRA?

A) Repeat IGRA testing
B) Repeat IGRA testing
C) Start treatment for latent TB infection with daily INH + B6 X 6-9 months
D) Start treatment for latent TB infection with weekly INH + rifapentine + B6 X 12 weeks

INFECTIOUS DISEASE BOARD REVIEW AUGUST 20-24 2022 BOARD REVIEW DAY 4

#49 A 26-year-old woman living with HIV previously experienced virologic failure on an efavirenz-containing regimen (no old genotype available), but has been virally suppressed on tenofovir alafenamide (TAF)/emtricitabine + dolutegravir for 2 years and is interested in the new injectable regimen, cabotegravir/rilpivirine.

What do you advise?

A) Cabotegravir/rilpivirine is a reasonable choice for her
B) Cabotegravir/rilpivirine is not FDA approved for women
C) Cabotegravir/rilpivirine should not be given with a history of virologic failure on an NNRTI-containing regimen
D) Cabotegravir/rilpivirine is associated with neural tube defects, so she must commit to using contraception

BR4 – Board Review: Day 4

Moderator: Roy Gulick, MD

INFECTIOUS DISEASE BOARD REVIEW AUGUST 20–24 2022 BOARD REVIEW DAY 4

#50 A 54-year-old man on tenofovir alafenamide (TAF)/emtricitabine/bictegravir has difficulty refilling his medications and decides to take them every other day.

At his next follow-up visit, 3 months later, his HIV RNA is 2320 copies/ml.

A repeat viral load is 4544 copies/ml and a genotype shows reverse transcriptase M184V and integrase G140S and G148H substitutions.

INFECTIOUS DISEASE BOARD REVIEW AUGUST 20–24 2022 BOARD REVIEW DAY 4

#50 What do you recommend?

A) Continue present ART regimen

B) Obtain integrase phenotype

C) Change bictegravir to darunavir/ritonavir

D) Add darunavir/ritonavir to current regimen

E) Double the bictegravir dose

INFECTIOUS DISEASE BOARD REVIEW AUGUST 20–24 2022 BOARD REVIEW DAY 4

#51 A man from Cameroon West Africa now living in the U.S. is referred to you for evaluation.

He had an episode of pneumocystis pneumonia and was successfully treated. The hospital documented that the patient had the following:

- HIV Elisa Positive for HIV1-2
- Routine Viral Load: <50 copies/ml
- CD4 Count: 125 cells/uL
- CBC and Chem 12: Unremarkable

The HIV Elisa was confirmed as positive for HIV 1/2 at another commercial laboratory. This laboratory confirmed the routine viral load <50 copies/ml.

INFECTIOUS DISEASE BOARD REVIEW AUGUST 20–24 2022 BOARD REVIEW DAY 4

#51 How would you interpret these results and manage the patient?

A) The patient is not infected with HIV-1 or HIV-2

B) The patient is infected with HIV-2 but has low-level viremia and needs no therapy at this time

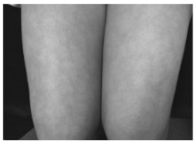
C) The patient should be started on tenofovir DF-3TC-efavirenz

D) The patient should be started on emtricabine-tenofovir DF and darunavir-ritonavir

E) The patient is infected with HIV-1 but does not need therapy because he is a long-term non progressor

INFECTIOUS DISEASE BOARD REVIEW AUGUST 20–24 2022 BOARD REVIEW DAY 4

#52 A 23-year-old nurse, 8 weeks pregnant, sought advice from her obstetrician.



For the past two weeks she has been taking care of a hospitalized child with sickle cell disease and aplastic crisis.

For the past five days she has had low grade fever, headache, the mildly pruritic rash shown here and aching joints with stiffness in her hands and feet.

She had all the usual childhood vaccinations, was taking no medications, lived alone with her husband, and had no pets.

INFECTIOUS DISEASE BOARD REVIEW AUGUST 20–24 2022 BOARD REVIEW DAY 4

#52 The major concern for her unborn infant would be which of the following:

A) deafness

B) hydrops fetalis

C) thrombocytopenia

D) congenital heart disease

E) developmental delay

INFECTIOUS DISEASE BOARD REVIEW AUGUST 20-24 2022 BOARD REVIEW DAY 4

#53 A 33-year-old woman is referred to you for "her third episode of cellulitis of the left ear."

- Her first episode was 17 months ago.
- The second episode was 8 months ago.
- The most recent began four days ago and is still clinically evident.

The two earlier episodes seemed to respond very slowly to antibiotic treatment.

She has had pierced ears since childhood and no history of specific ear trauma.

INFECTIOUS DISEASE BOARD REVIEW AUGUST 20-24 2022 BOARD REVIEW DAY 4

#53 She was raised in the Philippines but has lived in the United States since age 7.

She has always enjoyed excellent health, although she has had a problem of chronic nasal stuffiness for a few years.

On exam she is afebrile.

The left pinna is diffusely red and tender except for the lobe. The pinna seems to be slightly bent forward compared with the right side. There is a saddle-nose deformity.

The rest of the exam is normal.

INFECTIOUS DISEASE BOARD REVIEW AUGUST 20-24 2022 BOARD REVIEW DAY 4

#53 Which of the following is the most likely diagnosis?

A) Recurrent streptococcal cellulitis
B) Relapsing polychondritis
C) Syphilis
D) Granulomatosis with polyangiitis
E) Leprosy

INFECTIOUS DISEASE BOARD REVIEW AUGUST 20-24 2022 BOARD REVIEW DAY 4

#54 A 40-year-old HIV-uninfected male returns from a State Department assignment in India where he was well other than occasional episodes of self-limited diarrhea.

He was PPD negative when he departed.

He is PPD positive upon return, with 20 mm of induration. He has no symptoms and a chest radiograph is normal.

Baseline laboratory values are normal including liver function tests. He has been vaccinated for HBV and HAV and is HCV seronegative.

INFECTIOUS DISEASE BOARD REVIEW AUGUST 20-24 2022 BOARD REVIEW DAY 4

#54 He is started on a regimen of INH 300 mg per day plus pyridoxine 25 mg since his physician is more comfortable with that regimen than newer, CDC recommended regimens.

He returns after 4 weeks of taking INH and pyridoxine. He is asymptomatic and reports taking his drugs daily with very few missed doses.

Upon routine lab testing his ALT = 65 IU/L (ULN=33) and his AST =90 units (ULN=48 IU/L). Total bilirubin is 0.6 mg/dl.

INFECTIOUS DISEASE BOARD REVIEW AUGUST 20-24 2022 BOARD REVIEW DAY 4

#54 The best option for management at this point is:

A) Continue his current regimen with the patient told to report any symptoms immediately and recheck enzymes in 2-4 weeks
B) Continue current regimen but measure acetylation rate to determine safety of continuation
C) Double the dose of pyridoxine but continue the INH
D) Perform an IGRA (Interferon-Gamma Release Assays (IGRA) to determine if prophylaxis is really needed
E) Abandon plan to provide TB prophylaxis and monitor patient closely for symptoms and obtain Chest x-ray q6 months x 3 years

INFECTIOUS DISEASE BOARD REVIEW AUGUST 20–24 2022 **BOARD REVIEW DAY 4**

#55 **A 35-year-old sexually active heterosexual man with multiple weekly contacts 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 is not recommended for this heterosexual male.

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)

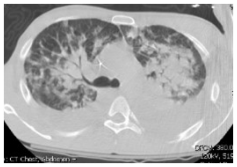
D) TAF/emtricitabine "on demand"

E) Cabotegravir "on demand"

INFECTIOUS DISEASE BOARD REVIEW AUGUST 20–24 2022 **BOARD REVIEW DAY 4**

#56 **A 27-year-old male presented with two (2) months of progressive dyspnea. He had noted the appearance of purple indurated lesions over his anterior chest.**

Chest CT found nodular perihilar lung lesions, prominent interlobular septae, and pleural effusions. (Fig)



INFECTIOUS DISEASE BOARD REVIEW AUGUST 20–24 2022 **BOARD REVIEW DAY 4**

#56 **He was remarkably hypoxemic with room air pO_2=59mmHg.**

Bronchoscopy revealed some purple lesions in the bronchus; bronchoalveolar lavage revealed no pathogens on special stains; cytology was unremarkable.

BAL CMV PCR was positive at 2000 copies/mL (log_{10} 4.40IU/ml.)

Skin biopsy found endothelial cells with nuclei that stained positive for HHV8 on immunocytochemistry.

INFECTIOUS DISEASE BOARD REVIEW AUGUST 20–24 2022 **BOARD REVIEW DAY 4**

#56 **He was found to be HIV positive with a CD4 of 8 cells/uL and a viral load of 80,000 copies/uL. Pleural fluid was bloody but cytology did not show malignant cells.**

Blood PCR results: CMV 5000 copies/uL (log_{10} 4.82 IU/ml); EBV 4500 copies/mL (log_{10} 2.40 IU/ml); HHV 8 = 200 copies/mL; HHV6 = 500 copies/mL.

Antiretroviral therapy was begun following usual guideline recommendations.

INFECTIOUS DISEASE BOARD REVIEW AUGUST 20–24 2022 **BOARD REVIEW DAY 4**

#56 **The most useful additional drug for treatment of his diffuse pulmonary disease would be which of the following:**

A) Cidofovir

B) Ganciclovir

C) Foscarnet

D) Liposomal doxorubicin

E) Cyclophosphamide

INFECTIOUS DISEASE BOARD REVIEW AUGUST 20–24 2022 **BOARD REVIEW DAY 4**

#57 **An 18-year-old man in excellent prior health presents with hypotension, and shortness of breath.**

He has had abdominal pain and worsening fever for 3 days with occasional diarrhea.

Physical examination reveals an acutely ill young man with conjunctival injection, tachycardia to 120, fever of 38.7 and mild abdominal tenderness.

Four weeks ago he was diagnosed with COVID-19 after several cases occurred on his basketball team. He had mild illness and recovered, although he hasn't started to workout with his team yet.

INFECTIOUS DISEASE BOARD REVIEW AUGUST 20–24 2022 **BOARD REVIEW DAY 4**

#57

- **His chest x-ray is normal except for mild cardiomegaly and perihilar infiltrates.**
- **CRP is elevated at 29 mg/L, WBC is 7.0 with 75% neutrophils, platelets are 110,000/ul, hemoglobin is 12 gm/dL.**
- **His d-dimer is elevated, ferritin is midrange elevated at 850 ug/L, BNP and troponin-I are mildly elevated.**
- **EKG is normal except for sinus tachycardia.**

INFECTIOUS DISEASE BOARD REVIEW AUGUST 20–24 2022 **BOARD REVIEW DAY 4**

#57

- **Echocardiogram shows global decrease in contractility.**
- **Multiplex viral testing is positive for rhinovirus/enterovirus and SARS-CoV-2.**
- **A test for serum antibody to SARS-CoV-2 nucleocapsid protein is positive.**

INFECTIOUS DISEASE BOARD REVIEW AUGUST 20–24 2022 **BOARD REVIEW DAY 4**

#57 **The most likely explanation for his illness is:**

A) Enterovirus
B) TTP (Thrombotic thrombocytopenic purpura)
C) Immune response to his recent COVID-19 illness
D) Active viral replication of SARS-CoV-2
E) Adenovirus

INFECTIOUS DISEASE BOARD REVIEW AUGUST 20–24 2022 **BOARD REVIEW DAY 4**

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

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

INFECTIOUS DISEASE BOARD REVIEW AUGUST 20–24 2022 **BOARD REVIEW DAY 4**

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

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

INFECTIOUS DISEASE BOARD REVIEW AUGUST 20–24 2022 **BOARD REVIEW DAY 4**

#59 **A 68-year-old man with metabolic syndrome is hospitalized for same-day surgery to repair an inguinal hernia.**

Six hours post-op, he develops fever and ankle pain. His medications are an oral hypoglycemic, a statin, and a thiazide diuretic.

He has had no recent travel. He has a new kitten that frequently scratches him.

BR4 – Board Review: Day 4

Moderator: Roy Gulick, MD

INFECTIOUS DISEASE BOARD REVIEW AUGUST 20-24 2022 **BOARD REVIEW DAY 4**

#59 **On exam, he is obese, in pain, and has a temperature of 101.4°F.**

He has scratches on both hands without evidence of infection. His right ankle is swollen, warm and red, and painful on active and passive motion.

His white blood cell count is 13,350 (90% polys). His uric acid is normal.

An ankle joint fluid aspirate has a WBC count of 51,400 (90% polys). Gram stain of the joint fluid shows many WBCs but no organisms.

INFECTIOUS DISEASE BOARD REVIEW AUGUST 20-24 2022 **BOARD REVIEW DAY 4**

#59 **The most likely diagnosis in this patient is which one of the following?**

A) *Bartonella henselae* arthritis

B) *Pasteurella multocida* arthritis

C) Gout

D) Pseudogout

E) *Staphylococcus aureus* arthritis

INFECTIOUS DISEASE BOARD REVIEW AUGUST 20-24 2022 **BOARD REVIEW DAY 4**

#60 **A 37-year-old male lab tech presents 60 minutes after exposure to a needlestick from an HIV+ man undergoing routine blood draw.**

The patient whose blood was being drawn takes abacavir/lamivudine + darunavir/ritonavir with his last HIV RNA 62 copies/ml and CD4 553.

What do you recommend as initial management?

A) No post-exposure prophylaxis (PEP)

B) Start tenofovir DF/emtricitabine/efavirenz X 4 weeks

C) Start tenofovir DF/emtricitabine + atazanavir/ritonavir X 4 weeks

D) Start tenofovir DF/emtricitabine + dolutegravir X 4 weeks

40

Syndromes that Masquerade as Infections

Dr. Karen Bloch

40 – Syndromes that Masquerade as Infections

Speaker: Karen C. Bloch, MD

INFECTIOUS DISEASE BOARD REVIEW AUGUST 20-24 2022

Syndromes that Masquerade as Infections

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

7/17/2022

INFECTIOUS DISEASE BOARD REVIEW AUGUST 20-24 2022

Disclosures of Financial Relationships with Relevant Commercial Interests

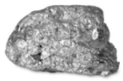
- **None**
- **But, Special Thanks to Dr. Bennett Lorber!**

ID Board Content

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

Mimics

- Many conditions masquerade as infections.
  - Fever almost universally present
  - 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”

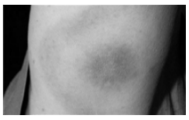
You say…..

YERSINIA (gastroenteritis)

Test taking tip

I say ”Bull’s-eye rash”

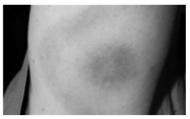
You say…..



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

2022 PREVIEW QUESTION

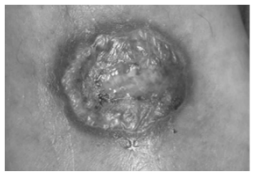
Sweet Syndrome is *most* likely to occur in a patient with which of the following illnesses?

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 cervical lymphadenopathy
  - Palpable spleen tip
  - No rash
- Labs
  - CBC
    - WBC=2.7, plt=53
    - Normal H/H
  - Normal Cr
  - AST/ALT=120/200
  - Alk phos=494, bili=1.9
  - Ferritin=35,148 mg/ml

Question 4

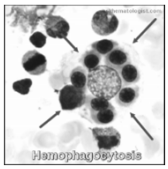
- What is the most appropriate next study?
  - A. Flow cytometry of whole blood
  - B. ANA profile
  - C. CMV PCR
  - D. Soluble IL-2 receptor level
  - E. Toxoplasma titer

Hemophagocytic Lymphohistiocytosis

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

HLH: Diagnostic Criteria

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



HLH Clues

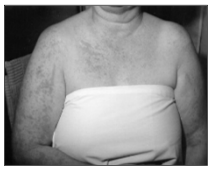
- EBV or other infection with progressive symptoms
- Massively elevated ferritin
- Cytopenia with negative ID evaluation

Case 5

- A 39-year-old woman is admitted 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

- 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 resolved with Tylenol and the rash is no longer present.

Question 5

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

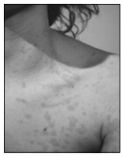
Adult Still's Disease (Adult Onset JRA)

Yamaguchi Criteria: (5 features with 2 major criteria)

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

Adult Still's Disease

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

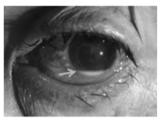
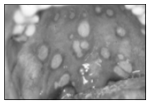
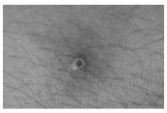

=


Koebner phenomenon (rash at pressure sites)

Case 6

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

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

Question 6

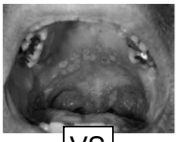
- The most likely diagnosis is?
  - A. Syphilis
  - B. Behçet's disease
  - C. Herpes simplex virus infection
  - D. Sarcoidosis
  - E. Cytomegalovirus infection

Behçet's disease

Pleomorphic vasculitis diagnosed clinically

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

Behçet's disease



VS

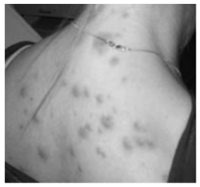
- Ulcers is the buzz word, but the trick is differentiation from infectious causes (HSV, coxsackie, etc)
- Additional Clues
  - Recurrence
  - Ocular findings
  - Pathergy (needle or IV site)

Case 7

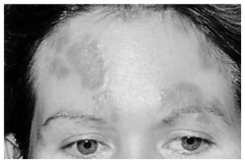
- A 38-year-old woman with AML is admitted with fever. She underwent induction chemotherapy 2 weeks prior, complicated by neutropenic fever that resolved with marrow recovery.
- She presents with a 1-day history of fever without localizing symptoms.
- Exam: T 101.4; P 98, Otherwise unremarkable.
- CBC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

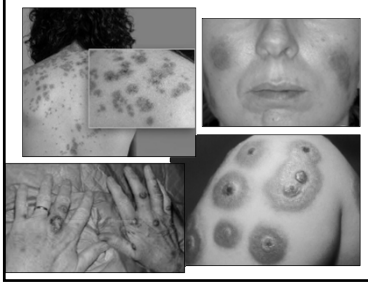
Question 7

- 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

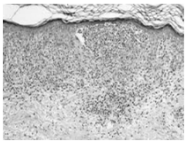
Skin Lesions in Sweet Syndrome



- 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)

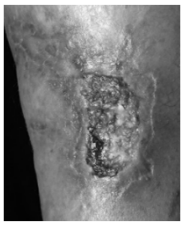


- Be suspicious in patients with malignancy (esp AML), IBD, recent URI, vaccination, pregnancy, or colony stimulating factor use in preceding 2 weeks

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?

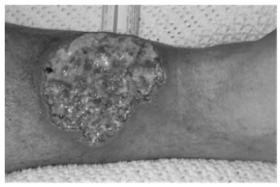
A. Ulcerative colitis
B. Cutaneous leishmaniasis
C. Amebic colitis
D. Cutaneous blastomycosis
E. Squamous cell cancer

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

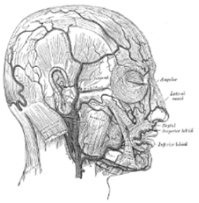
Question 9

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

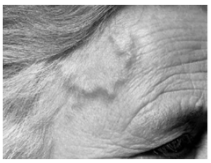
Giant Cell Arteritis

- 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:



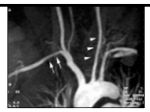
FUO in a patient >50 years PLUS

- 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 stiffne**ss** in proximal muscles of shoulder and hip girdle
  - Gel phenomenon (stiffness with inactivity)

Takayasu Arteritis



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

Case 10

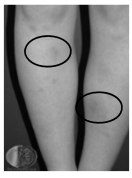
- A 37-year-old female presents with fever and joint pain. She is a long-distance runner and in excellent health.
- Three weeks prior she noted R knee pain after a long run. She was treated with a steroid injection with transient improvement, but subsequently developed bilateral ankle pain and redness.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

Exam:

T 100.5; Pulse 72; BP 110/70

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

Skin exam with painful pre-tibial nodules



Labs:

WBC 8.8 (76% segs)

CRP=167

Uric acid=4.4

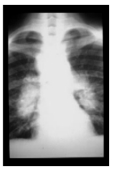
RF <15, Anti-CCP Ab negative

Question 10

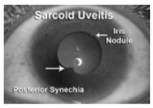
Which of the following is most likely to be diagnostic?

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

Sarcoidosis

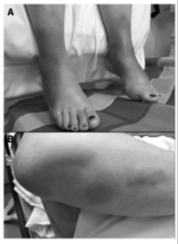


- Extra-pulmonary disease in ~1/3 of cases
- Lofgren Syndrome
  - Only form of sarcoid that is a clinical diagnosis
  - Triad of hilar LAN, acute arthritis, EN
  - Women, ankles (>90%), fevers common
- BUZZ WORDS
  - Hilar LAN, EN, uveitis, parotid enlargement
  - Non-caseating granulomas
  - Aseptic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



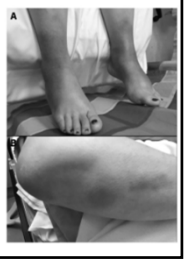
Erythema nodosum

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



Erythema nodosum

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



Case 11

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

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

Question 11

The most likely diagnosis is:

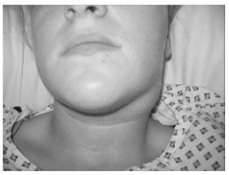
A. Hereditary angioneurotic edema
B. Familial Mediterranean fever
C. Systemic lupus erythematosus
D. Crohn's disease
E. Acute intermittent porphyria

Familial Mediterranean Fever

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

Case 12

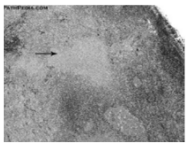
- A 26-year-old medical student presents with fever and cervical adenopathy.
- She was completely well until 9 days ago when she had the acute onset of fever and vague neck discomfort. She had no sore throat and no dental or scalp problems.



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

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

  Stains for AFB and fungi negative.



Question 12

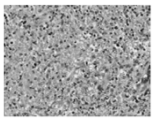
Which one of the following is the most likely diagnosis?

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

Kikuchi Disease

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

Kikuchi Disease

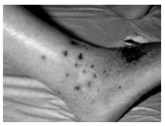


- Diagnosis by pathology:
  - necrotizing histiocytic infiltrate (not neutrophils) and fragments of nuclear debris.
- Buzz words and associations:
  - Acute onset fever and cervical adenopathy in young woman
  - Atypical lymphocytes (mono-like syndrome)
  - Path: necrotizing adenitis with histiocytosis

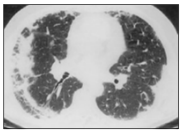
Case 13

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

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



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



- Skin nodule biopsy: granulomas

Question 13

Which one of the following is the most likely diagnosis?

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

EGPA

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

EGPA

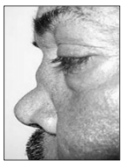
- Buzz words and associations:
  - Longstanding asthma
  - New infiltrates and eosinophilia (>10%) as steroids tapered.
  - Rash (tender nodules on extensor surfaces, purpura, ecchymosis, necrosis)
  - Fever UNCOMMON (until late)

Case 14

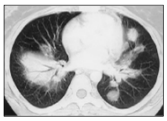
- A 38-year-old man is seen for a 6-week history of cough, intermittent fever and night sweats.
- He has had nasal stuffiness for 4-5 months with occasional epistaxis.
- He lives in Philadelphia, and 6 months ago traveled to Cincinnati on business.
- He has no pets and takes only an OTC decongestant.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

Exam:
- T 100.2; RR 18;

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



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

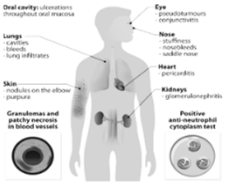


Question 14

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

Granulomatosis with polyangiitis (GPA)

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



Granulomatosis with polyangiitis

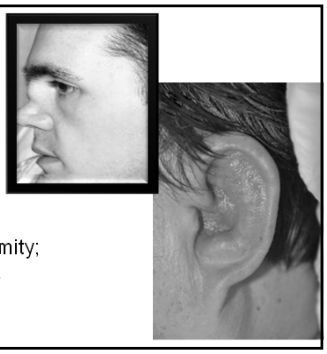
- Dx:
  Suggestive: Positive ANCA (~85% sensitivity)
  IFA: c-ANCA.
  ELISA: anti-proteinase 3 (PR3-ANCA)
  Diagnostic: Biopsy

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

Case 15

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

Case 15



Exam:

Afebrile

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

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

Labs: CBC normal

Question 15

The most likely diagnosis is?

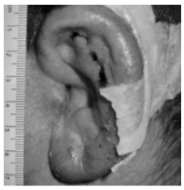
A. Malignant otitis externa
B. Leprosy
C. Granulomatosis with polyangiitis
D. Relapsing polychondritis
E. Congenital syphilis

Relapsing Polychondritis

--Immune-mediated condition.

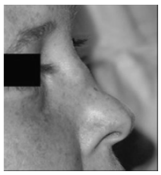
--Inflammation of cartilaginous structures, particularly ears, but also nose, eyes, joints, and airways.

--Clinical diagnosis.



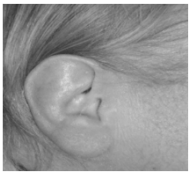
Saddle-nose Deformity

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



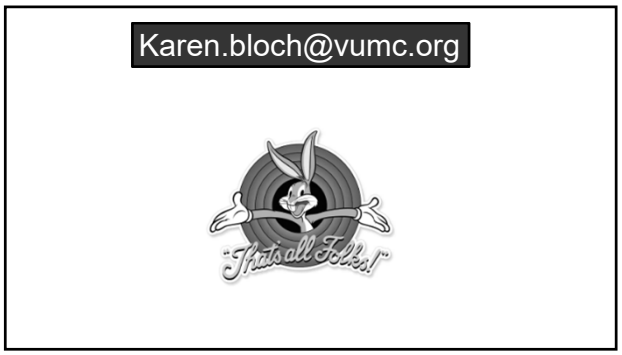
Relapsing Polychondritis

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



40 – Syndromes that Masquerade as Infections

Speaker: Karen C. Bloch, MD



41

Tuberculosis in Immunocompetent and Immunocompromised Hosts

Dr. Susan Dorman

41 - Tuberculosis in Immunocompetent and Immunosuppressed Hosts

Speaker: Susan Dorman, MD

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Tuberculosis in Normal and Compromised Hosts

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

7/6/2022

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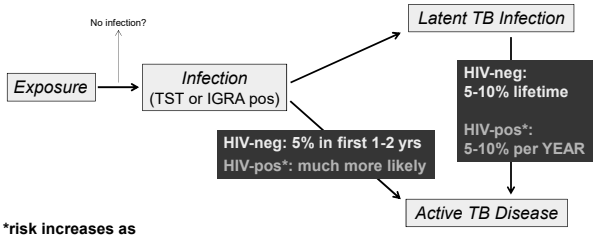
Disclosures of Financial Relationships with Relevant Commercial Interests

- **None**

Overview of TB Epidemiology

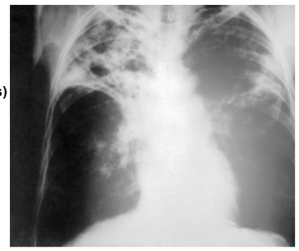


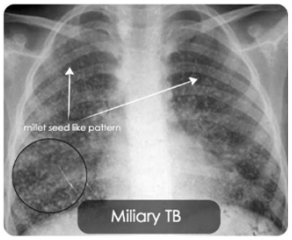
***risk increases as immunosuppression increases**

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

Active TB disease: clinical presentations

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





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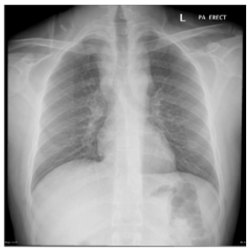

Tuberculous mediastinal lymphadenopathy

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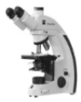
Active TB disease: clinical presentations

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

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

Disseminated
- Advanced HIV, significant iatrogenic immunosuppression
- Can present as sepsis
- Mycobacterial blood cultures, obtain respiratory specimens, other tissue specimens

Active TB disease: diagnosis

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

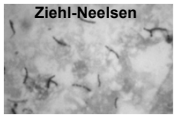
ADJUNCTIVE:
IGRA, TST: do not distinguish latent from active; NEG test does not rule out active TB
Chest X-ray, other radiology: can be suggestive of active TB; not specific
Histopathology: can be suggestive of active TB; not specific

Active TB disease: diagnosis

Smear microscopy for acid fast bacilli

* ***NEGATIVE SMEARS DO NOT EXCLUDE A DIAGNOSIS OF ACTIVE TB***

- Low sensitivity: takes a lot of bacilli (10,000 cfu/ml) to make a smear positive
- Overall around 50-60% sensitive for pulmonary TB
- Much less sensitive in advanced HIV (30-50%)
- In pulmonary TB, the yield of smear microscopy increases if multiple specimens obtained
- Not specific for M.tb (most mycobacteria look alike)
- Good PPV in TB endemic settings



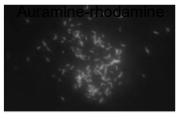


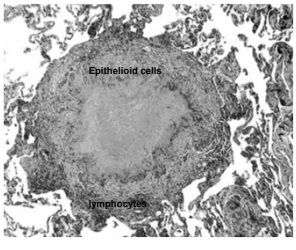
Image credits:
1. CDC/Dr. George P. Kubica
2. https://laboratoryinfo.com/auramine-rhodamine-staining-for-afb-principle-procedure-reporting-and-limitations/

Active TB disease: diagnosis

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

Active TB disease: diagnosis

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



Caseating granuloma

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

Question 1

PREVIEW QUESTION

38 y/o M physician, previously healthy, with periodic travel to South Africa for medical research work. Reports a positive TST six years ago, and admits poor adherence with a course of isoniazid preventive therapy at that time. Now with 5 weeks of fever, chills, night sweats, 10-lb wt loss, productive cough. CXR shows RUL cavitary lesion. Sputum GeneXpert MTB/RIF test result is "MTB detected" and "Rifampin resistance not detected" (culture results pending). HIV test is negative, liver chemistries are normal. What is the best course of action?

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

Active TB disease: treatment

1st line tx = RIPE

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

Always start with daily treatment

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

Active TB disease: treatment

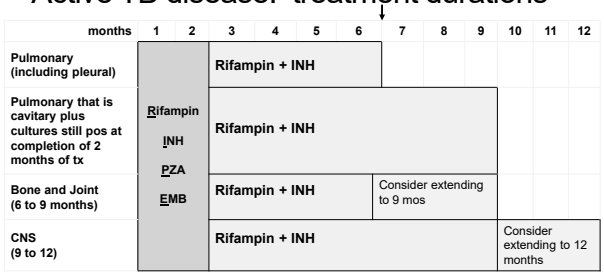
Extend continuation phase therapy for

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

Corticosteroids indicated for TB meningitis

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

Active TB disease: treatment durations



Question 2

The 38 y/o M physician is started on rifampin, isoniazid, PZA, ethambutol (plus pyridoxine) for presumed pulmonary TB. About 3 weeks later the culture grows *M. tuberculosis*, susceptible to those drugs. About 4 weeks into TB treatment the patient reports several days of progressive nausea, anorexia, abdominal discomfort. Liver function testing shows ALT 380, AST 270. He reports no alcohol consumption or acetominophen.

Which drug is **least** likely to be associated with liver toxicity?

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

Active TB disease: treatment

Drug adverse effects

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

Active TB disease: treatment

Drug-drug interactions: RIFAMPIN

- Potent inducer of hepatic cytochromes and uridine diphosphate gluconyltransferase; this results in increased metabolism (and decreased serum levels, potential decreased efficacy, potential need for increased doses) of other drugs metabolized by those enzymes
- Warfarin, hormonal contraceptives, methadone, corticosteroids, fluconazole, HIV PIs, HIV NNRTIs, HIV INSTIs, HIV CCR5 inhibitors, TAF*

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

Drug-resistant TB

- Risk factors for:
  - Contact with drug-resistant TB case
  - Prior h/o TB treatment, esp if non-adherent with tx
- **MDR=resistance to isoniazid plus rifampin**
- **XDR=MDR plus resistance to fluoroquinolones plus at least one of the injectable 2nd line drugs (amikacin, kanamycin, capreomycin)**
- Treat with multiple agents against which the isolate is susceptible
- Never add a single drug to a failing regimen
- Bedaquiline (Sirturo™): novel drug, novel target (Mtb ATP synthase), FDA-approved for pulm drug-R TB when effective tx cannot otherwise be provided; QT prolongation; half-life 4 months; restricted access

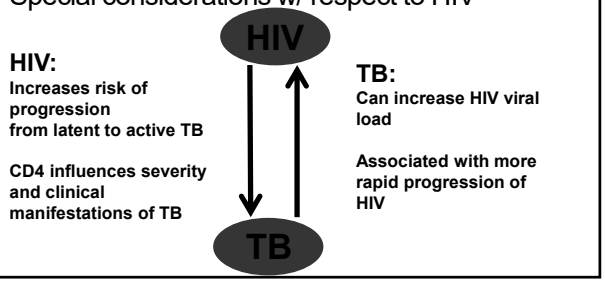
Question 3

IDBR 2022 PREVIEW QUESTION

24 y/o M from Zambia, in U.S. for community college, recently tested HIV-positive with CD4 400, not yet on ART. He has a prominent anterior cervical lymph node but is otherwise well-appearing with normal BMI, normal liver and renal chemistries, and mild anemia. Lymph node biopsy grows *M. tuberculosis* in culture. What is the best course of action with respect to the timing of TB therapy and HIV therapy?

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

Active TB disease: Special considerations w/ respect to HIV



Active TB disease: Special considerations w/ respect to HIV

Clinical Presentation

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

Active TB disease: Special considerations w/ respect to HIV

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

Drug-drug interactions

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

Active TB disease: Special considerations w/ respect to HIV

When to start ART

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

- HIV-infected pregnant women with active TB should be started on ART as soon as feasible (for maternal health and PMTCT)
- **TB meningitis: be cautious** (high rates of AEs and death in RCT); guidelines recommend not starting ART within first 8 weeks

Question 4

30y/o F with HIV, CD4=20, viral load >1 million copies/mL, with microbiologically confirmed pulmonary TB. She was not on ART at the time of TB diagnosis. At the time of TB dx, treatment with rifampin, INH, PZA, ethambutol (plus pyridoxine) was started immediately. She tolerated TB treatment well, and DTG-based ART was started 12 days later, with appropriate bid dosing of DTG. **Four weeks after ART was started she reports new headaches, as well as R-sided weakness that is confirmed on physical exam.** Which is most appropriate:

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

Active TB disease: Special considerations w/ respect to HIV

Immune reconstitution inflammatory syndromes (IRIS)

PARADOXICAL WORSENING of TB when ART started after TB treatment initiated

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

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

Active TB disease: Special considerations w/ respect to HIV

Immune reconstitution inflammatory syndromes (IRIS)

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

Active TB disease: Special considerations: transplant recipients

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

Active TB disease: Special considerations: TNF-alpha inhibitors

- ***TNF-alpha inhibitors markedly increase the risk of active TB if infected***
  - Can present with atypical TB (e.g. non-cavitary pulm dz, extrapulmonary, disseminated)
  - Increased TB morbidity, mortality
  - Full monoclonal IgG1 mabs most potent (ie infliximab, adalimumab, golimumab)
- ***Test for latent TB infection (TST or IGRA) prior to starting anti-TNF agents***
  - If LTBI, then initiate LTBI tx prior to starting anti-TNF
  - Limited data on optimal duration of delay between initiating LTBI treatment and initiating anti-TNF treatment (some say 2-8 weeks)

Question 5

24 y/o U.S. born M whose wife (with whom he lives) was recently diagnosed with smear-positive pulmonary TB. During a contact investigation, the 24 y/o M had a strongly positive IGRA assay, and is referred to you. He has no other known TB contact, and reports a negative TST years ago. What is the most appropriate next course of action?

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

Latent TB infection (LTBI): diagnosis

Tuberculin skin test

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

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

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

Latent TB infection (LTBI): diagnosis

Interferon gamma release assays (IGRAs)

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

Latent TB infection (LTBI): diagnosis

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

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

Latent TB infection (LTBI): treatment

Preferred

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

Alternative

- Isoniazid daily for 6 months (or 9 months)

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

Latent TB infection (LTBI): treatment

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

Bacille Calmette-Guerin (BCG)

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

Bacille Calmette-Guerin (BCG)

Immunotherapy for bladder cancer

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

THANK YOU

Susan Dorman [DORMAN@MUSC.EDU]

42

Non-AIDS-Defining Complications of HIV/AIDS

Dr. Michael Saag

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

Speaker: Michael Saag, MD

IDBR INFECTIOUS DISEASE BOARD REVIEW AUGUST 20-24 2022

Non AIDS-Defining Complications of HIV/AIDS

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

7/19/2022

IDBR INFECTIOUS DISEASE BOARD REVIEW AUGUST 20-24 2022

Disclosures of Financial Relationships with Relevant Commercial Interests

- **None**

CASE 1

IDBR INFECTIOUS DISEASE BOARD REVIEW AUGUST 20-24 2022 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

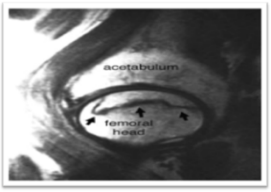
QUESTION #1

IDBR INFECTIOUS DISEASE BOARD REVIEW AUGUST 20-24 2022 PREVIEW QUESTION

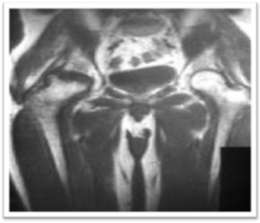
Which if the following is the most likely underlying cause of his hip pain?

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, 02 sat 97%
- Pertinent findings
- Neuro: CNII-XII intact, strength 1+ all extremities except 4+ hand/wrist and ankles.
- NI reflexes. Alert, oriented.

CASE 2: Labs

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

IDBR 2022 PREVIEW QUESTION

Which of the following is the most likely diagnosis?

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

CASE 3

IDBR 2022 PREVIEW QUESTION

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

QUESTION #3

IDBR 2022 PREVIEW QUESTION

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

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

CASE 4

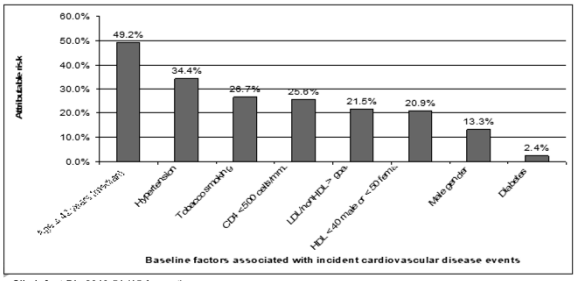
- 55 year old man presents with complaints of crushing chest pain
- HIV diagnosed 10 years ago
- Initial HIV RNA 340,000; CD4 43 cells/ul
  - Now HIV RNA < 50 c/ml; CD4 385 cells/ul
- Initally Rx with ZDV/3TC / EFV;
  now on ABC/3TC/ EFV
- On no other medications / smoker
- ECG shows acute myocardial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

QUESTION #4

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

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

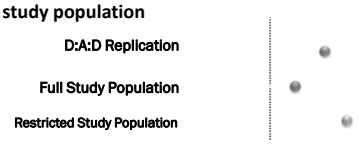
Low CD4⁺ T Cell Count Is a Risk Factor for Cardiovascular Disease Events in the HIV Outpatient Study



Clin Infect Dis 2010;51 (15 August)

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

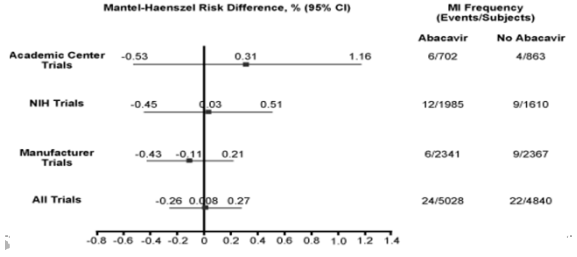
Adjusted hazard ratios of MI among persons with recent ABC use (vs. no recent ABC use): replication of the D:A:D model, NA-ACCORD model in the Full study population, and NA-ACCORD model in the Restricted study population



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

FDA meta-analysis

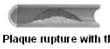
26 randomized, controlled ART trials of abacavir. 16 GSK studies, 5 NIH, 5 academic centers. 5032 received ABV and 4842 non-ABV (CROI 2011)



MI Classification Protocol

Universal Definition of MI:

Primary MI (Type 1 'traditional' MI atherosclerosis)



Plaque rupture with thrombus

Secondary MI (Type 2 supply-demand mismatch)

Vasospasm

Secondary MIs common in HIV-infected individuals before age 50

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

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

CASE 5

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

QUESTION #5

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

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

Bonus Question:

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

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

CASE 6

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

Hb 8.2 gm/dl; Plt count 21,000; Creatinine 2.0
Rare schizocytes on peripheral blood smear

QUESTION #6

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

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

CASE 7

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

140 | 101 | 5 Gluc 100
4.2 | 28 | 1.1 eGFR = 65 ml/min

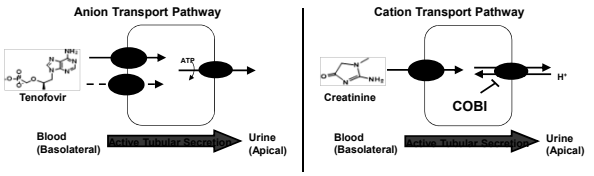
- Started on TAF/FTC+ Dolutegravir; No other medications
- Returns 4 weeks later, labs unchanged except creatinine now 1.3 mg/dl (eGFR 55)

QUESTION #7

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

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

Tenofovir and COBI Interact with Distinct Renal Transport Pathways

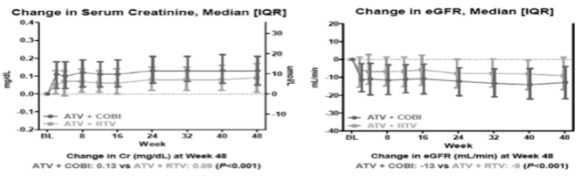


The active tubular secretion of tenofovir and the effect of COBI on creatinine are mediated by distinct transport pathways in renal proximal tubules

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

Changes in Serum Creatinine and eGFR Study 114

- COBI increases serum creatinine by inhibiting renal creatinine secretion[1]
- COBI does not affect actual glomerular filtration rate[2]



Gallant IAS 2012

CASE 8

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

QUESTION #8

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

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

CASE 9

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

QUESTION # 9

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

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

CASE 10

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

QUESTION # 10

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

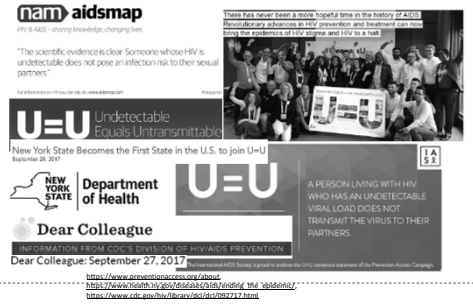
A. Virtually zero risk (< 0.2%)
B. Very low risk (< 2%)
C. Possible (<10 %)
D. It depends on which ARV regimen he's on

PARTNERS Study

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

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

U=U: Undetectable=Untransmittable



https://www.preventionaccess.org/about
https://www.health.ny.gov/diseases/aids/providers/dhd_letter.htm
https://www.cdc.gov/hiv/library/dcl/dcl0927l7.html

CASE 11

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

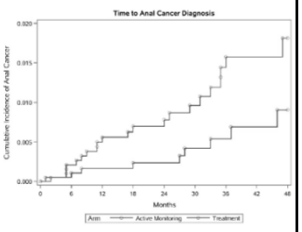
QUESTION # 11

Which of the following should be performed?

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

Treatment of HSIL reduces risk of anal cancer by 57%

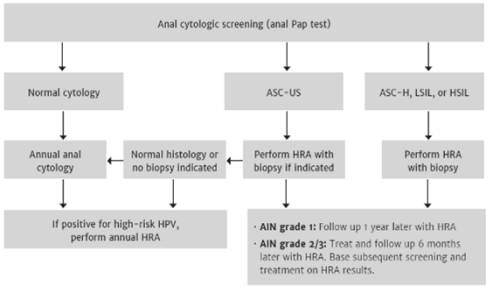
- **30 anal cancers diagnosed** in median f/u of 25.8 months
  - 9 in Treatment arm (173/100,000 PY)
  - 21 in Active Monitoring arm (402/100,000 PY)
- 8 study-related serious AEs:
  - 7 in treatment arm (3 pain, 3 abscess, 1 skin ulceration)
  - 1 in monitoring arm (infection)



Anal dysplasia

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

Figure 1. Follow-up of Anal Cytologic Screening Results



Recommendations: Screening

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

7/31/2022 NYSDOH AIDS Institute Clinical Guidelines Program

Contact me:

msaag@uabmc.edu

43

Respiratory Viral Infections including Influenza, Immunocompetent, and Immunocompromised Patients

Dr. Andrew Pavia

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

Speaker: Andrew T. Pavia, MD

IDBR INFECTIOUS DISEASE BOARD REVIEW AUGUST 20-24 2022

Respiratory Viral Infections Including Influenza, Immunocompetent, and Immunocompromised Patients

Andrew T. Pavia, MD
Chief of the Division of Pediatric Infectious Diseases
George and Esther Gross Presidential Professor
University of Utah

7/13/2022

IDBR INFECTIOUS DISEASE BOARD REVIEW AUGUST 20-24 2022

Disclosures of Financial Relationships with Relevant Commercial Interests

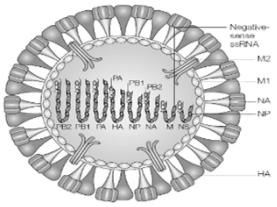
- **Commercial Interests: Antimicrobial Therapy Inc, WebMD, Merck**

What you need to know for the boards

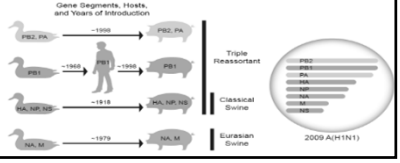
- Minimal virology
- Epidemiology including H7N9
- Diagnosis
- Complications
- Treatment
- Vaccines

Influenza virus

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



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



Clinical findings of influenza

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

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

Speaker: Andrew T. Pavia, MD

Groups at Risk for Complications of Influenza

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

PREVIEW QUESTION

Question #1

- A 45-year-old international agricultural researcher presents in June in the US with fever, cough, diarrhea, myalgia, sore throat, and dyspnea. He is hypotensive and hypoxemic.
- CBC shows mild leukopenia, chemistry panel and LFT's are normal.
- Three days prior to the onset of his illness he was inspecting poultry operations Jiangsu Province, China.

PREVIEW QUESTION

Question #1 Continued

Assuming the he acquired his severe respiratory illness from the poultry he was inspecting, the most likely diagnosis would be:

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

What makes a human influenza strain

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

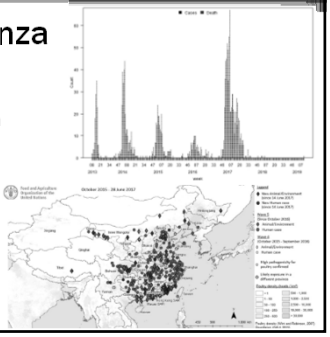
Influenza A viruses infecting humans

- H1N1*: Emerged in 1918. Re-emerged in 1977
- H2N2: 1956-1977 but replaced by H3N2
- H3N2*: Emerged in 1968 (Hong Kong flu)
- H3N2v: Assorted swine associated variants
- H5N1*: Emerged 2003 in Hong Kong. Current strain causing severe outbreak in birds but not humans
- H7N9*: Caused >130 cases of severe disease 2013; >200 in second wave; ongoing
- H7N3: Isolated cases in farm workers
- H7N7: H7 viruses associated with conjunctivitis
- H9N2: Sporadic cases associated with poultry
- H10N3: First human case 2021

* Currently causing human disease

H7N9 Avian influenza

- > 1500 cases in 5 years
- 22% case fatality
- Avian to human transmission
- Family clusters with human to human documented
- Some oseltamivir resistance
- Exported cases
  - US x 2, Canada, Hong Kong, Taipei
- Largely disappeared after avian vaccine

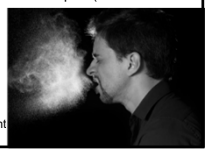


43 - Respiratory Viral Infections Including Influenza, Immunocompetent, and Immunocompromised Patients

Speaker: Andrew T. Pavia, MD

Influenza Transmission

- Incubation period: 1-4 days (average: 2 days)
- Serial interval: estimated 3-4 days among household contacts
- Shedding:
  - Adults: 1 day before symptoms; 5-7days after illness onset
  - Young children: 1-2 days before illness onset; 10 or more days after symptom onset
  - Immunocompromised or severely immunosuppressed persons: weeks to months
- Large droplets (up to 6 feet) most important. Fomite and small droplet (true airborne) may contribute.
- Standard plus droplet precautions recommended
- "Use caution" for aerosol generating procedures
- Monitor and manage ill health care personnel



http://www.cdc.gov/flu/professionals/infectioncont

Question #2

An 18 year old high school student develops chills, fever, cough, myalgia in January. She is prescribed azithromycin, rest and NSAIDS. Fever and cough continue and she becomes progressively dyspneic and weak. On admission T 39, P 150, RR 24-30, BP 120/50. She has crackles throughout both bases and a gallop. Influenza PCR positive

- WBC =9000/mm3 (60% polys, 30% bands)
- Creatinine 1.9
- BNP and troponin markedly elevated
- CXR shows diffuse bilateral infiltrates and cardiomegaly
- Requires V-A ECMO

Question #2 Continued

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

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

Mild complications of influenza

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

Severe complications of influenza

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

Influenza associated hemorrhagic pneumonitis

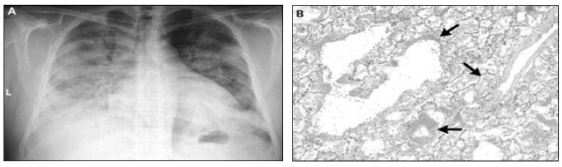


Photo: Perez-Padilla. *NEJM* 009; 361 (7): 680

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

Speaker: Andrew T. Pavia, MD

Non-respiratory complications of influenza

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

Question #3

- A 20 year old woman is 18 days out from HSCT in January on and engrafted 3 days ago.
- She develops fever, hypoxemia, bilateral lung infiltrates and is intubated.
- A nasal swab is negative by rapid test for influenza.

Question #3 Continued

Which of the following is the most appropriate course of action (regardless of other actions you may take)?

A. Do not initiate anti-influenza therapy due to result of rapid test. The timing suggests idiopathic pulmonary syndrome (engraftment)
B. Initiate anti-influenza therapy empirically and send tracheal aspirate or BAL for influenza PCR
C. Send IgG and IgM for influenza
D. Send RSV EIA and initiate empiric IV ribavirin

Diagnosis



Diagnosis of influenza

- Performance of all tests depends on prevalence of virus in community and specimen quality
- Clinical diagnosis: up to 80% PPV during peak
- Rapid influenza detection tests have low-moderate sensitivity 10-70% (less for H1N1); reasonably specific
- Positive antigen test in peak season high PPV; negative test should not be used for decisions
- PCR/NAAT recommended by IDSA Guidelines, rapid platforms expanding. When flu is circulating, test for both SARS-COV-2 and flu
- Serology useless for clinical diagnosis

Influenza in transplant pearls

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

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

Speaker: Andrew T. Pavia, MD

Question #4

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

Question #4 continued

Which of the following is correct?

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

ACIP and IDSA Guidelines for Antiviral Use 2022

- Antiviral treatment is recommended for patients with confirmed or suspected influenza as soon as possible for:
  - Who are hospitalized regardless of duration of symptoms
  - Have severe, complicated or progressive illness regardless of duration of symptoms
  - Outpatients with confirmed or suspected influenza who are at higher risk for influenza complications

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

ACIP Guidelines for Antiviral Use 2022 (con't.)

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

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

CDC Antiviral Treatment Recommendations

- Empiric antiviral therapy should be offered to pregnant women and women up to 2 weeks postpartum
- Pregnancy should not be considered a contraindication to therapy.
- Treatment duration
  - NAIs: 5 days
  - Baloxavir: single dose
- Initiating treatment within 2 days of symptoms results in improved outcomes
  - Substantial reduction in morbidity and mortality

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

Baloxavir

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

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

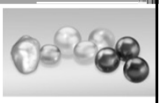
43 - Respiratory Viral Infections Including Influenza, Immunocompetent, and Immunocompromised Patients

Speaker: Andrew T. Pavia, MD

Antiviral Prophylaxis

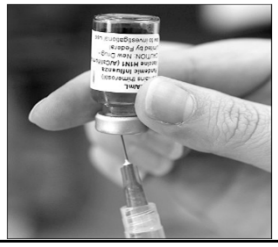
- Chemoprophylaxis should not replace vaccination
- Oseltamivir, zanamivir, baloxavir 70-90% effective in trials
- Prophylaxis may increase selection of resistant viruses
- PEP is recommended to control influenza outbreaks in nursing homes
- PEP can be considered for high risk persons with unprotected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

Influenza antiviral pearls



- Antivirals not effective after 48 hours in outpatients with uncomplicated flu but show benefit out to 5 daysin hospitalized patients
- Double dose oseltamivir not more effective
- Resistance to oseltamivir occurs most often through a specific point mutation H275Y in H1N1 viruses (functionally same as H274Y in N2).

Vaccines



ACIP Recommendations for Influenza vaccination 2021-2022

- Routine influenza vaccination is recommended for all persons aged 6 months and older.
- "During the COVID-19 pandemic, reducing the overall burden of respiratory illnesses is important to protect vulnerable populations at risk for severe illness, the healthcare system, and other critical infrastructure."
- All vacines now quadrivalent (QIIV = Quadrivalent inactivated influenza vaccine) H1N1, H3N2, B Yamagata, B Victoria

Vaccine pearls

- Efficacy varies by year and group
- Generally 50-70%; lower in elderly, children < 2, renal disease, immunosuppressive therapy and transplant pts.
- In HIV, response related to CD4 count
- Major mismatch occurs at least every 10 years
- Egg adaptation may lower efficacy

Vaccine pearls (con't.)

- Enhanced vaccines recommended for those >65
  - High dose inactivated, adjuvanted, recombinant
- All influenza vaccines can be given to those with egg allergy.
- For those with anaphylaxis to egg, consultation with allergist no longer recommended. Anaphylaxis to flu vaccine is still a contraindication

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

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Egg Allergy

- Persons with a history of egg allergy who have experienced only hives after exposure to egg should receive flu vaccine. Any licensed and recommended flu vaccine (i.e., any form of IIV or RIV) that is otherwise appropriate for the recipient's age and health status may be used.
- Persons who report having had reactions to egg involving symptoms other than hives… or who required epinephrine or another emergency medical intervention, may similarly receive any licensed and recommended flu vaccine (i.e., any form of IIV or RIV) that is otherwise appropriate for the recipient's age and health status. If a vaccine other than ccIIV4 or RIV4 is used, the selected vaccine should be administered in an inpatient or outpatient medical setting (including but not necessarily limited to hospitals, clinics, health departments, and physician offices).
- A previous severe allergic reaction to flu vaccine, regardless of the component suspected of being responsible for the reaction, is a contraindication to future receipt of the vaccine.

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

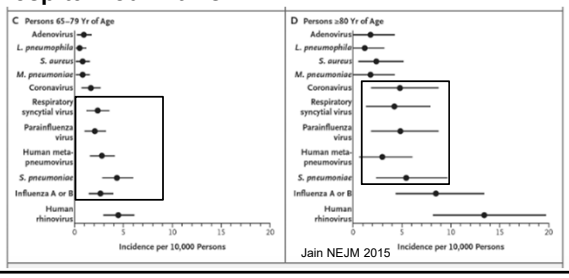
Other important respiratory viruses Adenovirus, RSV, hMPV, parainfluenza, coronaviruses, hantaviruses (and more)

Photograph by Adam Clark

What you may be tested on

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

Incidence of pathogens in older adults hospitalized with CAP



Jain NEJM 2015

Findings which may suggest viral vs bacterial CAP: beware the overlap!

Characteristic	Viral	Bacterial
Onset	Gradual	Sudden
Season	Winter, associated with viral outbreaks	Slightly less seasonal
Host	Older age, more cardiac and pulmonary disease	Any age
Exam	Wheezing	Consolidation
CBC	Leukopenia	Leukocytosis
Procalcitonin	< 0.1	>0.5
CRP	Lower	Higher
CXR (big overlap)	Interstitial, multilobar	Consolidated, effusion

Diagnosis of respiratory viruses in adults

- Generally shed less virus than children
- Sensitivity depends on test and specimen. Flocked swab and swabbing nose and throat may be better
- Virus may be present in lower respiratory tract (TA/BAL) but not upper in patients with pneumonia
- PCR most sensitive. FDA cleared multiplex platforms available
- Testing is critical in immunocompromised and transplant patients with respiratory symptoms
- Consider testing in hospitalized elderly

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

Speaker: Andrew T. Pavia, MD

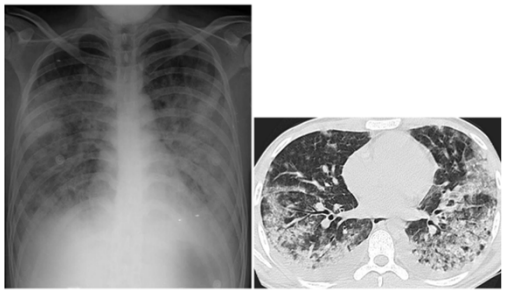
Respiratory Viruses in HSC Transplant Patients

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

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

Case

- A 20 year old soldier undergoing advanced infantry training presents in March with several days of fever, cough, chest pain, tachypnea, hypoxia and conjunctivitis with this CXR.
- No travel, hiking, animal exposures
- WBC 3.0, platelets 160, CRP 2.5, AST 75



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

Question #5

2 days later he is in ICU on high levels of support.
You suspect:

A. Pneumococcal pneumonia
B. *Borrelia hermsii* with capillary leak and ARDS
C. Adenovirus
D. Hantavirus pulmonary syndrome
E. MRSA pneumonia
F. Group A streptococcus with TSS

Question #5

2 days later he is in ICU on high levels of support.
You suspect:

A. Pneumococcal pneumonia
B. *Borrelia hermsii* with capillary leak and ARDS
C. Adenovirus
D. Hantavirus pulmonary syndrome
E. MRSA pneumonia
F. Group A streptococcus with TSS

Adenovirus

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

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

Speaker: Andrew T. Pavia, MD

Adenovirus in transplant patients

- More common with Campath (alemtuzumab)
- URI progresses to LRI in about half, with high mortality
- May disseminate and cause severe hepatitis, encephalitis
- May cause hemorrhagic cystitis, tubulointerstitial nephritis
- May lead to loss of graft in SOT patients; HLH
- Diagnosis by PCR of respiratory secretions, blood, pathology of organ biopsy
- Cidofovir, Brincidofovir have been used for Rx

Question #7

- A 75 yo man with COPD, history of MI is admitted in January with progressive dyspnea, cough, tachypnea, low grade fever. ROS is positive for rhinitis.
- He has been spending time with young grandchild who has bronchiolitis.
- Rapid Covid test negative. CXR shows bilateral perihilar infiltrates but no consolidation or effusion

Question #7 Continued

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

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

Question #8

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

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

RSV

- Most common cause of LRTI in children
- Common cause of URI with rhinitis in adults. AE-COPD, worsened CHF, asthma exacerbation and pneumonia in elderly and immunocompromised
- Transmitted by large droplet and contact; Late fall to spring (usually December- April)
- As common as influenza among hospitalized persons > 65

Falsey NEJM 2005, Widmer 2012

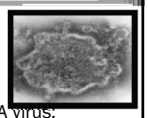
RSV

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

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

Speaker: Andrew T. Pavia, MD

Human Metapneumovirus



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

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

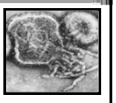
RSV, hMPV in older adults

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

What's on the horizon?

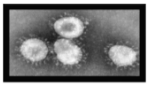
- Multiple vaccine candidates for RSV +/- hMPV in clinical trials
- Several small antivirals for RSV failed in phase 3
- New candidates in clinical trials

Parainfluenza virus



- Paramyxovirus with 4 subtypes 1-4
- Spring and fall seasonality
- Causes URI, bronchiolitis, croup, pneumonia in children. Parainfluenza 3 more severe.
- Causes URI, cough illness and viral pneumonia in adults
- May cause severe disease in transplant patients and all respiratory viruses be associated with COP (formerly known as BOOP)

Other Human Coronaviruses



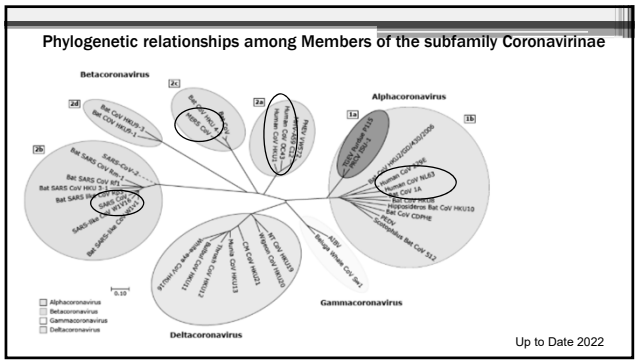
- HuCoV 229e, HuCoV OC43
  - "Older" associated predominantly with URI
- HuCoV HKU1, HuCoV NL63
  - Recently described using molecular techniques. Associated with URI and some pediatric and adult pneumonia
- May be detected on newer multiplex platforms (Luminex, FilmArray). Do not cross react with SARS-CoV-2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

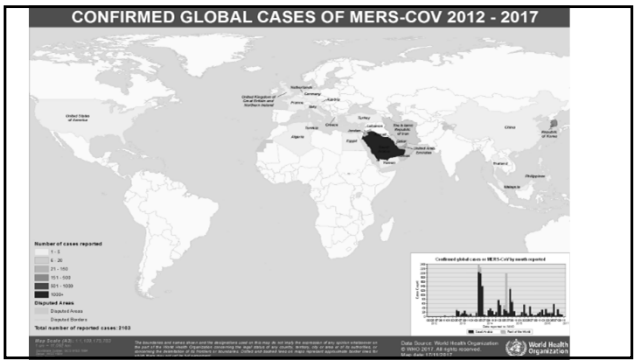
MERS coronavirus

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

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

Speaker: Andrew T. Pavia, MD





Question #9

- A 35 yo man is admitted to the ICU in July with fever, respiratory failure, hypotension.
- 5 days PTA he complained of having the "flu;" fever, malaise, myalgia, mild abd pain.
- History: Recently camped in cabins at Yosemite National Park which has had rodent infestations issues.
- Has parakeet, dogs, cat had kittens recently, owns a hot tub. 2 kids in daycare have URI.

Question #9 (con't.)

- Labs: Hct 52; WBC 6.0 (20% bands, 45% polys, 2+ atypical lymphs), platelets 90K,
- AST 105, PT 18, PTT 25
- CXR: Rapidly progressing bilateral infiltrates leading to white out

Question #9 (con't)

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

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

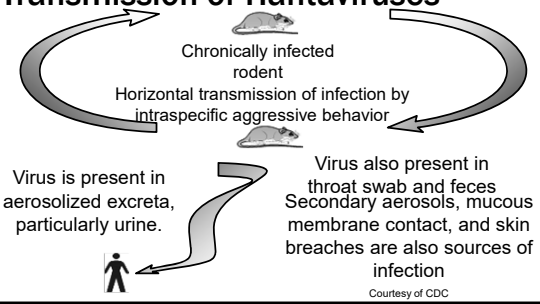
Hantavirus Pulmonary Syndrome HPS

- First described in a 1993 outbreak in the 4 Corners
- Outbreak in 2012 Yosemite. Endemic cases of HPS in much of US, Chile, Argentina
- Caused by specific North American and Latin American hantaviruses – member of Bunyaviridae family.
  - Previously unrecognized viruses cause HPS, Sin Nombre virus, Black Creek Canal, New York virus
  - Prior to the HPS outbreak, the only known hantaviruses were those that caused HFRS

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

Speaker: Andrew T. Pavia, MD

Transmission of Hantaviruses



Courtesy of CDC

Stages of Hantavirus Pulmonary Syndrome (HPS)

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

HPS-Cardiopulmonary Phase

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

HPS-Cardiopulmonary Phase

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

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

44

Pharyngitis Syndromes including Group A Strep Pharyngitis

Dr. Karen Bloch

44 - Pharyngitis Syndromes and Group A Strep

Speaker: Karen C. Bloch, MD

IDBR INFECTIOUS DISEASE BOARD REVIEW AUGUST 20-24 2022

Pharyngitis Syndromes and Group A Strep

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

7/17/2022

INFECTIOUS DISEASE BOARD REVIEW AUGUST 20-24 2022

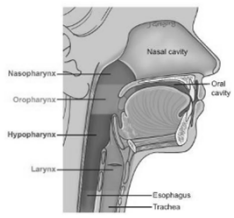
Disclosures of Financial Relationships with Relevant Commercial Interests

- **None**
- **But, Special Thanks to Dr. Bennett Lorber!**

Think Like a Realtor

Think Like A Realtor

Pharyngitis

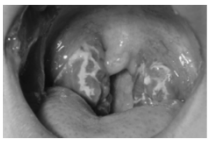


- Small square footage
- Micro-neighborhoods
- Regional differences

Case 1

INFECTIOUS DISEASE BOARD REVIEW AUGUST 20-24 2022 PREVIEW QUESTION

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



44 - Pharyngitis Syndromes and Group A Strep

Speaker: Karen C. Bloch, MD

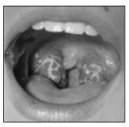
Question 1

IDSA 2022 PREVIEW QUESTION

What is the most appropriate antimicrobial treatment?

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

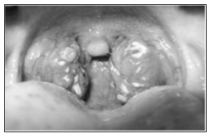
Group A streptococcus

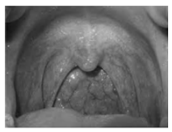


- AKA *Streptococcus pyogenes*
- 5-15% sore throats in adults
- Usually *self-limited* infection (even untreated)

Differentiating Pharyngitis

GAS VS **Viral pharyngitis**





Differentiating Pharyngitis

GAS
- 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

How Specific are Clinical Findings?

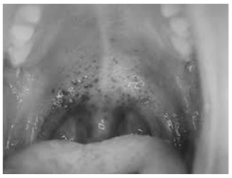
- Modified CENTOR score
  - Can't cough
  - Exudate
  - Nodes
  - Temperature
  - OR age <15 yr (+1) or >44 years (-1)

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

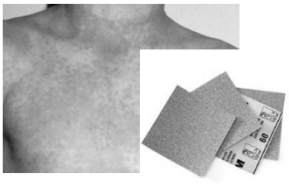
IDSA guidelines recommend antibiotics only following a RADT positive testing.

Streptococcal Clues

- Palatal petechia



- Scarletina

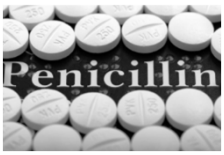


Laboratory Diagnosis

- 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

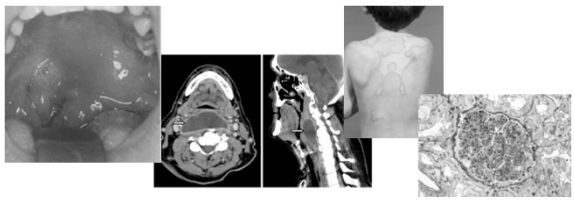


PCN Allergic:

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

Secondary Complications

- Infectious complications
- Immunologic complications



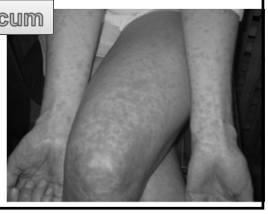
Pharyngitis and….

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

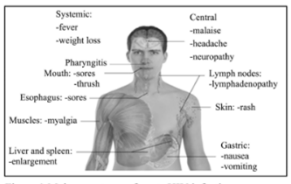
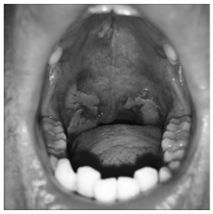


Figure 1 Main symptoms of acute HIV infection

- 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-2 • Usually with initial infection • Tonsilar 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

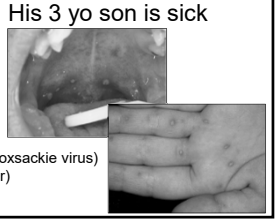
Adenovirus

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



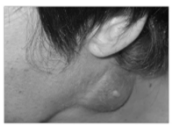
- Caused by enteroviruses (most common Coxsackie virus)
- More common in kids (often serve as vector)

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

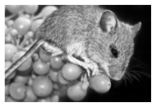
Question 2

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

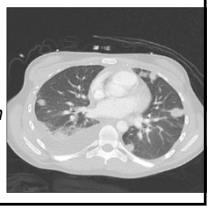


Pharyngitis and Chest Pain

- 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

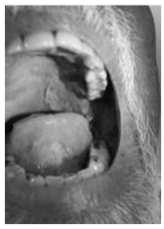


Pharyngitis & TNF-alpha inhibitors

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

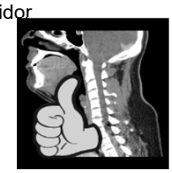
Oropharyngeal Histoplasmosis

- Can mimic oral malignancy
- Denotes disseminated disease



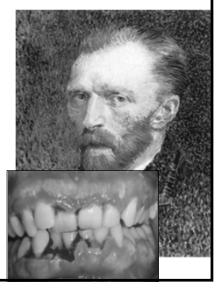
Extra-Tonsillar Infections: 1

- 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

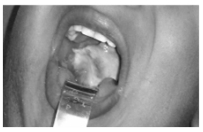
Case 3

2022 PREVIEW QUESTION

- 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.

2022 PREVIEW QUESTION

- 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

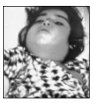
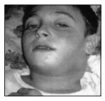
2022 PREVIEW QUESTION

The most likely diagnosis is?

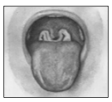
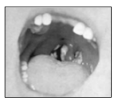
A. Streptococcal pharyngitis
B. Kawasaki disease
C. Vincent angina
D. Diphtheria
E. Candida

Buzz words and Visual Associations

Bull neck:

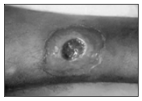




Grey pseudomembrane: extends onto palate or uvula; bleeds when scraped

Other clues

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



Noninfectious Mimics

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

44 - Pharyngitis Syndromes and Group A Strep

Speaker: Karen C. Bloch, MD

45

Core Concepts: Antiviral Drugs

Dr. Andrew Pavia

45 - Core Concepts: Antiviral Drugs

Speaker: Andrew T. Pavia, MD

IDBR INFECTIOUS DISEASE BOARD REVIEW AUGUST 20-24 2022

Core Concepts: Antiviral Drugs

Andrew T. Pavia, MD
Chief of the Division of Pediatric Infectious Diseases
George and Esther Gross Presidential Professor
University of Utah

7/13/2022

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Disclosures of Financial Relationships with Relevant Commercial Interests

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

What you need to know

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

Herpes Viruses

Herpes Viruses

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

Herpes Virus Resistance Testing

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

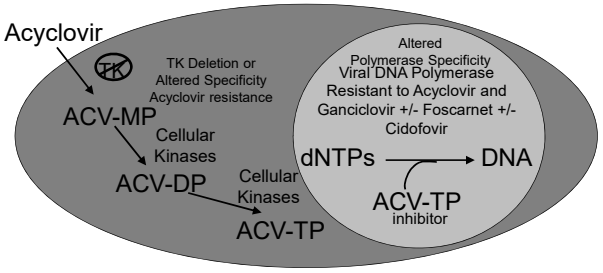
45 - Core Concepts: Antiviral Drugs

Speaker: Andrew T. Pavia, MD

Acyclovir and Valacyclovir

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

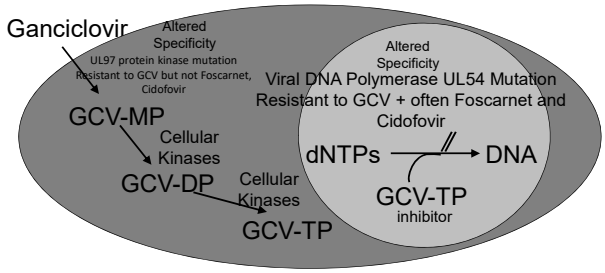
Acyclovir Mechanism of Action Mechanism of Resistance Within Virus



Ganciclovir and Valganciclovir

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

Mechanism of Action of Ganciclovir Mechanism of Resistance Within Virus



Foscarnet

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

Cidofovir

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

Letermovir

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

Hepatitis B

Therapy for Hepatitis B

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

HBV Therapy

Resistance Concerns if Patient Has HBV/HIV Coinfection

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

Influenza

Influenza Therapy

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

Influenza Therapy

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

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

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

SARS-CoV-2

SARS-CoV-2

- Remdesivir
  - Mechanism
    - Acts as nucleoside analog
    - Inhibits RNA-dependent RNA polymerase
  - Resistance
    - Resistant mutant selected for by serial passage in vitro, but none detected in clinical samples (with very limited data)
- Molnupiravir
  - Mechanism
    - Acts as nucleoside analog
    - Causes "catastrophic errors" in replication
- Nirmaltrevir/ritonavir (Paxlovid)
  - Inhibits Mpro (main protease) required to cleave viral polyproteins
  - Several mutations identified in Mpro that confer resistance but at fitness cost
  - Clinical importance remains under investigation

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

Agenda Day 5: Wednesday, August 24, 2022

AM Moderator: Kieren Marr, MD					
#	Start		End	Presentation	Faculty
46	8:00 AM	-	9:00 AM	Infections in the Neutropenic Cancer Patient and Hematopoietic Stem Cell Recipients	Kieren Marr, MD
47	9:00 AM	-	9:45 AM	Photo Opportunities: Images You Should Know for the Exams	Jack Bennett, MD
FC10	**9:45 AM**	**-**	**10:00 AM**	**Faculty Q&A**	**Drs. Marr (Moderator) and Bennett**
48	10:00 PM	-	10:30 PM	Pneumonia: Some Cases that Could be on the Exam	Paul Auwaerter, MD
49	10:30 AM	-	11:130 AM	Lots of Protozoa	Edward Mitre, MD
	11:30 AM	-	12:00 PM	Lunch Break	
PM Moderator: Paul Auwaerter, MD					
BR5	**12:00 PM**	**-**	**12:45 PM**	**Board Review Day 5**	**Drs. Auwaerter (Moderator), Bennett, Marr, Masur, Nelson Mitre, and Rose**
50	12:45 PM	-	1:30 PM	Bone and Joint Infections	Sandra Nelson MD
51	1:30 PM	-	2:15 PM	Ticks, Mites, Lice, and the Diseases They Transmit	Paul Auwaerter, MD
52	2:15 PM	-	3:00 PM	Worms and More Worms	Edward Mitre, MD
FC11	**3:00 PM**	**-**	**3:15 PM**	**Faculty Q&A**	**Drs. Auwaerter (Moderator) Mitre, Nelson**
53	3:15 PM	-	3:45 PM	Lyme Disease	Paul Auwaerter, MD
54	3:45 PM	-	4:00 PM	Penicillin Allergies	Sandra Nelson, MD
55	4:00 PM	-	4:45 PM	Kitchen Sink: Syndromes Not Covered Elsewhere	Stacy Rose, MD

46a

Infections in the Neutropenic Cancer Patient and Hematopoietic Stem Cell Recipients

Dr. Kieren Marr

46a - Infections in the Neutropenic Cancer Patient and Hematopoietic Stem Cell Recipients

Speaker: Kieren Marr, MD

INFECTIOUS DISEASE BOARD REVIEW AUGUST 20-24 2022

Infections in the Neutropenic Cancer Patient and Hematopoietic Stem Cell Recipients

Kieren Marr, MD
Adjunct Professor of Medicine, Oncology and Business
Johns Hopkins University School of Medicine
Johns Hopkins Carey School of Business

7/17/2022

INFECTIOUS DISEASE BOARD REVIEW AUGUST 20-24 2022

Disclosures of Financial Relationships with Relevant Commercial Interests

- **Consultant: Cidara Therapeutics**
- **Employment: Sfunga Therapeutics**
- **Ownership Interests: Pearl Diagnostics, Sfunga Therapeutics**

Goals of This Review

- Focus on testable complications specific to the immunocompromised host
  - Types of immune – suppressing drugs and diseases
  - Recognition of specific "neutropenic syndromes"
    - Skin lesions
    - Invasive fungal infections
    - Neutropenic colitis

Fundamentals: Underlying disease risks

- Immune defects associated with underlying malignancy (and prior therapies)
  - AML and myelodysplastic syndromes (MDS)
    - Qualitative and quantitative neutropenia
  - Lymphoma
    - Functional asplenia
  - CLL and multiple myeloma
    - Hypogammaglobulinemia
  - Aplastic anemia
    - Severe, prolonged neutropenia

Fundamentals: Therapeutic risks

- Recognize risks with cytotoxic therapy (neutropenia)
  - Prolonged (>10 days) and profound (< 500 cells / mm3) leads to high risks for severe bacterial and fungal infections
    - Bacteremia, pneumonia, candidemia, aspergillosis
    - Outcomes tend to be poor – preventative therapies important
- Recognize infectious risks with other biologic therapies that immunosuppress
  - T cell suppressing agents and 'targeted' biologics
    - Viral and fungal infections

Immune modulating anti-cancer drugs

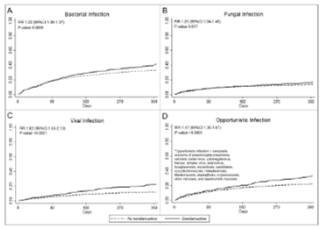
- Drugs that impact neutrophils
  - Many cytotoxic agents
    - Bacterial infections, fungal infections
- Drugs that impact T cells
  - Purine analogs (fludaribine, cladribine, clofarabine) and temozolomide
    - CD4+ T cell dysfunction: Herpes viruses (CMV, VZV), intracellular bacteria, fungi (PJP, Aspergillus)

46a - Infections in the Neutropenic Cancer Patient and Hematopoietic Stem Cell Recipients

Speaker: Kieren Marr, MD

Bendamustine

- Nitrogen-based alkylating agent and antimetabolite
- Indolent non-Hodgkins lymphomas, CLL
- Neutropenia *and lymphopenia* (months - years)
- Higher risks for infections (bacterial, CMV, PJP, histoplasmosis)



Fung et al. Clin Infect Dis 68(2): 247-55

Biological Therapies

- Generally broken into three categories
  - Biological response modifiers. Exert effects by stimulating immune system (ex. CSFs)
  - Gene therapies
  - Targeted therapies (mAbs and small molecule enzyme inhibitors)

Table 1. Novel targeted therapies: immune sequelae.

Target	Agents	B-Cell Depletion	T-Cell Depletion	HGG [1]	Neutropenia
CD20	Rituximab Ofatumumab Obinutuzumab	+++	-	+	++ [2]
CD52	Alemtuzumab	++	+++	+	+ [3]
CD38	Daratumumab	+	+	-	+
SLAMF7	Elotuzumab	-	-	-	-
CD19/CD3	Blinatumomab	+++	+	++	++
BTK	Ibrutinib Acalabrutinib Zanubrutinib	++	-	+	+
PI3K	Idelalisib Copanlisib Duvelisib	++	+	-	+
JAK	Ruxolitinib	-	+	-	-
BCL-2	Venetoclax	-	-	-	++

Plus signs indicate relative effect (e.g., mild, moderate, significant). [1] Hypogammaglobulinemia. [2] Late neutropenia may occur (median time 175 days, Dunleavy et al.). [3] Neutropenia typically resolves in 2–4 weeks.

Little et al. J Fungi 7, 1058

Key anti-CD Monoclonal Abs

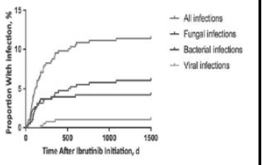
- Common antibodies that impact B and T cells
  - Rituximab (anti-CD20)
    - B cell depletion: CLL, lymphoma
    - Prolonged B cell (6 – 9 mo.); neutropenia can occur
    - Loss of vaccine responses, responses to encapsulated bacteria (pneumonia). Hepatitis B reactivation, PML, PJP
  - Alemtuzimab (anti-CD52)
    - T and B cell depletion for a long time (about 6 months): lymphoma, leukemia, BMT (graft vs. host disease treatment)
    - Herpes viruses (esp. CMV), fungal infections (PJP, Aspergillus)

Tyrosine kinase inhibitors

- BCR – ABL Tyrosine – kinase inhibitors
  - Inhibit signal transduction through BCR-ABL oncogene (ex. imatinib, dasatinib, nilotinib)
    - CML. Think T and B cells (VZV, Hep B reactivation)
    - Autoimmune pneumonitis and colitis (infection mimic), steroids
    - Aspergillosis and other IFI

Bruton's tyrosine kinase inhibitors

- Ibrutinib
- B cell development, macrophage phagocytosis
- Lymphoid malignancies (ex. CLL, lymphomas)
- Single-center review: 11%
- Fungal, bacterial infections
  - Aspergillosis (including CNS)
- Autoimmune – idiopathic drug "toxicities": colitis, pneumonitis



Varughese et al. Clin Infect Dis 2018; 67(5): 687-92
Bercusson A. Blood 2018 132(18): 1985-88
Blez et al. Haematologica 2019 (in press)

46a - Infections in the Neutropenic Cancer Patient and Hematopoietic Stem Cell Recipients

Speaker: Kieren Marr, MD

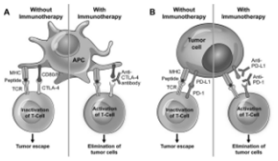
Phosphoinositide 3-kinase (PI3K) inhibitors

- Selective small molecule inhibitors of the B-cell receptor pathway (idelalisib)
- Decreased T-reg, inhibition NK, neutropenia
- Possibly increased IFI (esp. with combo)
- NBV screening, consider antiviral prophylaxis in HBsAg negative or anti HBc-positive patients

Maschmeyer et al. Leukemia 33, 844-62 (2019)

Checkpoint inhibitors

- Block immune checkpoints that regulate T cell activation / function – multiple tumors
- Targeting PD-1 on T cells (pembrolizumab, nivolumab, cemiplimab) or PD-L1 on tumor cells (atezolizumab, avelumab, durvalumab)
- Targeting CTLA-4 on T cells (ipilumumab)
- Induce colitis, pneumonitis
- Increased risks for infection in people receiving concurrent steroids, TNF-α targeting agents for above



Soularue et al. BMJ gut 2018

JAK inhibitors

- Janus kinase inhibitor (Ruxolitinib)
- Inhibit DC, CD4+ fx, decreased T-reg, NK
- HBV: screening, prophylactic entecavir in HBsAg - / anti-HBc-positive
- Tb screening

Maschmeyer et al. Leukemia 33, 844-62 (2019)

Venetoclax

- Inhibits anti-apoptotic BCL2 – family proteins (AML, lymphoid malignancies)
- Sometimes given with hypomethylating agents for AML (ex. azacytidine)
  - Severe, prolonged neutropenia – bacterial, fungal infections
  - Drug interactions may limit use of azole prophylaxis
    - Cyp3a inhibition requires VEN dose decrease / toxicities
    - Aspergillosis increasingly recognized

Neutropenic "syndromes"

Question #1

35 year old woman with AML day 15 after induction therapy.

Fever, chills, diffuse erythematous rash. Blood culture + GPC in chains

Exam – 100/62, HR 120, grade 2 oral mucositis, and a diffuse, blanching, erythematous rash. CXR - bilateral diffuse infiltrates. She is receiving levofloxacin and acyclovir.

This is most consistent with infection with which of the following organisms?

A. Streptococcus pneumoniae
B. Coagulase-negative *Staphylococcus*
C. Enterococcus faecalis
D. Streptococcus mitis
E. Stomatococcus mucilaginosus

46a - Infections in the Neutropenic Cancer Patient and Hematopoietic Stem Cell Recipients

Speaker: Kieren Marr, MD

Viridans Streptococci

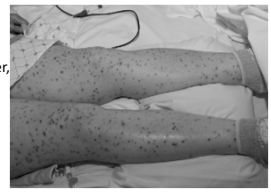
- Key points: neutropenia, mucositis, high-dose cytosine arabinoside, fluoroquinolone
- Can present with fever, flushing, chills, stomatitis, pharyngitis
- VGS shock syndrome:
  - After 24-48 hours, hypotension in 1/3 of cases
  - Rash, shock, ARDS in 1/4 of cases (similar to toxic shock)
- Endocarditis unusual (<10%)
- *S. mitis*, *S. oralis*
- Vancomycin
- Mortality high (15-20%)

Testable contexts: Breakthrough Bloodstream Infections

- Typical patient- neutropenic, progressive sepsis
- Recognize holes in protection, specific syndromes
  - ARDS, rash, quinolones, mucositis → viridans Streptococci
  - Sepsis with β-lactams → Stenotrophomonas, ESBL
  - Sepsis with carbepenems → KPC
  - Lung and skin lesions → *P. aeruginosa*, Fungi
  - Skin lesions, gram + → *Corynebacterium jeikeium*
  - Mucositis (upper, lower tract) → *Fusobacterium* spp., *Clostridium spp.*, *Stomatococcus mucilaginosis*

Question #2

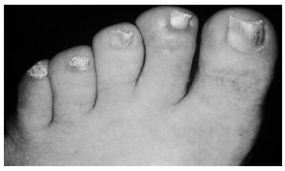
59 year old woman with AML with neutropenia for 25 days. She has been febrile for 6 days, and is receiving meropenem, vancomycin, and acyclovir. New skin lesions that are small, papular, and tender, with no central ulceration.



A. *Rhizopus* spp.
B. Varicella zoster virus
C. *Cryptococcus neoformans*
D. Vancomycin resistant Enterococci
E. *Candida tropicalis*

Fusarium

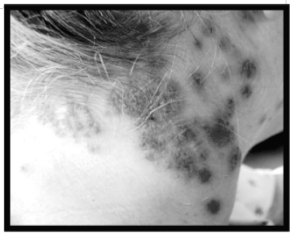
- Invasive pulmonary disease with skin lesions
- Locally invasive infections in neutropenic patients
  - Keratitis
  - Onychomycosis



Question #3

50-year-old woman with newly diagnosed AML developed tender, pruritic papules and plaques on her neck. She had been febrile 38.7°C for the past several days and had received a dose of G-CSF 3 days earlier, with rapid WBC increase (900 ANC). Most likely etiology:

A. *Candida albicans*
B. Sweet's syndrome
C. *Aspergillus niger*
D. Varicella Zoster Virus
E. *Pseudomonas aeruginosa*



Haverstock, C. et al. Arch Dermatol 2006;142:235-b-240-b.

Sweet's syndrome

- Acute febrile neutrophilic dermatosis
- Variants: classic (idiopathic), malignancy-associated, drug induced
- Tender erythematous plaques and nodules typical; also bullous, cellulitic, necrotizing lesions
- Classic stem: neutropenia resolving with GCSF assist, fever, skin lesions, cultures - negative
- Steroids

46a - Infections in the Neutropenic Cancer Patient and Hematopoietic Stem Cell Recipients

Speaker: Kieren Marr, MD

Question #4

70 yr old woman with AML, neutropenic for 15 days, s/p induction chemotherapy develops fever, diarrhea, and abdominal pain. Exam - decreased bowel sounds and tenderness with deep palpation in her RLQ. CT shows inflammation in cecum. Levofloxacin and fluconazole prophylaxis. 4 days prior to her admission for chemotherapy, she ate Chinese food with fried rice.

Which is the most likely etiology?

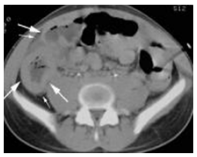
A. Norovirus

B. Clostridioides (Clostridium) difficile

C. Mixed anaerobic and aerobic bacteria

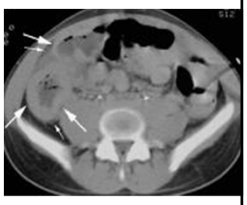
D. Candida albicans

E. Bacillus cereus



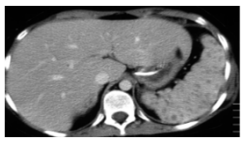
Neutropenic Enterocolitis

- Neutropenic enterocolitis (typhlitis)
  - Necrotizing inflammation with transmural infection of damaged bowel wall
  - Mixed infection with gram-negative, gram-positive, anaerobic bacteria, fungi
  - Can be accompanied by bacteremia
    - Hint: mixed, anaerobic (*C. septicum, C. tertium, B. cereus)*
  - Medical and (less often) surgical management



Hepatosplenic Candidiasis

- Inflammatory response to fungi invaded by portal vasculature
- Presentation after engraftment: abdominal pain, increased LFTs (alk phosph), fever, leg / flank pain
- Differential: other fungi, bacteria, lymphoma
- *C. albicans* most common
  - Amphotericin B primary therapy followed by prolonged fluconazole, echinocandins



Summary: PEARLS

- Recognize typical infections associated with neutropenia and/or other immune suppression (biologic inhibitors of cellular defenses)
- Predict breakthrough bloodstream pathogens based on therapy
- Know specific syndromes
  - *S. viridans* sepsis – ARDS
  - Differential of skin lesions
  - Neutropenic patients - IFI
    - Pulmonary
    - Bloodstream
    - Hepatosplenic candidiasis
  - GI tract enterocolitis

Thank you

kmarr4@jhmi.edu

46b

Selected Syndromes in Stem Cell Transplant Recipients

Dr. Kieren Marr

46b - Selected Syndromes in Stem Cell Transplant Recipients

Speaker: Kieren Marr, MD

IDBR INFECTIOUS DISEASE BOARD REVIEW AUGUST 20-24 2022

Selected Syndromes in Stem Cell Transplant Recipients

Kieren Marr, MD
Adjunct Professor of Medicine, Oncology and Business
Johns Hopkins University School of Medicine
Johns Hopkins Carey School of Business

7/17/2022

IDBR INFECTIOUS DISEASE BOARD REVIEW AUGUST 20-24 2022

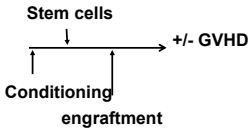
Disclosures of Financial Relationships with Relevant Commercial Interests

- **Consultant: Cidara Therapeutics**
- **Employment: Sfunga Therapeutics**
- **Ownership Interests: Pearl Diagnostics, Sfunga Therapeutics**

PEARLS

- **Fundamentals – risks (temporality)**
  - **Early – mucositis, neutropenia**
  - **Late – GVHD (steroids, asplenia, T cell dysfunction)**
- **Syndromes**
  - **Early pulmonary syndromes**
    - **Bacterial, fungal pneumonia**
    - **Non-infectious: Alveolar hemorrhage, IPS**
  - **Late pulmonary syndromes**
    - **CMV, respiratory viruses, IFI**
    - **Non-infectious: BOOP**
- **Hemorrhagic cystitis**
  - **BK**
  - **Non-infectious: conditioning**
- **Diarrhea – colitis – hepatitis**
  - **Herpes viruses**
  - **Non-infectious: GVHD**
- **Neurologic syndromes**
  - **Herpes viruses (+HHV-6), west nile, angio-invasive, toxoplasmosis, PML (JCV)**
  - **Non-infectious: PRES, antibiotics**

Fundamentals of BMT



- Immune risks for infection are temporal
  - Neutropenia (early, w/in 30 days)
    - Bacterial infections
    - Fungal infections
  - Impaired cellular and humoral immunity (later, post-engraftment)
    - Bacterial infections
    - Fungal infections
    - Viral infections

Fundamentals of BMT

- Autologous (self) vs. allogeneic (other)
- Types of allogeneic donors
  - Related, HLA – matched (MR)
  - Related, HLA - mismatched (haploidentical)
  - Unrelated, HLA – matched (MUD) or Unrelated, HLA – mismatched (MM-URD)
- Types of stem cells
  - Bone marrow
  - Peripheral blood
  - Cord blood
- Types of conditioning regimens
  - Myeloablative
  - Nonmyeloablative

Approach for the boards

- Know common infections and non-infectious mimics
- Approach stems in context
  - Patient's age, disease, history impact risks after BMT
  - What kind of BMT did the patient have?
  - Is the patient early vs. late after BMT?

Type of BMT and timeline impacts immunity, drugs and exposures

46b - Selected Syndromes in Stem Cell Transplant Recipients

Speaker: Kieren Marr, MD

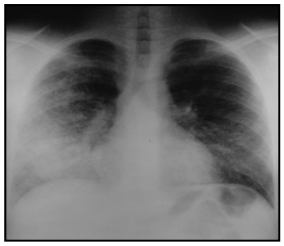
Case #1

42 year old M AML 20 days after a matched unrelated donor BMT (nonmyeloablative) develops fever, cough, pulmonary infiltrates. Pre-transplant: HSV+, VZV+, CMV D+/R-

Exam– 98% sat on 2L nc, T 38.3, crackles RLL

Labs- Cr 2.2, WBC 1200 cells/mL, plt 122

He's currently receiving acyclovir and fluconazole for prophylaxis.



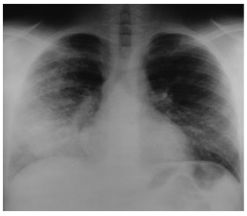
Case #1

What is the most likely cause of his current process?

A. *Candida albicans*
B. *Klebsiella pneumoniae*
C. CMV
D. Parainfluenza virus
E. Hemorrhage

Pulmonary Complications

- Bacterial pathogens
  - *P. aeruginosa, Streptococci*, Legionella, *S. aureus*
  - Aspiration events with severe mucositis early after BMT
  - Encapsulated sinopulmonary pathogens late after BMT
- Filamentous fungi early and late (*A. fumigatus)*



Pulmonary Complications (Con't)

- Respiratory virus infection follows seasonal epidemiology
  - Increased risk for lower tract involvement
  - Influenza, RSV, Parainfluenza 3, Human metapneumovirus
  - Adenovirus: reactivation and acute infection (particular issue with kids)
- Herpes viruses
  - CMV with prolonged impairment in cellular immunity
  - HSV classically described with prior airway manipulation

Early non-infectious lung injury

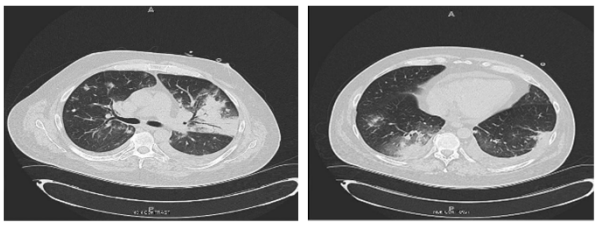
- Diffuse alveolar hemorrhage
  - Bleeding in alveolar space, heterogeneous etiology
    - Vasculitis, drug-induced injury, cancer-chemotherapy / thrombocytopenia
- Idiopathic pneumonia syndrome
  - Within 1st 120 days of BMT, non-infectious
  - Risks: conventional ablative conditioning, acute GVHD (inflammatory pathogenesis?)

Case #2

A 46 year old male 18 months s/p HLA mismatched BMT. History of GVHD skin, GI tract, and BOOP 3 months ago, treated with steroids. One month s/p Parainfluenza 3 URI, with chest CT - tree-in-bud opacities in LLL. Received levofloxacin for 10 days.

He now has increasing shortness of breath and cough.

Case # 2 (con't.)



Case # 2 (con't.)

Blood cultures no growth. Sputum – LF GNR. Serum galactomannan is negative. What is the most likely cause of his current process?

A. *Cryptococcus neoformans*
B. *E. coli*
C. MRSA
D. *Aspergillus fumigatus*
E. *Fusarium* spp.

DDx of Late pulmonary syndromes

- Infectious
  - CMV disease
  - Respiratory virus infections
  - PJP
- Non-infectious
  - Bronchiolitis obliterans syndromes

CMV Infection after BMT

- Reactivation occurs in seropositive patients (R+).
  - Reactivation alone triggers cytokine storm, GVHD, disease
  - Risk for *disease* dependent on immunity
    - Highest risk group for disease after BMT: D- / R+
      - No transferred immunity to CMV
      - This is different than SOT, where highest risk group is D+ / R-
- Primary infection in seronegative patients (R-) from community, positive graft (D+) or blood products (rare)

CMV Disease

- Pneumonitis
  - Indolent cough, fever, SOB, interstitial infiltrates
- Gastrointestinal disease
  - Esophagitis, colitis, hepatitis (rare)
- Encephalitis, retinitis less frequent

CMV Disease after BMT (con't.)

- Treatment concepts
  - Pre-emption with ganciclovir driven by PCR
    - Not prophylaxis (SOT) with ganciclovir (toxicities)
    - Prophylaxis of R+ patients with letermovir
  - Induction therapy with maintenance GCV
  - Resistance to GCV is *rare* (as opposed to SOT)
    - Most failures are due to steroids, T cell depletion
    - Recipe for GCV – resistance: long exposure to suboptimal doses of GCV in a patient with poor cellular immunity
    - Refractory disease can be due to Res and intolerance (neutropenia)
      - Miribavir (inhibits UL-97 kinase) approved for refractory treatment

46b - Selected Syndromes in Stem Cell Transplant Recipients

Speaker: Kieren Marr, MD

Pneumocystis Pneumonia

- Common late after BMT
  - Steroid receipt, T-cell depletion
- Prophylaxis at least 6 months
  - Bactrim
  - Toxicities
    - Dapsone, atovaquone, aerosolized pentamidine
      - Less effective, other infections occur**
- Late diagnoses occur
  - BAL DFA less sensitive

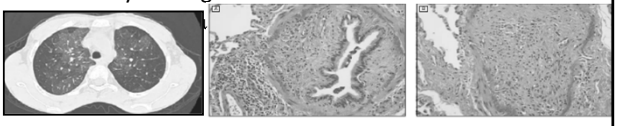
Toxoplasmosis

- Clusters of disease reported in BMT patients
  - T-depleted BMT
  - Some early. Acquisition vs. reactivation?
- Regions with high seroprevalence screen for disease with pre-emptive therapy
- Pneumonia, encephalitis, fever

Isa et al, ID Week 2014
Meers et al. Clin Infect Dis, 2010 Apr 15;50(8):1127-34

Bronchiolitis Obliterans

- Chronic GVHD of lung
  - Allorecognition of lung antigens
- Circumferential fibrosis of terminal airways ultimately leading to airflow obstruction



Williams JAMA 2009

A. Obliteration of bronchiolar lumen
B. Inflammation between the epithelium and the smooth muscle

Case #3

35 yr old F, 80 days after allogeneic BMT with 5 days of anorexia, nausea, epigastric pain, and diarrhea. CMV D-/R+, HSV+, VZV+.
Exam: faint maculopapular rash on upper body. Afebrile.
Meds: acyclovir, TMP-SMX and fluconazole.
ANC 1000, ALC 250. LFTs normal.

What is the most appropriate initial work-up and management?

A. Perform serum VZV PCR
B. Empiric corticosteroid treatment
C. Send C. diff toxin and start oral vancomycin
D. CMV PCR, stool C. diff, bacterial culture
E. #D *and* upper, lower endoscopy

Graft vs. Host Disease (GVHD)

- Acute (early after HSCT)
  - Fever
  - Rash
  - GI: hepatic, colon
- Chronic (later after HSCT)
  - Skin changes (lichen planus, sceroderma)
  - Hepatic (cholestatic)
  - Ocular (keratoconjunctivitis)
  - GI (oral, dysphagia)
  - Pulmonary syndromes

DDx of GI Disease in BMT

HEPATITIS

- GVHD
- Herpes viruses (CMV, VZV)
- Hepatitis B virus
  - Increased viral replication and liver damage
  - Hepatitis not common during neutropenia

DIARRHEA

- GVHD
- CMV
- C. difficile
- Norovirus (chronic diarrhea mimicking GVHD)
- Adenovirus

Adenovirus Infection after BMT

- More common in children, high risk BMT
  - Severe GVHD and steroids
- Enteritis, cystitis, upper respiratory infection, pneumonia, encephalitis, hepatitis
- No controlled treatment studies
  - Taper immunosuppression
  - Cidofovir most active in vitro
  - Ribavirin not effective in larger studies

Case #4

53 year old F 7 yrs s/P allo BMT presents with fever, chills, rigors. H/O severe chronic GVHD skin. PE – T 39.2. tachycardia, tachypnea, hypotension. Skin thick, cracked (Sjogren-like). Social- dog and two cats, no recent exposures. Labs- WBC 8200 / mm3, platelet 43,000/mm3. CT of her chest, abdomen, pelvis - splenic atrophy. Blood cultures positive for gram-negative rods after 5 days.

Most likely cause of her current condition:

A. Fusobacterium nucleatum
B. Eikenella corrodens
C. Capnocytophaga canimorsus
D. Acinetobacter baumannii

Case #5

40 year old M day 60 after allogeneic BMT from unrelated donor, with bloody urine for 6 days. Has skin GVHD, receiving a prednisone taper (1 mg/kg/day). Exam, faint diffuse erythematous rash. Cr 1. LFTs normal. CMV pcr negative.

The most likely etiology is:

A. Cyclophosphamide
B. CMV
C. EBV
D. BK
E. JC virus

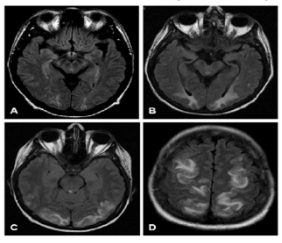
DDx of Hemorrhagic Cystitis

- Conditioning related (early)
  - Cyclophosphamide
- BK virus (later)
- Adenovirus (later)

DDx of Neurologic Syndromes

- Infection
  - Herpes viruses: HSV, CMV, HHV6*
  - West nile virus
  - JCV – PML (especially with T-depleting Abs)
  - Pulmonary – CNS lesions
    - Invasive fungal infections
    - Nocardia
    - Toxoplasmosis
- Drugs: carbapenems, cefepime, PRES*

Posterior reversible encephalopathy (PRES)



- Usually early after HSCT (within 1st 3 months)
- Calcineurin inhibitors: Cyclosporin*, tacrolimus
- Seizures, visual changes, MS changes

46b - Selected Syndromes in Stem Cell Transplant Recipients

Speaker: Kieren Marr, MD

HHV-6 after BMT

- HHV-6 seroprevalence > 95% after age 2
  - Early reactivation common after BMT 38-60% SCT (type B)
  - Clinical correlates reported: rash, marrow suppression, delayed platelet engraftment, idiopathic pneumonitis
- Meningoencephalitis**
  - Nonspecific presentation (confusion, memory loss, EEG / MRI: temporal)
  - Early - within 60 days of BMT
  - RFs: MM/URD or UCB SCT, anti-T-cell
- Diagnosis: PCR of CSF
- Chromosomal integration
- ACV-resistant. Treat with ganciclovir, foscarnet, cidofovir

VZV Infection after BMT

- Multidermatomal lesions
- Primary viral pneumonia
- Encephalitis
- Hepatitis
  - Classic: abd pain, transaminitis late
  - Can occur without skin lesions
- VZV seropositive
- Severe GVHD, acyclovir prophylaxis effective long term
- Recent study: 1% rate of infection, high rate after 1 yr

Baumrin et al. Biol Blood and Marrow Trans 2019 (in press)

PEARLS

- **Fundamentals – Risks (temporality)**
  - **Early – mucositis, neutropenia**
  - **Late – GVHD (steroids, asplenia, T cell dysfunction)**
- **Syndromes**
  - **Early pulmonary syndromes**
    - **Bacterial, fungal pneumonia**
    - **Non-infectious: Alveolar hemorrhage, IPS**
  - **Late pulmonary syndromes**
    - **CMV, respiratory viruses, IFI**
    - **Non-infectious: BOOP**
- **Hemorrhagic cystitis**
  - **BK**
  - **Non-infectious: conditioning**
- **Diarrhea – colitis – hepatitis**
  - **Herpes viruses**
  - **Non-infectious: GVHD**
- **Neurologic syndromes**
  - **Herpes viruses (+HHV-6), west nile, angio-invasive, toxoplasmosis**
  - **PML**
  - **Non-infectious: PRES, antibiotics**

Thank you

kmarr4@jhmi.edu

47

Photo Opportunities: Images You Should Know for the Exams

Dr. John Bennett

47 - Photo Opportunities: Images You Should Know for the Exams

Speaker: John Bennett, MD

IDBR INFECTIOUS DISEASE BOARD REVIEW AUGUST 20-24 2022

Photo Opportunities: Images You Should Know for the Exams

John E. Bennett, MD
Bethesda, Maryland

7/12/2022

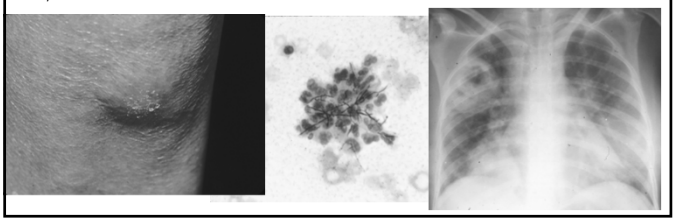
INFECTIOUS DISEASE BOARD REVIEW AUGUST 20-24 2022

Disclosures of Financial Relationships with Relevant Commercial Interests

- **None**

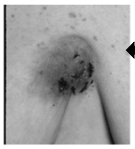
A 65 yr old woman receiving high dose prednisone for breast cancer metastatic to bone was admitted for fever and cough of two weeks' duration.. She was found to have cavitary lung lesions and a skin abscess on her abdomen. Aspirate of the lesion showed branching Gram positive bacilli. The most likely result of culture is which of the following:

a. Actinomyces neuii
b. Rhodococcus equi
c. Aggrigatibacter actinomycetemcomitans
d. Nocardia nova
e. Mycobacterium chelonae



A 53 yr WF from a W. Virginia presented with a draining sinus over her right lower parasternal area of six weeks duration. She had lost about 15 pounds of weight, chronic dry cough and low grade fever. She had felt a little better with two ten-day courses of Keflex but the drainage had never stopped. Chest xray and CT showed a continguous infiltrate in the right middle lobe.

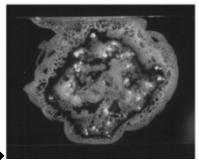
- She had been unemployed, lived on a farm, took care of horses, chickens and dogs. She had a history of alcohol and tobacco abuse. No sick contacts.
- Physical examination was otherwise normal. CBC showed a WBC of 12,500 and a hematocrit of 32%. Images of her chest, her CT and pus from the draining sinus are shown on the next slide.

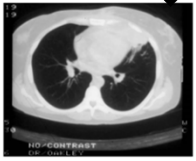


Anterior chest wall

CT chest

Smear of pus





The most likely diagnosis is which of the following:

a. Tuberculosis
b. Prevotella melaninogenica infection
c. Staphylococcus aureus infection
d. Actinomycosis
e. Nocardiosis

This 40-year-old crab fisherman working in the Chesapeake Bay waters came in with low grade fever and a painful rash on his hand of three days' duration. He cut his hand several days ago on a crab spine.

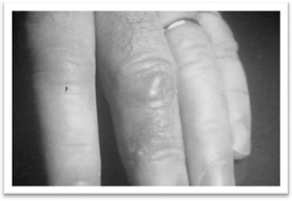
The probable organism is which of the following:

A. Curved gram negative rod

B. Seagull-shaped gram negative rod

C. Gram positive coccus

D. Gram positive bacillus



47 - Photo Opportunities: Images You Should Know for the Exams

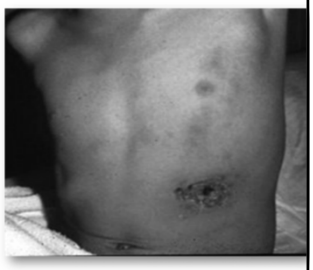
Speaker: John Bennett, MD

This 16-year-old Navajo child was brought to the Four Corners Hospital in Arizona because of high fever and the lesions shown. He looks quite ill.

His mother thought he might have been bitten by a rat while he was sleeping, because he awoke crying of pain in the abdominal lesion and had seemed to be playing normally the day before. She had seen a dead rat in the garage a few days prior.

On exam, he had a temp of 40°C and the lesions seen. Both the lesion and the axillary area was very tender. Gram stain of the skin lesion found no organisms. The most probable cause is which of the following:

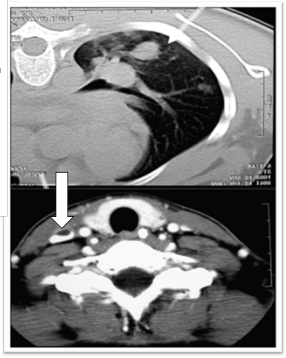
A. Streptobaccillus moniliformis
B. Spirillum minus
C. Eikenella corrodens
D. Yersinia pestis
E. Pasteurella multocida



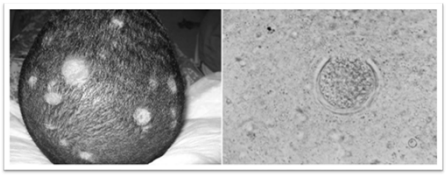
Question #6

An 18-year-old male had the acute onset of sore throat, followed in two days by high fever. On presentation in the emergency room he was acutely ill, with a temperature of 105°F. Chest x-ray, followed by the CT shown here, showed a nodule in the left lower lung field. Swelling and tenderness in the right anterior cervical triangle led to the CT with IV contrast shown here. Blood cultures were likely to reveal which of the following:

A. Aerobic Gram positive rod
B. Aerobic Gram negative rod
C. Anaerobic Gram positive rod
D. Anaerobic Gram negative rod
E. Endemic mycosis



This 21-year-old African American male college student in Tucson, Arizona was seen because of low grade fever, malaise and scalp lesions progressing over the past 3 weeks. He had visited Nogales, Mexico with some of his fraternity brothers six months earlier and had sex with a prostitute. About a month ago, he was drunk at a party, fell into a pond and required resuscitation. A skin biopsy is shown below.

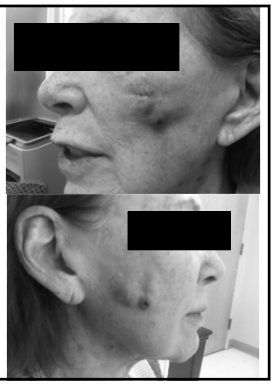


The most likely etiologic agent is found in which of the following locations:

A. Pond scum
B. Dirt
C. Genital lesions
D. Bat droppings
E. Pigeon droppings

75 yr woman from Brazil had a fat transplant from buttocks to both cheeks for cosmetic reasons. Four months later she presented with slowly progressive painless swelling in the operative sites. Most probable cause is:

A. Idiopathic nodular panniculitis
B. Phaeohyphomycosis
C. Nocardia brasiliensis
D. Botryomycosis
E. Mycobacterium chelonae

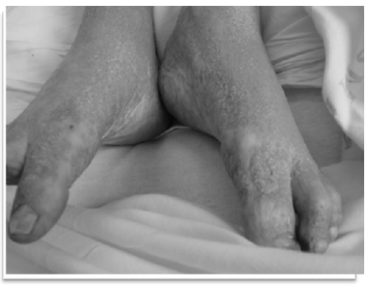


Question #13

This 67-year-old man was brought to the hospital by the police in Washington, DC in because he was sleeping on a grate in bitter cold weather and, when asked to move along by the police, began muttering incoherently. In the emergency room he was combative and had to be restrained. He was admitted for observation and had numerous skin lesions such as the one shown.

Which of the listed tests is most likely to be informative?

A. Wet mount of skin scraping
B. Fungal culture of skin scraping
C. Acid fast smear of skin scraping
D. Serum VDRL
E. HIV ELISA

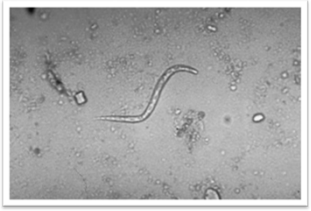


Question #15

This is the stool examination of a 72-year-old Caucasian West Virginia coal miner was referred for an unexplained eosinophilia of 18% with a normal WBC of 8,000. He had retired from the mines 18 years ago and spent most of his time gardening at home. He had been receiving isoniazid, rifampin, and ethambutol for tuberculosis for six months and the referring physician did not want to stop his antituberculous medication to see if the eosinophilia would go away.

The likely source from which he picked up this organism is which one of the following:

A. Poorly cooked pork
B. Fecaly contaminated ground water in the mines
C. His dog
D. Insect bite



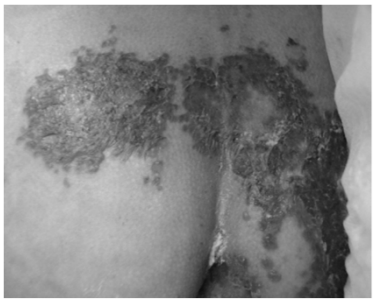
47 - Photo Opportunities: Images You Should Know for the Exams

Speaker: John Bennett, MD

Question #1

This 35yr Peruvian woman with chronic myelogenous leukemia in blast crisis was admitted for allogeneic hematopoietic stem cell transplantation from her sister. On admission, this extensive painful rash was found on the gluteal area of her buttocks. She complained that the area had been painful for several days at the hospital in Peru where she was awaiting transfer to NIH but she was not certain when the rash started. She was afebrile but weak and markedly granulocytopenic from prior chemotherapy. The most likely diagnosis is which of the following

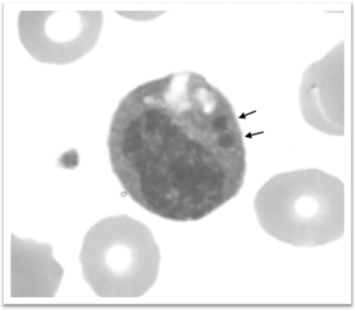
A. Herpes zoster
B. Herpes simplex
C. Ecthyma gangrenosa
D. Aspergillosis



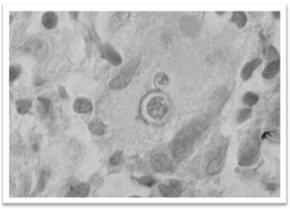
Question #24

The patient with this peripheral blood smear was bitten by a:

A. Deer tick
B. Dog tick
C. Deer fly
D. Kissing bug (triatome)



Question #27



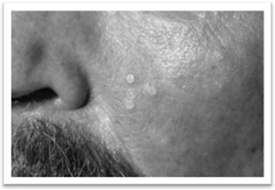
A 55-year-old recent immigrant from Brazil and former banana plantation foreman had facial lesions which had not responded to cephalexin. PAS stain of biopsy is shown. What is the probable organism?

A. Rhinosporidium seerberi
B. Paracoccidioides brasiliensis
C. Treponema pallidum subsp pertenue
D. Leishmania brasiliensis
E. Klebsiella pneumoniae subsp rhinoscleromatis

Question #30

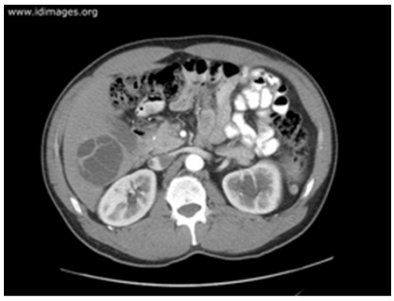
This 44-year-old man with AIDS has an organism in his skin. Which is most likely site for infection to spread?

A. Conjunctiva
B. Buccal mucosa
C. Brain
D. Blood stream
E. Draining lymph nodes



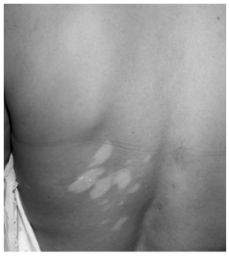
50 yr old man had this CT done because of RUQ pain after an auto accident. He was afebrile and had normal WBC and liver function tests. He had immigrated from rural Greece 10 years earlier. He often ate food his family sent from Greece. The probable source of the lesion is:

A. Dog stool
B. Colon cancer
C. Human stool
D. Smoked Greek sausage
E. Soft cheese from Greece



40 yr old woman from Dominican Republic found to have hypopigmented confluent patches on her back on routine physical exam. Sensation of light touch seemed diminished over the lesions. Punch biopsy of the skin showed well formed epitheloid granulomata. Fite stain for acid fast bacilli was negative. Which of the following is the most likely to be helpful in diagnosis:

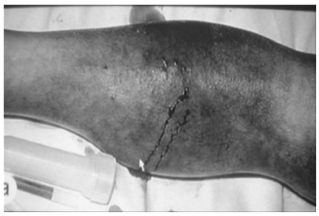
a. Fite stain on more sections
b. Repeat biopsy for mycobacterial culture
c. Silver (GMS) stain of the biopsy for fungi
d. Blood test for angiotensin converting enzyme (ACE)
e. Skin scraping for wet mount microscopy



47 - Photo Opportunities: Images You Should Know for the Exams

Speaker: John Bennett, MD

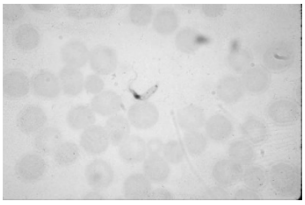
A previously healthy young female had the onset of pain in her calf and a red, tender rash on her calf. She was unaware of preceding trauma. In the photo, the bleeding was from an unsuccessful needle aspirate.She was given cephalexin but the progressively excruciating pain increased and came to the emergency room about 48 hours after onset. Her vital signs were normal except for a temperature of 102. There was no rash outside the calf, which was red, tensely swollen and tender. A soft tissue film showed no gas. WBC was 15,000 with 80% PMN and 5% bands



The clinical presentation is most consistent with which of the following:

A. Streptococcus pyogenes
B. Clostridium perfringens
C. Staphylococcus aureus
D. Mixed infection with anaerobes and aerobic bacteria
E. Vibrio vulnificans

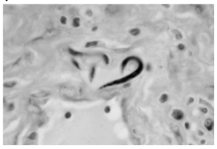
A 56-year-old car salesman from Birmingham, AL, returned two weeks ago from a photo safari in an East African game park, and presented with fever, intermittent mildly pruritic rash, malaise, and easy fatigue of one week's duration. A blood smear is shown below.



He was bitten by

A. Fly
B. Flea
C. Mosquito
D. Kissing bug
E. tick

5.This 25-year-old female Peace Corps worker returned from a year of service in Nigeria. She felt well but had developed a pruritic, maculopapular rash while in Nigeria that was diagnosed on return home as eczema but did not resolve with topical steroids and interfered with sleep. On exam, she had an asymptomatic subcutaneous nodule near her left elbow that had been present for several weeks. Biopsy of the nodule is shown.



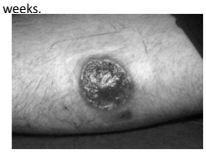
If not appropriately treated, she may return with which of the following:

A. Keratitis
B. Lymphedema
C. Eosinophlic pneumonia
D. Encephalitis

47 - Photo Opportunities: Images You Should Know for the Exams

Speaker: John Bennett, MD

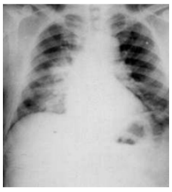
A 23-year-old Chilean male returned to the United States after a week's vacation back home, during which he went to the Western part of Peru, which is dense jungle, for white water rafting.
He was not ill during the week, though he had numerous insect bites during the rafting trip. About two weeks after his return, he noted a pruritic red papule on this arm, which enlarged slowly and ulcerated. There were no systemic symptoms, no pus and no lesions anywhere else on his body. He had been given cephalexin for one week with no response.A punch biopsy showed chronic inflammation with abundant histiocytes, plasma cells and lymphocytes but no giant cells. Special stains for bacteria and fungi were negative. Culture grew no fungus over four weeks and only skin flora on bacterial culture. Mycobacterial cultures at 30°C were negative at four weeks.



WHAT WAS THE LIKELY SOURCE OF INFECTION?

A. Kissing (reduviid) bug
B. Contaminated water
C. Thorny bush
D. Sandfly bite
E. Mosquito bite

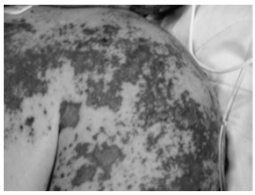
This 50-year-old man had been working in Massachusetts as a caretaker at a Nantucket golf course, mowing the lawn and trimming the bushes during the past three weeks of the summer.
He developed a painful ulcerated lesion on his hand, soon associated with high fever, painful axillary adenopathy on the same arm and a dry cough.



WHAT IS THE LIKELY SOURCE OF THIS INFECTION?

A. Disposing of a dead squirrel
B. Cleaning the swimming pool
C. Nicking his hand on a rusty nail
D. Scratch from his roommates kitten
E. Thorn from decaying vegetation

This rash was found on a stuporous adult one morning. He had appeared well the night before other than some “flu like” symptoms. :



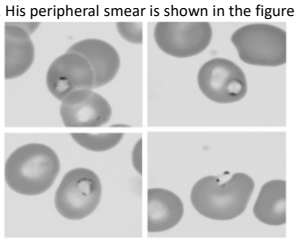
Blood cultures of this patient are likely to grow which of the following

A. Gram negative cocci
B. Gram positive cocci
D. Gram negative bacilli
D. Gram positive bacilli

47 - Photo Opportunities: Images You Should Know for the Exams

Speaker: John Bennett, MD

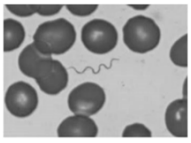
A 40-year-old patient with HIV (CD4= 200) has just returned from a beach vacation in New York State and now presents with fever, profound shock, and a hemoglobin of 6g/dl. He is intubated and started on pressors. Lab values suggest severe hemolysis. His peripheral smear is shown in the figure



The treatment of choice for the most likely cause of this patient's illness is

A. Doxycycline
B. Imipenem
C. Atovaquone and azithromycin
D. Mefloquine
E. Artemether-lumefantrine (Coartem)

You are called to see a patient in the ICU in Washington, DC with ARDS (adult respiratory distress syndrome.
The patient is a previously healthy woman who had been recently seen in the ER after presenting in April with fever, chills, mylagias, and dehydration. She had just returned from her country cabin in the rural California mountains.
Because her evaluation was non-specific other than mild LFT abnormalities, she was rehydrated and sent home without antimicrobial therapy.
The next day she returned to the ER and was readmitted with fever, hypotension, and respiratory failure. Laboratory testing revealed a WBC of 3400/µL, hemoglobin level of 11.4 g/dL, and platelet count of 19000/µL.
The following was seen on peripheral smear (see photo):



The most likely reservoir of this pathogen was:

A. Another human
B. Aquatic birds
C. Lake Fish
D. Rodents
E. Deer

48

Pneumonia: Some Cases that Could be on the Exam

Dr. Paul Auwaerter

48 – Pneumonia: Some Cases that Could be on the Exam

Speaker: Paul Auwaerter, MD

INFECTIOUS DISEASE BOARD REVIEW AUGUST 20-24 2022

Pneumonia: Some Cases that Could be on the Exam

Paul G. Auwaerter, MD
Sherrilyn and Ken Fisher Professor of Medicine
Clinical Director, Division of Infectious Diseases
Johns Hopkins University School of Medicine

7/17/2022

INFECTIOUS DISEASE BOARD REVIEW AUGUST 20-24 2022

Disclosures of Financial Relationships with Relevant Commercial Interests

- **Consultant: EMD Serono, Humanigen**
- **Ownership Interest: Johnson & Johnson, Wellstat**

Community-acquired Pneumonia: Meta-analysis Traditional culture + PCR for "atypicals" + viruses

Pathogen	Total (%)*
None	4380 (61.3)
Etiology	3279 (48.7)
• *S. pneumoniae*	33%
• *H. influenzae*	8.6%
• *S. aureus*	4.9%
• *M. catarrhalis*	2.4%
• Gram negatives	6.0%
• Mycobacteria	1.8%
• Other bacteria	1.94%

- 12 modern studies
  - 2005-2019
  - Inpatient n = 4399
  - In- & outpatient = 2752
  - Outpatient = 0
- Hospital mortality: 12-15%

Shoar and Musher, Pneumonia (2020) 12:11

*Etiologic agents percentages

Community-acquired Pneumonia: Meta-analysis Traditional culture + PCR for "atypicals" + viruses

Pathogen	Total (%)*
None	4380 (61.3)
Etiology	3279 (48.7)
• *Mycoplasma pneumoniae*	8.9%
• *Legionella pneumoniae*	6.2%
• *C. pneumoniae*	2.9%
• *Pneumocystis*	0.2%
• *Influenza*	9.2%
• *Rhinovirus*	11.5%
• Parainfluenza or RSV	9.3%
• Bacterial + viral coinfection	5.9%

- 12 modern studies
  - 2005-2019
  - Inpatient n = 4399
  - In- & outpatient = 2752
  - Outpatient = 0

Shoar and Musher, Pneumonia (2020) 12:11

*Etiologic agents percentages

Case 1

- 55 M 6d fever, malaise, severe headache, dry cough, myalgia
- PMH: HTN
- Meds: Lisinopril/HCT
- SH: Married, suburban Maryland,
  - Works in long-term care facility
  - Visited pet shop 10d earlier
    - Parakeets, cockatiels
  - Confided infidelity in last month

Exam: ill-toxic, 40ºC P88
BP100/70 RR18 O2 97% RA
Lungs: clear
Neck: supple
Cor: no murmurs
Skin: no rashes
LP: pending
Labs:
WBC 5200, 26% B
Sputum: 1+ PMNs, no organisms

Question 1

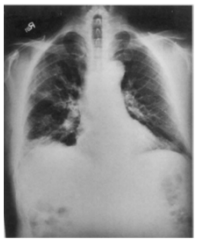
Which antibiotic will lead to the most rapid improvement?

A. Ceftriaxone

B. Gentamicin

C. Doxycycline

D. Trimethoprim/sulfamethoxazole

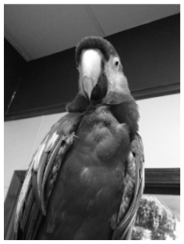


48 – Pneumonia: Some Cases that Could be on the Exam

Speaker: Paul Auwaerter, MD

Chlamydia psittaci

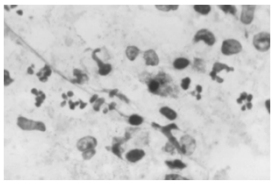
- AKA parrot fever, psittacosis, ornithosis
- Underdiagnosed
  - 1.03 % in studies of CAP
  - < 50 cases/yr in US
  - Most "atypical pneumonia"
- Risks: exposure to birds
  - May be healthy or ill
  - Pets, poultry, pigeons
  - Native birds
    - Lawn mowing



Hogerwerf L et al, Epidemiol Infect. 2017;145(15):3096

Microbiology

- Two states:
  - Extracellular: infectious, elementary body
    - Bird feces or respiratory secretions → aerosol → human
    - Direct contact
  - Intracellular: replicative



May appears as intracellular Gram negatives

Chlamydia psittaci

- Range of illness:
  - Mild, bronchitic to severe/ARDS
  - Clue: temperature/pulse dissociation
  - Also seen with Salmonella typhi, C burnetti, Chlamydia, Dengue
- Diagnosis:
  - Molecular/PCR, sputum (best)
  - Acute/convalescent serology (microimmunofluorescence, MIF)
  - Culture: tissue culture (difficult)
- Treatment:
  - Preferred: doxycycline
  - Alternatives:
    - Macrolides
    - Fluoroquinolones

Wolff BJ et al, Diagn Microbiol Infect Dis 2018;90(3):167-170
Hogerwerf L et al, Epidemiol Infect 2017;145(15):3096-3105

Helpful clues for "Atypical" CAP

Clinical feature	C. psittaci	C. pneumoniae	M. pneumoniae	L. pneumophila
Cough	++	+	++	+
Sputum	-	+	++	+++
Sore throat	-	++	-	-
Headache	+++	+	-	+
Confusion	+	-	-	++
CXR change	Minimal	Minimal	More than sx	Multifocal
Low Na^+	-	-	-	++
Doxycycline response	Rapid, < 48h	Prompt	Prompt	Slower

Adapted from Stewardson, Grayson. Inf Dis Clin N Amer 2010; 24(1):7

Case 2

69M c/o fever and dyspnea x 3 days
-Dry cough, pleuritic chest pain
-In nursing facility for L foot, C1-2, L4-5 osteomyelitis + MRSA bacteremia
Vancomycin (5d, rash) → Ceftaroline (4d, hives) → Daptomycin (11d)

PMH: Diabetes, HTN, COPD, R BKA, bedbound
SH: 40 PPD smoker, now vaping, Baltimore MD resident, hx substance use
Meds: methadone, insulin, nifedipine, Lisinopril/HCT, inhalers

PE: T101.4°F, P 106, RR 24, 02 sat 90% on 6L O_2
No lymphadenopathy, no JVD
Lungs: poor air movement, basilar crackles bilaterally
Cor: no murmur
Ext: no edema

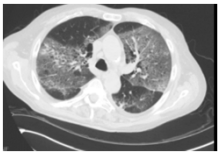
6.0 / 9.5 / 300K 54%^{N}, 12%^{L}, 24%^{E}

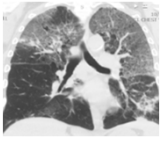
ESR 150 mm/hr NI LFTs
CRP 15 mg/dL (0.0-0.5)

Question 2

The pneumonia is most caused by

A. Vaping-associated pulmonary injury (VAPI)
B. Allergic bronchopulmonary aspergillosis
C. Ceftaroline
D. Daptomycin
E. Strongyloides





Case courtesy of L. Leigh Smith, M.D.

48 – Pneumonia: Some Cases that Could be on the Exam

Speaker: Paul Auwaerter, MD

Acute eosinophilic PNA due to daptomycin [FDA black box warning]

May present like atypical pneumonia or interstitial fibrosis

- Acute
  - Older men (40% > 60 yrs)
  - Daptomycin duration median 19d [2-54d]
  - Fever, dyspnea and cough
  - Hypoxemia
    - Pulse oxygen saturation [SpO_2] <90% on RA or PaO_2 <60 mmHg
  - Diffuse pulmonary opacities
- Need to exclude alternative causes
  - e.g., fungal or parasitic PNA
  - Improvement with drug cessation
- Hypersensitivity reaction (early)
  - Acute & subacute
  - Ground glass findings +/- effusions
  - Eosinophilia (peripheral or BAL)
    - BAL cell count > 25% eosinophils
- Later presentations
  - Interstitial pneumonitis
  - Bronchiolitis obliterans
  - Mixed ground glass, fibrosis, consolidation

Hirai et al. J Infect Chemother 2017;23(4):245
Lai et al. CID 2010;5(1):737

Drug-induced pneumonitis/pneumonia

- Treatment:
  - Discontinue = resolution
  - Corticosteroids: no proven role, but often used
    - If significant hypoxemia: prednisone 40-60 mg PO daily with taper x 14d.
- Other drugs: incomplete list
  - Antibiotics:
    - INH
    - Daptomycin
    - Nitrofurantoin
    - Sulfonamide abx
    - Minocycline
    - Ampicillin
  - CV:
    - Amiodarone
    - Flecainide
  - Chemotherapy:
    - Bleomycin
  - Others
    - NSAIDs
    - Phenytoin

Case 3

67M COPD, alcoholic liver disease, diabetes, pancreatic CA

POD #5 s/p Whipple developed nausea, vomiting, fever, cough, confusion and hypoxemia → respiratory failure

Labs
WBC 18,000 15%^{B}, 60%^{P}
Glucose 310 Na 128 sCr 1.7
AXR: no ileus

Intubation → ICU, respiratory sample:
Heavy PMNs, no organisms on Gram stain

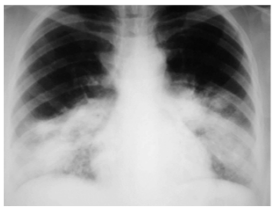
Therapy:
Vancomycin and piperacillin/tazobactam x 3 d

No improvement, febrile, respiratory culture negative
ID consultation called

Question 3

You are aware of a recent *Legionella mcdadei* outbreak in the hospital. Which test below, would most help you securing a diagnosis of *L. mcdadei* pneumonia?

A. Legionella urinary antigen
B. Legionella culture of respiratory secretions
C. Legionella PCR, respiratory
D. Legionella direct fluorescent antigen (DFA) stain of respiratory sample
E. Paired Legionella acute/convalescent serology



Pre-intubation CXR

Legionella pneumonia

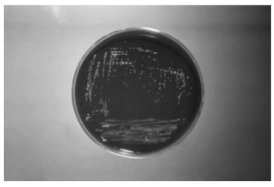
- Risks factors (and who to test)
  - Travel beyond home (e.g., hotel, hospital) last two weeks
    - May cause HAP
  - Severe pneumonia/ICU
  - Proximity to known outbreaks
  - Age > 50 yrs
  - Smoking
  - Comorbidities: diabetes, liver/renal dz, COPD, immunosuppressed
- Acquisition:
  - Aerosolization
  - Drinking water (aspiration)

1976 Bellvue Stratford Hotel, Philadelphia

Legionella

- Environmental/water pathogen
  - Ponds, lakes
  - Water systems (hot > cold), chillers, misters, A/C
  - May be nosocomial pathogen
- Legionellosis
  - Legionnaires' disease (99%)
    - Pneumonia
    - Most typical of the atypicals
  - Pontiac Fever (1%)
    - Febrile, flu-like illness
- Microbiology: 60 species
  - *L. pneumophila* serotype 1 (most common)

Legionella culture



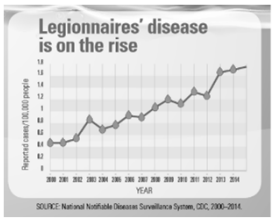
Culture media: BCYE agar
Small, pearly white colonies

48 – Pneumonia: Some Cases that Could be on the Exam

Speaker: Paul Auwaerter, MD

Outbreaks: Known and Unknown Sources

- 5,000 cases/year U.S.
  - 20 Outbreaks
- 4X > cases since 2000
- 90% of CDC investigations caused by insufficient water system management
- WHERE?
  - Hotels
  - Long-term Care Facilities
  - Hospitals



Outbreaks: Known and Unknown Sources

MacIntyre CR, et al Emerg Microbes Infect 2018;7:36

Legionella diagnostics

Test	Sensitivity (%)	Specificity (%)	Notes
Culture	20-80	100	Slow, technically difficult, BCYE agar Detects all species
Urinary Ag	70-100	95-100	Only *L. pneumophila* serogroup 1, rapid, may cross-react occasionally w/ other serogroups
PCR	95-99	99	Not FDA approved, home-brew tests, some are specific for *L. pneumophila*
DFA	25-75	≥ 95	Technically demanding
Paired serology	80-90	> 99	Not helpful for acute care, 5-10% population with (+) titers

Source: CDC, https://www.cdc.gov/legionella/clinicians/diagnostic-testing.html (accessed 6/23/21)
Avni, J Clin Micro. 2016;54(2):401–11; Muldyermans, Eur J Clin Microbiol Infect Dis 2019

	Legionnaires' disease	Pontiac fever
Clinical	Pneumonia	Flu-like symptoms
CXR	Consolidation, multifocal	No infiltrates
Epidemiology	Sporadic & epidemic	Epidemic
Onset after exposure	2-10 days	24-48 hrs
Attack rate	< 5%	> 90% (including healthy)
Diagnosis	Sputa: Culture Molecular tests DFA Urine antigen	No recovery of organism by culture Acute/convalescent serology Urine antigen, up to 50% in some reports
Mortality	10-30%	0 %

Case 4

23M cough, malaise, dyspnea, fever x 1 wk, just returning from overseas

PMH: negative, no asthma

Meds: atovoquone/proguanil

ROS: no diarrhea, had rash on feet/legs post marathon now resolved

SH: Laguna Phuket (Thailand) triathlon 3 wks earlier

Non-smoker

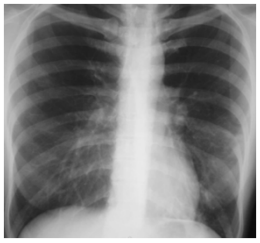
PE: Appears ill, BP 98/70, P 100
T 38.5ºC
No lymphadenopathy
Bronchial breath sounds lower fields, occasional wheezing
No murmur
No hepatosplenomegaly, abdominal tenderness
No rash

Studies

WBC 18,000
63N, 13L, 24E

CXR: mild bilateral patchy infiltrates

Blood smear: no parasites

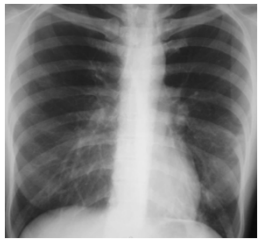


48 – Pneumonia: Some Cases that Could be on the Exam

Speaker: Paul Auwaerter, MD

Which of the following is the most likely explanation?

A. Allergic bronchopulmonary aspergillosis
B. Hookworm infection
C. Malaria
D. Tropical pulmonary eosinophilia
E. Drug reaction



Löffler's syndrome

- Fever, malaise
- Respiratory symptoms: none—mild—moderate
- Migratory pulmonary infiltrates
- Peripheral eosinophilia
- Migration of parasites
- Dx:
  - Larvae in respiratory specimen
  - Stool O & P
- Treatment
  - Anti-helminthics
  - Corticosteroids
  - May spontaneously resolve

Acute eosinophilic pneumonia

- Features
  - Fever, cough
  - Hypoxemia
  - Diffuse, bilateral infiltrates
  - Eosinophils
    - Peripheral
    - BAL (> 10%)
    - Lung biopsy
- Drug causes:
  - Antibiotics:
    - Daptomycin
      - 38 reported cases (2018)
        - Male, elderly
        - Renal failure
      - Black box warning
    - Nitrofurantoin
    - Minocycline
    - Ampicillin
    - Sulfonamides
- Others:
  - NSAIDs
  - Phenytoin
  - L-tryptophan

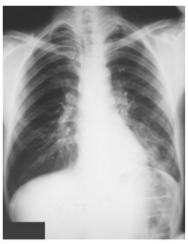
Uppal, Antimicrob Resist Infect Control 2016;5:55;
Higashi, Intern Med 2018;57(2):253-258

Acute or chronic eosinophilic pneumonia

- Helminthic
  - Migration (Loffler's)
    - Ascaris
    - Hooksworms
    - Strongyloides
  - Lung invasion
    - Paragonimiasis
- Tropical Pulmonary Eosinophilia
  - Wuchereria bancrofti
  - Brugia malayi
- Idiopathic hypereosinophilia
- Acute eosinophilic pneumonia
- Chronic eosinophilic pneumonia
- Allergic bronchopulmonary aspergillosis (ABPA)

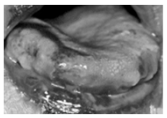
Case 5:

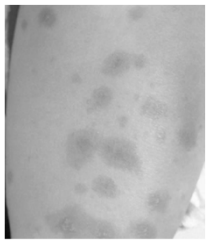
- 18F c/o fever, dry hacking cough, malaise x 3d
- Allergy: erythromycin (N/V)
- Appears well, T38ºC, RR 16, P 80, BP 110/70
  - Oropharynx: normal
  - TMs: normal
  - Chest: some crackles left lower lobe



Case 5

- Azithromycin prescribed
- Next day, full body rash and mucosal lesions develop





48 – Pneumonia: Some Cases that Could be on the Exam

Speaker: Paul Auwaerter, MD

Case 5

What is the most likely etiology?

A. Mycoplasma pneumoniae
B. Enterovirus D68
C. Measles
D. Lyme disease
E. Drug reaction (azithromycin)

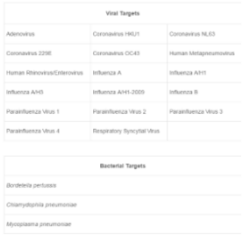
Mycoplasma pneumoniae

- "Walking pneumonia"
  - CXR: appears worse than patient
- < 10% may have extra-pulmonary manifestations
  - Stevens-Johnson syndrome (SJS), E. multiforme
    - Most common infectious cause (children/adolescents)
    - Male > female
  - Hemolytic anemia
  - Hepatitis
  - CNS: encephalitis, meningitis

Mycoplasma pneumoniae

Finding/method	Pro	Con	Notes
Bullous myringitis		Description w/ experimental infection	Urban legend that is wrong or if true, rare
Molecular	High sensitivity & specificity	Limited FDA approvals, Expensive platforms needed	New gold standard In house assays not standardized
Serology	Available commercially	Non-specific Acute/convalescent	False +'s and –'s Not timely
Culture	100% specific Antibiotic susceptibilities	Poor sensitivity Time consuming	Only reference labs Special transport media Difficult to perform
Cold agglutinin titers	Occur in 50-70%	Non-specific	Association w/ hemolysis

Respiratory Molecular Targets, a current FDA-approved example



Film Array
Multiplex, 20 pathogens
Results in 1 hr

Viruses and some bacteria
Sensitivity: 87, 98-100%
Specificity: 89, 99-100%

Leons, Front Microbiol. 2016; 7: 448

Case 6

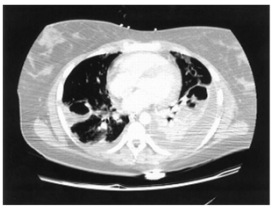
31F fever, cough, myalgia, headache, dyspnea over 1 week ago
- No help w/ azithromycin x 3d
- 18 mos daughter, recent bronchitis

PMH: not significant
SH: ½ ppd smoker

PE: ill
T38.3, RR 35, BP 125/70, P 128

Coarse breath sounds, rales bilateral and decreased L base

Case 6



Data:
WBC: 11, 300 38%P, 48%B

RA ABG: 7.37/35/58

Sputum Gram stain: > 25 WBC/hpf
Some Gram (+) cocci
Sputum Cx: pending

Respiratory Film Array:
Influenza (+)
RSV (+)

48 – Pneumonia: Some Cases that Could be on the Exam

Speaker: Paul Auwaerter, MD

Case 6

Pt placed on oseltamivir, ceftriaxone and azithromycin. Which of the below should be recommended by the ID consultant?

A. Disregard RSV as likely false positive
B. Institute ribavirin PO for RSV
C. Continue ceftriaxone, but replace azithromycin with moxifloxacin
D. Change from oseltamivir to peramivir injection
E. Attempt aspiration of left pleural fluid, start linezolid

Era of molecular diagnostics

- Increasing recognition of co-pathogens
  - Multiple viruses
  - Virus + bacteria
- Still need to consider pathogens not in multiplex panels
- Mixed infections:
  - Johansson CID 2010; 50:202
    - Pathogens detected: 67%
    - Mixed: 12%
  - Jain NEJM 2015;373:415
    - Pathogens detected: 38%
    - Mixed: 3%
- Positive values from asymptomatic controls
  - Especially viral
  - Prolonged shedding (especially immunocompromised)

GOOD LUCK ON THE EXAM

"In the Mortality Bills, pneumonia is an easy second, to tuberculosis; indeed in many cities the death-rate is now higher and it has become, to use the phrase of Bunyan 'the captain of the men of death.'"
— William Osler

49

Lots of Protozoa

Dr. Edward Mitre

49 – Lots of Protozoa

Speaker: Edward Mitre, MD

IDBR INFECTIOUS DISEASE BOARD REVIEW AUGUST 20–24 2022

Lots of Protozoa

Edward Mitre, MD
Bethesda, MD

7/25/2022

IDBR INFECTIOUS DISEASE BOARD REVIEW AUGUST 20–24 2022

Disclosures of Financial Relationships with Relevant Commercial Interests

- **None**

Protozoa

Protozoa - Extraintestinal	Protozoa - Intestinal
Apicomplexa Plasmodium Babesia (Toxoplasma)	**Apicomplexa** Cryptosporidium Cyclospora Cystoisospora
Flagellates Leishmania Trypanosomes (Trichomonas)	**Flagellates** Giardia Dientamoeba
Amoebae Naegleria Acanthamoeba Balamuthia	**Amoebae** Entamoeba
	Ciliates Balantidium

National Institutes of Health

National Institute of Allergy and Infectious Diseases **Not Protozoa**

Kingdom Fungi: Microsporidiosis agents
Kingdom Chromista: Blastocystis

Protozoa

Protozoa - Extraintestinal	Protozoa - Intestinal
Apicomplexa Plasmodium Babesia (Toxoplasma)	**Apicomplexa** Cryptosporidium Cyclospora Cystoisospora
Flagellates Leishmania Trypanosomes (Trichomonas)	**Flagellates** Giardia Dientamoeba
Amoebae Naegleria Acanthamoeba Balamuthia	**Amoebae** Entamoeba
	Ciliates Balantidium

National Institutes of Health

National Institute of Allergy and Infectious Diseases **Not Protozoa**

Kingdom Fungi: Microsporidiosis agents
Kingdom Chromista: Blastocystis

Question 1: A 54 yo woman presents with fever, chills, and oliguria one week after travel to Malaysia.

Vitals: **39.0** ° C, HR 96/min, RR 24/min, **BP 86/50**

Labs: Hct 31%, platelets14,000/μl, Cr of 3.2 mg/dL.

Peripheral blood smear has intraerythrocytic forms that are morphologically consistent with *Plasmodium malariae*.

National Institutes of Health

The most likely infectious agent causing the patient's illness is:

A. Plasmodium malariae
B. Plasmodium knowlesi
C. Plasmodium vivax
D. Plasmodium falciparum
E. Babesia microti

National Institute of Allergy and Infectious Diseases

P. knowlesi

diagnosed in over 120 people in Malaysian Borneo

Lancet 2004;363:1017-24.

morphologically similar to *P. malariae*

usually a parasite of long-tailed macaques

increasingly recognized in Myanmar, Phillipines, Indonesia, and Thailand.

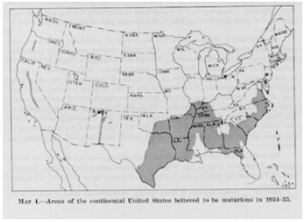
causes high parasitemia

highly morbid and can be lethal

MALARIA

one of the most important pathogens in the history of the world

CDC arose from national Malaria Control programs



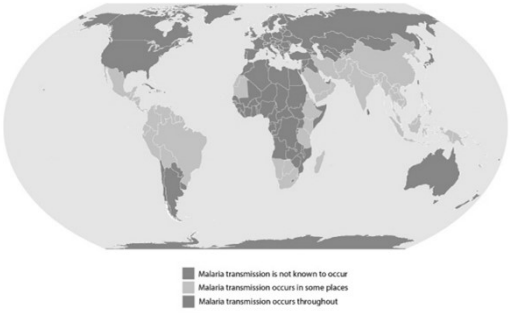
National Malaria Elimination Program: 1947- 1951
DDT spraying ~ 5 million homes and drainage of wetlands

→ Atlanta was chosen as the location 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
→ a main goal was to limit malaria at military training bases in the southern U.S.

CDC Name Changes (fyi)

1942-46:	Office of Malaria Control in War Areas (really the predecessor agency of the CDC)
1946-70:	Communicable Disease Center
1970-80:	Center for Disease Control
1980-1992:	Centers for Disease Control
1992-present:	Centers for Disease Control and Prevention

MALARIA EPIDEMIOLOGY



This map shows an approximation of the parts of the world where malaria transmission occurs.

https://www.cdc.gov/malaria/about/distribution.html

In non-immune patients, falciparum malaria is a medical emergency!!

→one of the most common causes of fever in a returned traveler

→ infected individuals can rapidly progress from appearing well to being critically ill

Family Feud: The Three Most Common Causes of Fever in a Returned Traveler.

1.
2.
3.

Family Feud: The Three Most Common Causes of Fever in a Returned Traveler.

1. **Malaria**
2. **Malaria**
3. **Malaria**

49 – Lots of Protozoa

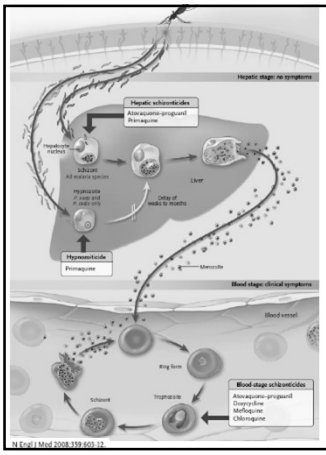
Speaker: Edward Mitre, MD

---Some helpful heuristics---

If patient has	make sure patient doesn't have
Fever and freshwater contact	----->
Fever and unpasteurized milk	----->
Fever and undercooked meat	----->
Fever and raw vegetables	----->
Fever and untreated water	----->
Fever and wild dog bite	----->
Fever and abdominal pain	----->
Fever and headache	----->
Fever and diarrhea	----->
Fever and cough	----->
Fever and dysuria	----->

---Some helpful heuristics---

If patient has	make sure patient doesn't have
Fever and freshwater contact	-----> Malaria
Fever and unpasteurized milk	-----> Malaria
Fever and undercooked meat	-----> Malaria
Fever and raw vegetables	-----> Malaria
Fever and untreated water	-----> Malaria
Fever and wild dog bite	-----> Malaria
Fever and abdominal pain	-----> Malaria
Fever and headache	-----> Malaria
Fever and diarrhea	-----> Malaria
Fever and cough	-----> Malaria
Fever and dysuria	-----> Malaria



Sporozoites
- **Infective stage**
- Come from mosquito

Liver schizont
- **Asymptomatic replicative stage**
- Become 10,000 to 30,000 merozoites

Hypnozoite
- Dormant liver stage in **vivax and ovale**
- Release merozoites weeks to months after primary infection

Merozoites
- Infect RBCs and develop into ring-stage trophozoites
- Mature into schizonts, which release merozoites which infect more RBCs

Gametocytes
- Infective stage for mosquitoes

characteristics of human malaria species

	P. falciparum	P. knowlesi	P. vivax	P. ovale	P. malariae
incubation	8 - 25 d	prob 8-25 d	~ 2 wks	~ 2 wks	~ 3-4 wks
hypnozoite	no	no	yes	yes	no
RBC age	any	any	young	young	old
parasitemia	high	high	< 2%	< 2%	< 1%
morbidity	high	high	high	moderate	low
mortality	high	moderate	low	low	low

Possible evolutionary defenses against malaria

Duffy antigen negative (*P. vivax* uses Duffy Ag to enter RBCs)

Sickle cell trait (increases survival during *P. falciparum* infection, perhaps by selective sickling of infected RBCs)

Glucose-6-phosphate dehydrogenase deficiency

(malaria parasites grow poorly in G6PD deficient RBCs, perhaps b/c this results in an overall increase in reactive oxygen species in RBCs)

Uncomplicated (mild) malaria

Symptoms: fevers, chills, headache, fatigue
***NOTE: abdominal pain presenting symptom in 20%**

→ ***periodicity of fevers not common when patients seen acutely***

Labs: Thrombocytopenia in 50%
mild anemia in 30%
typically no leukocytosis
may see evidence of hemolysis with mild increase T bili and LDH

Complicated (severe) malaria

- Cerebral malaria (altered mental status, seizures)
- Respiratory distress/pulmonary edema
- Severe anemia (hct <15% in children, <20% in adults)

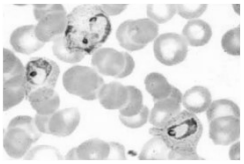
} Often seen in children of endemic countries. Adults more often get multiorgan failure.

- Renal failure
- Hypoglycemia
- Shock (SBP < 80 mm Hg or capillary refill > 3 seconds)
- Acidosis (often lactic acidosis)
- Jaundice (total bilirubin > 3 mg/dL)
- Bleeding disorder (spontaneous bleeding or evidence of DIC)

These complications primarily occur with *Plasmodium falciparum,* usually when parasitemia >2%.

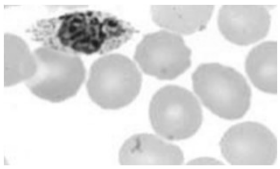
NOTE: in the absence of end organ damage, parasitemia >10% is often used as the cut-off to treat for severe malaria

P. vivax or ovale



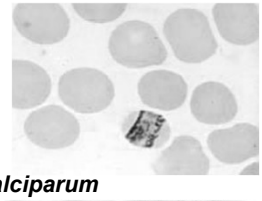
Both have
- intracellular Schüffner's dots
- enlarged infected cells

P. ovale



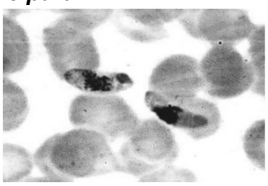
P. ovale
-elongated or oval
-6-12 merozoites (vs 12-24 for vivax)

P. malariae



-band form
(also seen in *P. knowlesi*)

P. falciparum



Banana shaped gametocyte

Malaria: Diagnosis

Rapid diagnostic (antigen capture) tests
→ sensitivity 95% for P. falciparum (about 85% for other species)

Binax Now® ICT assay for the detection of *Plasmodium falciparum* malaria according to the level of parasitemia

Parasitemia (no. of parasites/μL of whole blood)	Microscopy (no. positive)	NOW ICT (no. positive)	Sensitivity (%)
1–100	4	3	75.0
101–1,000	26	25	96.2
1,001–10,000	37	36	97.3
>10,000	34	33	97.1

Am. J. Trop. Med. Hyg., 69(6), 2003, pp. 589–592

for P. falciparum (T1) → tests for histidine-rich protein 2
for all species (T2) → tests for aldolase

Most false-negative antigen tests are due to low parasite burden. So, retest suspected patients that initially test negative.

Note: there are some false negative cases that have occurred due to mutations in HRP2 protein.

Question 2: A 33-year-old woman is traveling to Uganda to do field studies in anthropology. She is two months pregnant. Which of the following do you prescribe for malaria prophylaxis?

National Institutes of Health

A. Doxycycline
B. Chloroquine
C. Mefloquine
D. Atovaquone/progruanil
E. No prophylaxis

National Institute of Allergy and Infectious Diseases

Malaria Chemoprophylaxis (note: no vax for travelers)

CENTRAL AMERICA and MIDDLE EAST

	Pre-Exposure	During	Post-Travel
Chloroquine 500mg tabs	1 tab/wk x 2 wks	1 tab/wk	4 weeks
EVERYWHERE			
Atovaquone/proguanil 250/100mg	1 tab daily x 2 d	1 daily	7 days
Doxycycline 100mg tabs	none	1 daily	4 weeks
Tafenoquine* 100mg tabs	2 tab daily x 3 d	2 tab/wk	2 tab after 1 wk
Mefloquine (not SE Asia)** 250mg tabs	1tab/wk x 2-3 wks	1 tab/wk	4 weeks

* *Tafenoquine can precipitate severe hemolytic anemia in individuals that are G6PD deficient*

** *FDA black box warning in 2013 that mefloquine can cause neurologic symptoms, hallucinations, and feelings of anxiety, mistrust, and depression. Can also cause QT prolongation. Thus, many U.S. practitioners now reserve mefloquine for pregnant travelers to areas with chloroquine resistance*

Treatment of *P. falciparum*

Uncomplicated (no organ dysfunction, low parasitemia, able to take po)

if chloroquine sensitive area → chloroquine

if chloroquine resistant area
- → artemether/lumefantrine (Coartem) x 3 days
- → atovaquone/proguanil (Malarone) x 3 days
- → 2nd line: quinine x 3 days + doxycycline x 7 days

Severe

→ IV artesunate **FDA approved since May 2020**
(CDC malaria hotline: 770-488-7788 or -7100)

Note:
- Delayed-onset anemia common after Rx with artesunate
- Artemisin resistance has been reported in both SE Asia and parts of Africa
- IV quinidine has not been available in the U.S. since 2019

Treatment of *P. vivax*

chloroquine x 3 days and then…

- primaquine –weight based dosing and duration as determined by G6PD activity
  (usually 0.5 mg/kg primaquine base x 14 days if normal G6PD activity, if G6PD activity < 30% then can treat with 0.75mg/kg weekly for 8 weeks)

or

- tafenoquine (two 150 mg tabs)

→ Need to check G6PD status before administering primaquine OR tafenoquine as both can cause severe hemolysis in patients with G6PD deficiency

→ Primaquine requires cytochrome P-450 2D6 to be effective. Therefore, clinical failure to cure *P. vivax* can be due to low host levels of CYP450-2D6.
N Engl J Med 2013; 369:1381-1382

* Suggestions for all ID practitioners *

1) Make sure the facility where one works has the means to rapidly test for malaria

2) Ensure that hospital pharmacy has access to appropriate medications for treatment of malaria

Babesia

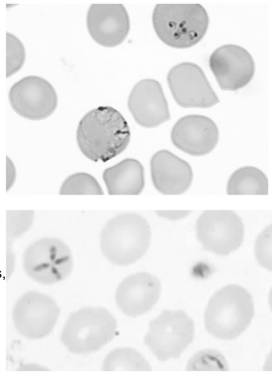
Transmission
- Ixodes ticks in Northeast and upper midwest →co-infection with Lyme and Anaplasma
- Transfusion (approx. 1/20k in NE if un unscreened…Ab screening tests approved by FDA in 2018)

Symptoms: fever, headache, chills, myalgias
less common: nausea, dry cough, neck stiffness, vomiting, diarrhea, arthralgias
→ severe disease: in HIV, asplenia

Labs: anemia, thrombocytopenia, mild increase LFTs, normal/low/high WBC

Diagnosis: small ring forms in RBCs, PCR, Ab merozoites can make tetrad ("Maltese cross")

Treatment: azithromycin + atovaquone (clindamycin + quinine is alternative)
→ Exchange transfusion for severe disease



CDC DpDx

Protozoa

Protozoa - Extraintestinal

Apicomplexa
Plasmodium
Babesia
(Toxoplasma)

Flagellates
Leishmania
Trypanosomes
(Trichomonas)

Amoebae
Naegleria
Acanthamoeba
Balamuthia

Protozoa - Intestinal

Apicomplexa
Cryptosporidium
Cyclospora
Cystoisospora

Flagellates
Giardia
Dientamoeba

Amoebae
Entamoeba

Ciliates
Balantidium

National Institutes of Health
National Institute of Allergy and Infectious Diseases

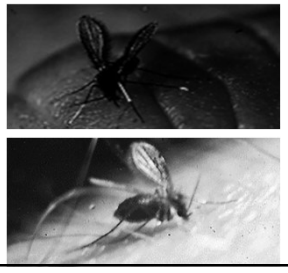
Not Protozoa
Kingdom Fungi: Microsporidiosis agents
Kingdom Chromista: Blastocystis

Leishmaniasis

→obligate intracellular protozoan infection
→transmitted by sand flies (noiseless, active in evenings)

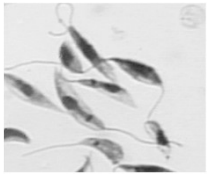
Lutzomyia
New world leishmaniasis

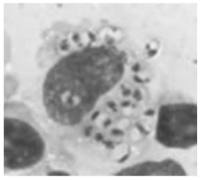
Phlebotomus
Old world leishmaniasis



Leishmania life cycle – Two stages

Promastigote	Amastigote
extracellular, in sand fly	Intracellular (macrophages)
2µm wide x 20µm long	Round or oval
+ flagella	Wright-Giemsa:
large central nucleus	dark-purple nucleus
band shaped kinetoplast	small rod shaped kinetoplast





CDC DpDx

Question 3: A 42 yo man from Bolivia presents with nasal stuffiness and is found to have nasal septal perforation. Biopsy demonstrates intracellular amastigotes consistent with Leishmania.

Which is the most likely species?

A. L. mexicana
B. L. braziliensis
C. L. peruviana
D. L. infantum chagasi
E. L. major

National Institutes of Health

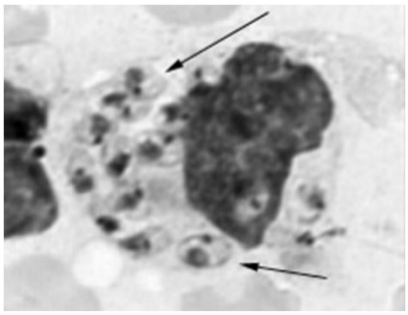
National Institute of Allergy and Infectious Diseases

Leishmania taxonomy and disease simplified

	Cutaneous	Mucosal	Visceral
NEW WORLD			
L. mexicana complex	X		
L. braziliensis	X	X	
L. infantum chagasi			X
OLD WORLD			
L. tropica	X		
L. major	X		
L. donovani			X
L. infantum chagasi			X

***note: *L. braziliensis* is in the Viannia subgenus. *L. V. guyanensis* and *L. V. panamensis* also cause mucosal disease. *L. peruviana* DOES NOT**

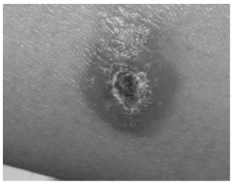
Here are some very clear amastigotes
→ intracellular organisms with nucleus and kinetoplast

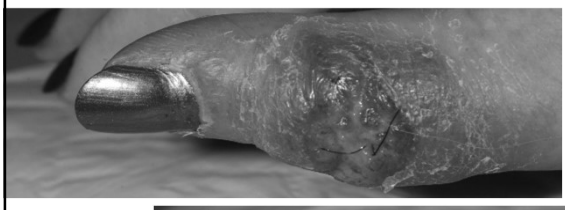


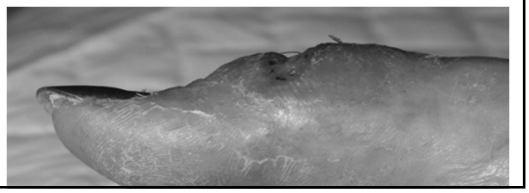
http://www.dpd.cdc.gov/dpdx/HTML/Leishmaniasis.htm

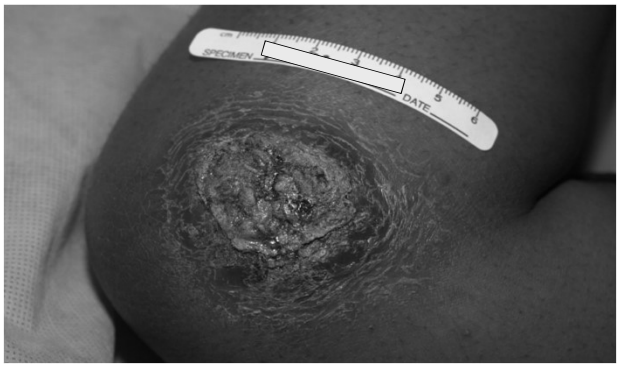
Cutaneous Leishmaniasis – Clinical Presentation

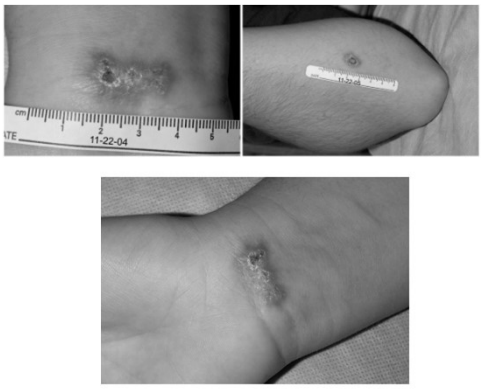
- **papule → nodule →ulcerative lesion → atrophic scar**
  - **ulcerative lesion may have:**
    - **induration,**
    - **scaliness**
    - **central depression**
    - **raised border**
- **takes weeks to months to develop**
- **usually painless, unless superinfected**
- **most lesions will eventually resolve on their own**

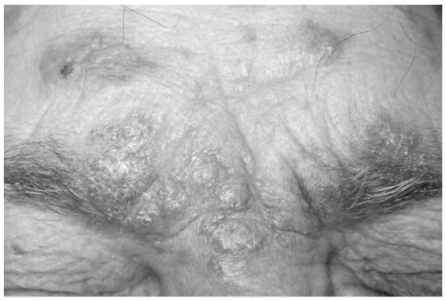












Cutaneous Leishmaniasis – Diagnosis

Definitive diagnosis is very helpful because

1. **Allows you to rule out other possibilities**
2. **May help in deciding whether and how to treat**

Diagnostic Tools (edge of ulcer skin: scraping, aspirate, punch)

Touch prep with examination under oil looking for amastigotes

Culture on triple N media (may take weeks to grow)

(Nicolle's modification of Novy and MacNeal's medium – biphasic)

Histology

PCR

Cutaneous Leishmaniasis – Treatment Recommendations

→ **Treat systemically if *L. (V.) braziliensis, guyanensis, panamensis***

→ **If not, ok to observe if there are:**

few lesions, they are < 5 cm, not on face/fingers/toes/genitals, normal host, no subcutaneous nodules

Treatment Options

local: heat with radiotherapy (FDA approved), cryotherapy, intralesional therapy

systemic

oral: miltefosine for certain species, especially New World CL species
ketoconazole, fluconazole (off-label)

IV: liposomal amphotericin B (off-label)

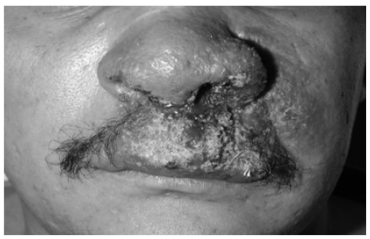
(June 2021:pentavalent antimony aka stibogluconate no longer avaialable from CDC on IND)

*****2016 IDSA GUIDELINES FOR TREATMENT OF LEISHMANIA*****
http://www.idsociety.org/Guidelines/Patient_Care/IDSA_Practice_Guidelines/Infections_by_Organism/Parasites/Leishmaniasis/

Mucosal leishmaniasis

Leishmania (Viannia) braziliensis, Guyanensis, panemensis

- dissemination to nasal mucosa
- slow, progressive, destructive
- can occur months or years after cutaneous ulcer



Treatment:
- oral miltefosine
  (FDA approved for *L. braziliensis*)
- IV lip. amphotericin (off-label)
- IV antimony (no longer 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)

49 – Lots of Protozoa

Speaker: Edward Mitre, MD

Visceral Leishmaniasis

L. donovani *(South Asia, East Africa)*

L. infantum chagasi *(Middle East, Central Asia, Mediterranean, Central and S. America)*

amastigotes in macrophages go to local LNs then hematogenously to liver, spleen, bone marrow

A peristent disease that can reactivate
TNF blockade, HIV CD4 < 200

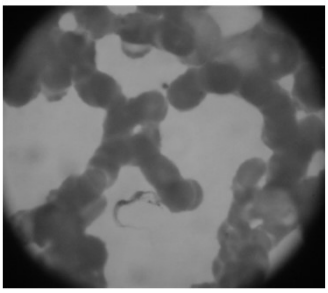
Weeks/months: fevers, chills, fatigue, hepatosplenomegaly

pancytopenia & hypergammaglobulinemia

Diagnosis: intracellular amastigotes in bone marrow or splenic aspirate
antibody to rK39 recombinant Ag (dipstick test)

Treatment: liposomal ampho B (FDA approved)
miltefosine (oral) FDA approved for *L. donovani*

Question 4: A 41 yo woman presented to a local emergency department with a one day history of fever associated with swelling and redness in her groin four days after returning from safari in Tanzania. Peripheral blood smear is obtained.



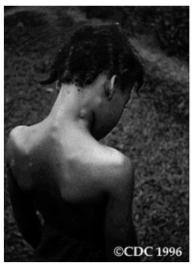
What is the most likely diagnosis?

National Institutes of Health

A. Leishmania donovani
B. Plasmodium vivax
C. Trypanosoma brucei
D. Wuchereria bancrofti
E. Leptospira interrogans

National Institute of Allergy and Infectious Diseases

African Trypanosomiasis (sleeping sickness)



Vector = tse tse fly (Glossina sp)

Trypanosoma brucei gambiense (W. Africa)
- humans as reservoirs
- progression over many months

Trypanosoma brucei rhodesiense (E. Africa)
- cattle and game park animals as reservoirs
- progression over weeks

DISEASE
within 5 days: chancre at Tse Tse fly bite
regional lymphadenopathy


W.H.O.

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 Trypanosomiasis - Life Cycle

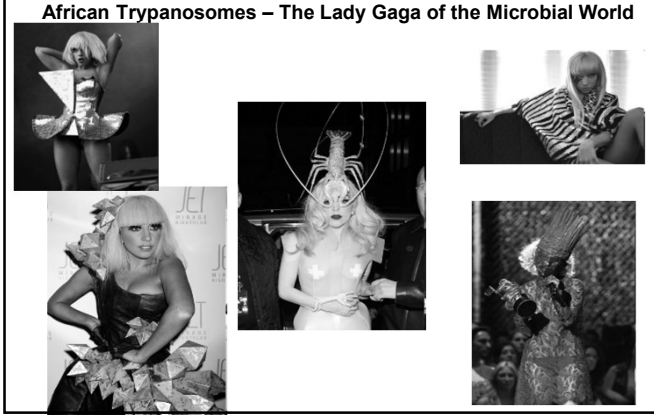
Q. Why are Trypanosoma brucei infections associated with persistently elevated IgM levels?

A. because they keep changing their outer surface protein
- T. brucei contains as many as 1000 genes encoding different VSGs (VSG = variant surface glycoprotein)
- each trypanosome expresses one, and only one, VSG at a time
- individual parasites can spontaneously switch the VSG they express

49 – Lots of Protozoa

Speaker: Edward Mitre, MD

African Trypanosomes – The Lady Gaga of the Microbial World



African Trypanosomiasis –Treatment

West African (T. gambiense)

If < 6 yo or < 20 kg: lumbar puncture

CSF < 5 WBC/ul → iv pentamidine

CSF > 5 WBC/ul → iv eflornithine + nifurtimox

If adult: confusion, ataxia, anxiety, abnl speech, motor weakness, abnl gait?

no suspicion of late disease → oral fexinidazole

if suspicion of CNS disease → obtain lumbar puncture

CSF < 100 cells/ul (non-severe 2nd stage) → oral fexinidazole

CSF > 100 cells/ul → iv eflornithine+ nifurtimox

East African (T. rhodesiense): Rx always guided by lumbar puncture

CSF < 5 WBC/ul → suramin

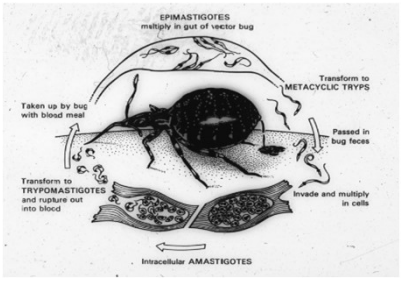
CSF > 5 WBC/ul → melarsoprol

Juy 16, 2021: Oral fexinidazole FDA approved for T. gambiense

Notes: 1) Melarsoprol associated with ~5% death rate due to reactive encephalopathy.
2) This is reduced by co-administration of corticosteroids.

Chagas disease

- transmitted by *Trypanosoma cruzi*
  (also blood transfusion and congenitally)
- vector: reduviid (triatomine) bugs
- reservoirs: opossums, rats, armadillos, raccoons, dogs, cats



Chagas – Clinical Disease

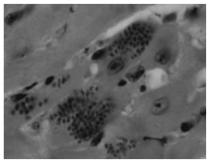
Acute (starts 1 week after infection, can persist for 8 weeks)

- fever
- local lymphadenopathy
- unilateral, painless periorbital edema

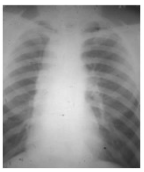
Indeterminate stage

- serology positive, no evidence of disease

Chronic



dilated cardiomyopathy, R>L
(CHF, syncope, arrythmia)



megaesophagus

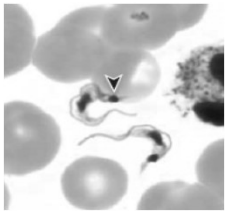
Chagas Diagnosis & Rx

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)



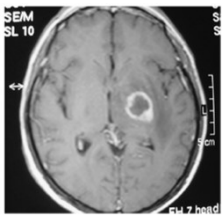
NOTE: U.S. blood supply screened for 1st time donors

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

49 – Lots of Protozoa

Speaker: Edward Mitre, MD

Protozoa

Protozoa - Extraintestinal

Apicomplexa
- Plasmodium
- Babesia
- (Toxoplasma)

Flagellates
- Leishmania
- Trypanosomes
- (Trichomonas)

National Institutes of Health

Amoebae
- Naegleria
- Acanthamoeba
- Balamuthia

Protozoa - Intestinal

Apicomplexa
- Cryptosporidium
- Cyclospora
- Cystoisospora

Flagellates
- Giardia
- Dientamoeba

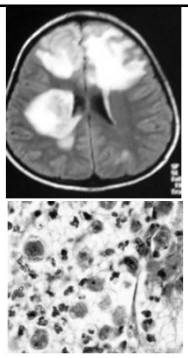
Amoebae
- Entamoeba

Ciliates
- Balantidium

National Institute of Allergy and Infectious Diseases **Not Protozoa**

Kingdom Fungi: Microsporidiosis agents
Kingdom Chromista: Blastocystis

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

National Institutes of Health
- [illegible] immunocompromised hosts
- chronic granulomatous keratitis (contact lens, LASIK)

Balamuthia mandrillaris
- likely enters through lower respiratory tract or broken skin
- transmission by solid organ transplantion has been reported
- subacute granulomatous encephalitis

National Institute of Allergy and Infectious Diseases
- [illegible] and immunocompromised hosts

Outcome → often fatal (amphotericin B, azoles, pentamidine, others tried)

Protozoa

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National Institute of Allergy and Infectious Diseases **Not Protozoa**

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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

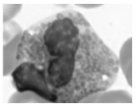
Intestinal Apicomplexa: clinical clues

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!

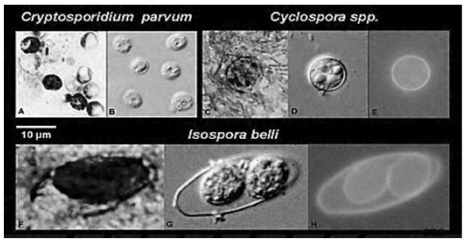
- abrupt onset with nausea, vomiting, and fever early
- anorexia, weight loss, fatigue late in course
- food associated outbreaks: raspberries, lettuce, herbs
- esp. Nepal, Peru, Guatemala

Cystoisospora belli
- no animal reservoirs known
- watery diarrhea
- may be associated with a peripheral eosinophlia!
  (the ONLY intestinal protozoa that does this)



Intestinal Coccidia characteristics

Pathogen	Size	Stain	Treatment
Cryptosporidium	4 μm	m acid-fast	(none) nitazoxanide or paromomycin
Cyclospora	10 μm	m acid-fast	TMP/SMX
Cystoisospora	20 μm	m acid-fast	TMP/SMX



Molecular tests

stool multiplex PCR detects cryptosporidium AND Cyclospora but NOT Cystoisospora

stool Ag tests commercially available for cryptosporidium

Morbidity and Mortality Weekly Report

Cryptosporidiosis Outbreaks — United States, 2009–2017

MMWR / June 28, 2019 / Vol. 68 / No. 25

Morbidity and Mortality Weekly Report

Cryptosporidiosis Outbreaks — United States, 2009–2017

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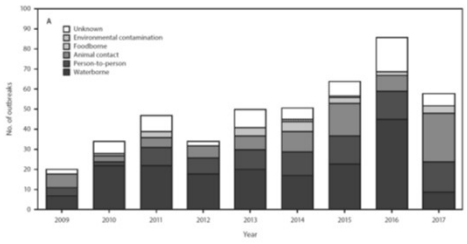

"The number of reported outbreaks has increased an average of approximately 13% per year."

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?

National Institutes of Health

A. Balantidium coli
B. Entamoeba histolytica
C. Giardia lamblia
D. Dientamoeba fragilis
E. Endolimax nana

National Institute of Allergy and Infectious Diseases

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)

49 – Lots of Protozoa

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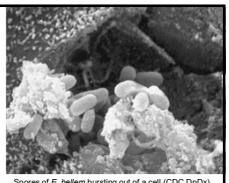
National Institute of Allergy and Infectious Diseases **Not Protozoa**

Kingdom Fungi: Microsporidiosis agents
Kingdom Chromista: Blastocystis

Microsporidia – obligate intracellular fungi!

→Produce extracellular, 1-2 micron, infective spores
→Spores have a coiled organelle called a polar tubule
→After ingestion, the spore germinates and the polar tubule is used to inject sporoplasm into a host cell

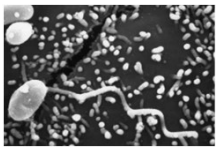


Spores of *E. hellem* bursting out of a cell (CDC DpDx)

Enterocytozoon bieneusi
- watery diarrhea
- biliary disease (cholangitis, acalculous cholecystitis)

Encephalitozoon intestinalis
- watery diarrhea
- biliary disease
- disseminated disease (liver, kidney, lung, sinuses)

Encephalitozoon cuniculi, hellem
- can cause disseminated disease of multiple organs, plus eye



Polar tubule inserted into a eukaryotic cell (CDC DpDx)

Many species (including *Vittaforma corneae*): punctate keratoconjunctivitis (contact lens use, after eye surgery, bathing in hot springs)

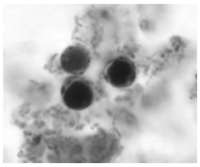
DIAGNOSIS: modified trichrome stain, Calcofluor white, IFA
TREATMENT: albendazole (not effective for *E. bieneusi*)

Blastocystis

What is it?

Nobody really knows!! Might be a protozoa.

Might also be a part of a new kingdom (Chromista!), with kelp and diatoms!



Blastocystis cyst-like forms , trichrome (CDC DpDx)

Forms are 5-40 microns wide. Anaerobic. Eukaryotic.
→ cystic, ameboid, granular, and vacuolar forms

Does it cause disease?
That's a good question!! Maybe.
Associated with watery diarrhea, abdominal discomfort, nausea, and flatulence.

Diagnosis: light microscopy of stool samples

Treatment?
metronidazole, tinidazole, TMP/SMX, or nitazoxanide (none FDA-approved)

Protozoan infections that can reactivate in the severely immunocompromised

- Toxoplasmosis
  - encephalitis with mass lesions
  - pneumonitis
  - retinitis
- Leishmania
  - reactivation of visceral and cutaneous reported
  - visceral with fever, hepatosplenomegaly, pancytopenia
- Chagas
  - encephalitis with mass lesions
  - hepatosplenomegaly and fevers
  - myocarditis in 40% that receive heart transplant b/c Chagas disease
- Malaria

Some other protozoa that can cause severe disease in immunocompromised

- Cryptosporidium
- Giardia
- Microsporidia
- Babesia
- Acanthamoeba

NOAA photo library

Edward Mitre, M.D.
edwardmitre@gmail.com

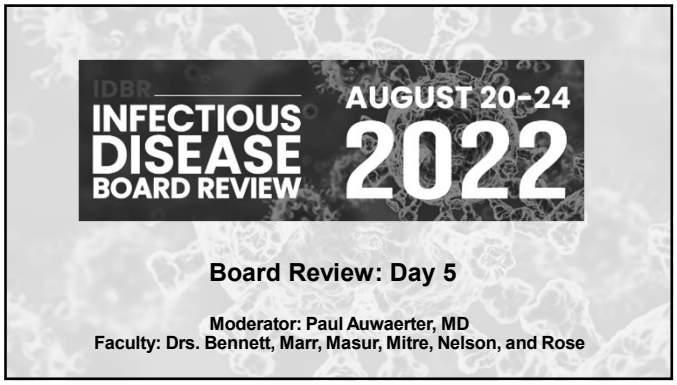
BR5

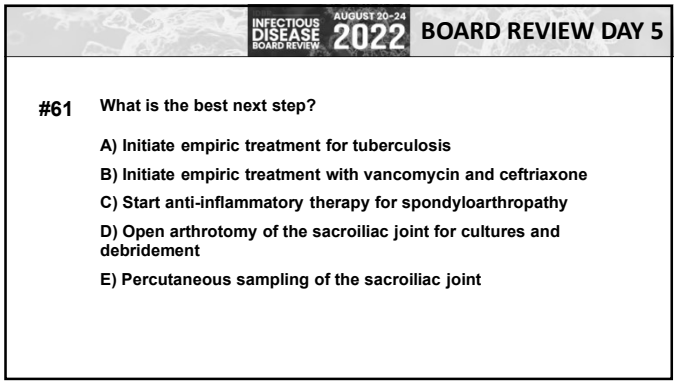
Board Review Session 5

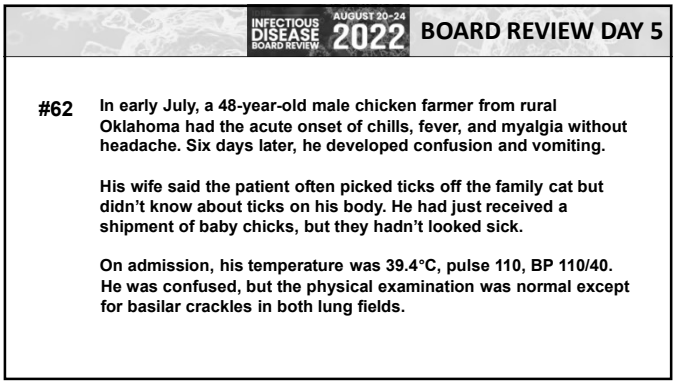
Drs. Auwaerter (Moderator), Bennett, Marr, Masur, Nelson, Mitre, and Rose

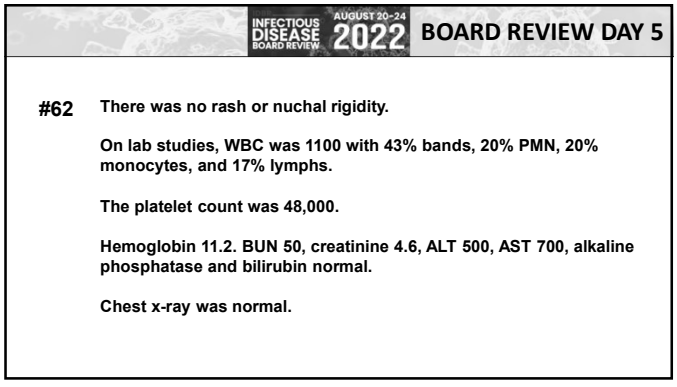
BR5 – Board Review: Day 5

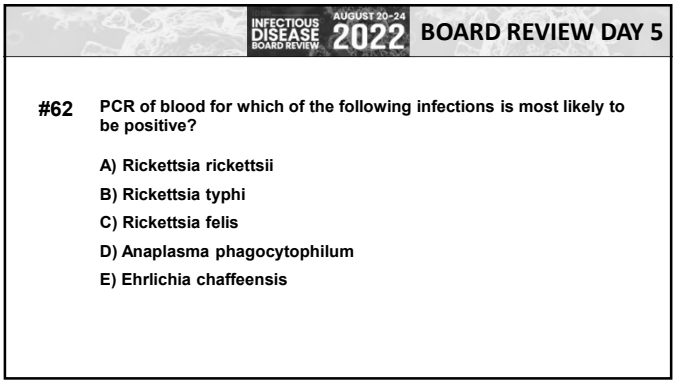
Moderator: Paul Auwaerter, MD











BR5 – Board Review: Day 5

Moderator: Paul Auwaerter, MD

INFECTIOUS DISEASE BOARD REVIEW AUGUST 20-24 2022 BOARD REVIEW DAY 5

#63 A 22-year-old male from Trinidad has had aplastic anemia since 2003. He is being prepared for a matched stem cell transplant from his brother after failing eltrombopag and several courses of horse anti-thymocyte globulin (ATG) and prednisone.

He is chronically neutropenic with a current absolute neutrophil count of 75/cu mm and platelet count of 15,000/cu mm.

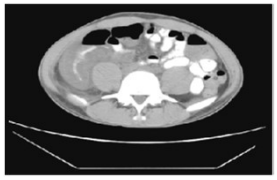
Renal and hepatic function are normal.

He is admitted to the ICU from clinic with fever, hypotension, and abdominal tenderness and distension with some rebound tenderness and only a few bowel sounds.

INFECTIOUS DISEASE BOARD REVIEW AUGUST 20-24 2022 BOARD REVIEW DAY 5

#63 He was started on vancomycin, and meropenem plus fluconazole.

Surgical consultation was obtained and a CT scan with oral and intravenous contrast was ordered:



INFECTIOUS DISEASE BOARD REVIEW AUGUST 20-24 2022 BOARD REVIEW DAY 5

#63 What would you recommend be added to his regimen of vancomycin/meropenem/fluconazole at this time?

A) Ivermectin

B) Surgical resection

C) Linezolid

D) Liposomal Amphotericin B

E) Nothing. Continue present management.

INFECTIOUS DISEASE BOARD REVIEW AUGUST 20-24 2022 BOARD REVIEW DAY 5

#64 An 80-year-old resident of a nursing home has severe dementia, type 2 diabetes mellitus and a chronic indwelling Foley catheter which is in place to manage his persistent incontinence.

He has no remarkable medical history and is quite healthy except for his dementia.

He has received antibiotics for presumed urinary tract infection twice in the last year.

INFECTIOUS DISEASE BOARD REVIEW AUGUST 20-24 2022 BOARD REVIEW DAY 5

#64 The nursing home staff decided to obtain a urinalysis and urine culture: they call you because the urine culture is growing Candida albicans with a colony count of 100,000 cfu/ml.

His UA shows 30-40 WBC and 10-20 RBC per HPF, with a 1+ leukocyte esterase.

He is in his usual state of health with no fever, no urinary symptoms that you can elicit from him, and no flank tenderness.

INFECTIOUS DISEASE BOARD REVIEW AUGUST 20-24 2022 BOARD REVIEW DAY 5

#64 What would you recommend?

A) Observe and do nothing more unless the patient becomes symptomatic

B) Observe but obtain repeat urinalysis and culture in one week

C) Change Foley catheter and give oral fluconazole for 1 week

D) Change Foley catheter and IV caspofungin for 1 week

E) Change the Foley catheter and order Amphotericin B deoxycholate bladder washes daily for 5-7 days

BR5 – Board Review: Day 5

Moderator: Paul Auwaerter, MD

INFECTIOUS DISEASE BOARD REVIEW AUGUST 20–24 2022 **BOARD REVIEW DAY 5**

#65 **A 58-year-old male underwent a right knee replacement 6 months earlier for severe osteoarthritis.**

He did well, but one month prior to admission, he was in a motor vehicle accident and had some trauma to the knee.

He subsequently had pain in the knee and later noted a draining hole in his right knee near the surgical site. He was febrile to 39°C and examination of the right knee revealed some swelling and erythema, and a sinus tract that was draining seropurulent material.

Cultures of the drainage revealed methicillin-resistant Staphylococcus aureus.

INFECTIOUS DISEASE BOARD REVIEW AUGUST 20–24 2022 **BOARD REVIEW DAY 5**

#65 **What would be the most appropriate approach in treating this patient's infection?**

A) 6-week course of parenteral antimicrobial therapy followed by life-long oral antimicrobial therapy

B) Surgical drainage of the knee with prosthesis retention followed by a 6 month course of antimicrobial therapy

C) Prosthesis removal and immediate reimplantation of a new prosthesis followed by a 6 week course of antimicrobial therapy

D) Prosthesis removal and reimplantation of a new prosthesis after 2-4 weeks of antimicrobial therapy followed by 6 months of antimicrobial therapy

E) Prosthesis removal and reimplantation of a new prosthesis after 6 weeks of antimicrobial therapy

INFECTIOUS DISEASE BOARD REVIEW AUGUST 20–24 2022 **BOARD REVIEW DAY 5**

#66 **An 8-year-old boy complains of itchiness of his buttocks that wakes him up at night.**

He has a 2-year-old sister who is in daycare.

A touch prep examination of the peri-anal region demonstrates pinworm eggs. The boy is treated with pyrantel pamoate twice, spaced two weeks apart.

Three weeks after the second treatment the boy returns again with complaints of peri-anal itching.

INFECTIOUS DISEASE BOARD REVIEW AUGUST 20–24 2022 **BOARD REVIEW DAY 5**

#66 **The most likely explanation for the boy's symptoms is:**

A) Resistant pinworm infection

B) Re-infection with pinworms

C) Dipylidium caninum

D) Non-infectious cause of peri-anal itching

INFECTIOUS DISEASE BOARD REVIEW AUGUST 20–24 2022 **BOARD REVIEW DAY 5**

#67 **A 64-year-old female with a history of chronic lymphocytic leukemia (CLL) for several years was recently diagnosed with Richter's transformation to diffuse large B cell lymphoma.**

Her oncologist recommended starting R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine and prednisone) chemotherapy given the advanced stage disease.

The patient has a history of recurrent and severe sinopulmonary infections and hypogammaglobulinemia. As a result, she has been on monthly intravenous immunoglobulin (IVIG) for the past two years.

INFECTIOUS DISEASE BOARD REVIEW AUGUST 20–24 2022 **BOARD REVIEW DAY 5**

#67 **The patient's hepatitis B serology obtained a year ago showed:**

- **HBsAg: nonreactive**
- **Total HBc Ab: positive**
- **HBsAb: positive**
- **HBV viral load: negative**

Her oncologist referred her to be seen by you for further recommendations about the patient's hepatitis B.

BR5 – Board Review: Day 5

Moderator: Paul Auwaerter, MD

INFECTIOUS DISEASE BOARD REVIEW AUGUST 20–24 2022 BOARD REVIEW DAY 5

#67 What is the most appropriate next step?

A) Treat only if monthly serum quantitative HBV viral load becomes positive while she gets treated with R-CHOP

B) Start tenofovir plus emtricitabine pre-R-CHOP

C) Start entecavir pre-R-CHOP

D) Administer a single hepatitis B vaccine booster dose

E) Review pre-IVIG hepatitis B serology before making a decision

INFECTIOUS DISEASE BOARD REVIEW AUGUST 20–24 2022 BOARD REVIEW DAY 5

#68 A 56-year-old woman presents to the urgent care clinic with a two-week history of worsening right knee pain. She has a history of rheumatoid arthritis for which she takes infliximab.

Two months ago she underwent a steroid injection to the right knee. She had transient improvement, but symptoms worsened two weeks ago with decreased range of motion, and more pain with ambulation.

She lives in New Hampshire, and when well enjoys walking in the woods with her dogs. One month ago she underwent a routine dental cleaning.

INFECTIOUS DISEASE BOARD REVIEW AUGUST 20–24 2022 BOARD REVIEW DAY 5

#68 On evaluation, she guarded against range of motion of the right knee; a small effusion is present.

She was found to have ESR of 74 and CRP of 53 mg/dL and on synovial fluid analysis, she had 42,000 WBCs (91% neutrophils), a negative gram stain, and few positive birefringent crystals.

Cultures are pending.

INFECTIOUS DISEASE BOARD REVIEW AUGUST 20–24 2022 BOARD REVIEW DAY 5

#68 What is the most likely diagnosis?

A) Calcium pyrophosphate crystal deposition disease (pseudogout)

B) Gout

C) Lyme disease

D) Septic arthritis

E) Chondrocalcinosis

INFECTIOUS DISEASE BOARD REVIEW AUGUST 20–24 2022 BOARD REVIEW DAY 5

#69 In July, a 25-year-old African-American male turkey farmer from rural North Carolina was taken to the Emergency Department because of fever and headache of approximately 48-hours duration. His farm had a few cows and dogs.

They drank unpasteurized milk from their cows. Occasionally he noted ticks on his body but could not remember when the last time was.

He didn't slaughter animals on the farm, but sent the turkeys elsewhere for processing. He sometimes walked around in stagnant water in the fields where he grazed the cows.

He had been healthy and took no medications.

INFECTIOUS DISEASE BOARD REVIEW AUGUST 20–24 2022 BOARD REVIEW DAY 5

#69 On examination:

- His temperature was 40° C, pulse 110 and BP 90/60.
- He was obviously ill and groaning from the headache but oriented x 3.
- No rash was seen.
- Slight but definite nuchal rigidity was found but no other neurologic signs.

BR5 – Board Review: Day 5

Moderator: Paul Auwaerter, MD

INFECTIOUS DISEASE BOARD REVIEW AUGUST 20–24 2022 BOARD REVIEW DAY 5

#69 Blood cultures were drawn, and ceftriaxone 2 gm q12h IV was begun.

- Lumbar puncture found WBC 40/cu ml, all lymphocytes and monocytes.
  - CSF protein was 45 mg/dL and glucose 55 mg/dL.
  - Gram stain was negative.
- WBC was 2,500/cu ml with a normal differential.
- Platelet count was 70,000/cu ml and hemoglobin 13 gm.
- Routine chemistries showed aminotransferases were slightly elevated, 1.5 times the upper normal limit.

INFECTIOUS DISEASE BOARD REVIEW AUGUST 20–24 2022 BOARD REVIEW DAY 5

#69 Which of the following is the most likely source of this infection?

A) Turkeys
B) Mosquitoes
C) Dog ticks
D) Unpasteurized milk
E) Stagnant water

INFECTIOUS DISEASE BOARD REVIEW AUGUST 20–24 2022 BOARD REVIEW DAY 5

#70 A 20-year-old college student who immigrated to the United States at the age of 15 years is referred to you because of a history of rheumatic fever.

The student had fever and arthralgias when she was 5 years old, and again when she was 15 years old.

The referring physician heard a heart murmur and obtained an echocardiogram which show mild mitral stenosis with a calcified mitral valve.

The physician agrees that she appears to have had rheumatic fever and now has rheumatic heart disease.

INFECTIOUS DISEASE BOARD REVIEW AUGUST 20–24 2022 BOARD REVIEW DAY 5

#70 What would you recommend to prevent a recurrence of rheumatic fever?

A) No antimicrobial prophylaxis
B) Amoxicillin daily until 5 years after her last episode of rheumatic fever
C) Benzathine penicillin monthly for 10 years after last attack, or until age 40 years, whichever is longer
D) Benzathine penicillin monthly for life
E) Procaine penicillin monthly for life

INFECTIOUS DISEASE BOARD REVIEW AUGUST 20–24 2022 BOARD REVIEW DAY 5

#71 A 25-year-old woman with cystic fibrosis and known pulmonary colonization with MRSA underwent bilateral lung transplant.

She was at high serologic risk for CMV and received intravenous ganciclovir IV, inhaled amphotericin B and oral fluconazole, and vancomycin and cefepime prophylaxis beginning on post-operative day 1.

She was extubated and transferred to the step-down unit with an unremarkable post-operative course until day 7 post-transplant when she became agitated and hypoxic.

Work-up included bronchoscopy with BAL cultures and blood cultures which were negative after 48 hours, but a blood ammonia level that was high.

INFECTIOUS DISEASE BOARD REVIEW AUGUST 20–24 2022 BOARD REVIEW DAY 5

#71 You recommend:

A) BAL PCR for Mycoplasma and *Ureaplasma* spp. and start antimicrobial therapy directed against these pathogens
B) Switch vancomycin to daptomycin
C) Stop fluconazole and start voriconazole
D) Switch ganciclovir to foscarnet out of concern for ganciclovir resistant CMV pneumonitis

BR5 – Board Review: Day 5

Moderator: Paul Auwaerter, MD

INFECTIOUS DISEASE BOARD REVIEW AUGUST 20–24 2022 BOARD REVIEW DAY 5

#72 A 20-year-old male with refractory lymphoma received an HLA-mismatched and T-cell depleted allogeneic stem cell transplant.

He engrafted on day 22, and developed a faint diffuse erythematous rash and low-grade fever on day 68.

He was diagnosed as acute graft vs. host disease (GVHD), for which he was treated with prednisone, which was ultimately tapered. The rash faded and he became afebrile.

He is receiving trimethoprim-sulfamethoxazole three times a week and twice daily valacyclovir for prophylaxis.

INFECTIOUS DISEASE BOARD REVIEW AUGUST 20–24 2022 BOARD REVIEW DAY 5

#72 On day 110, he developed fever to 38°C, dyspnea, cough, and a faint erythematous rash.

- His WBC was 7,000, with a normal differential.
- Chest CT scan demonstrated bilateral ground glass opacities but cultures and stains of a bronchoalveolar lavage for bacteria, fungi and pneumocystis were negative.
- Alkaline phosphatase was 309 U/L, AST 488 U/L, ALT 430 U/L, total bilirubin 1.9 mg/dl.
- Urinalysis revealed hematuria: 1500 RBC, 20 WBC, with no bacteria on stain.
- His CMV PCR on peripheral blood was undetectable.

INFECTIOUS DISEASE BOARD REVIEW AUGUST 20–24 2022 BOARD REVIEW DAY 5

#72 What is the most likely cause of this syndrome?

A) HSV
B) VZV
C) HHV6
D) Adenovirus
E) BK Virus

INFECTIOUS DISEASE BOARD REVIEW AUGUST 20–24 2022 BOARD REVIEW DAY 5

#73 A 40-year-old man from Ghana was visiting his daughter in the United States.

She sought medical care for her father who was constantly scratching himself, with generalized pruritus.

A 4 cm painless nodule was found on his right hip.

Biopsy of the nodule reveals cross-sections of very thin nematodes.

INFECTIOUS DISEASE BOARD REVIEW AUGUST 20–24 2022 BOARD REVIEW DAY 5

#73 The most likely cause of the nodule is:

A) Ascaris lumbricoides
B) Onchocerca volvulus
C) Schistosoma mansoni
D) Trichinella spiralis
E) Loa loa

INFECTIOUS DISEASE BOARD REVIEW AUGUST 20–24 2022 BOARD REVIEW DAY 5

#74 A 21-year-old female college varsity track and field athlete noted the onset of right knee pain and swelling for three weeks that has persisted despite taking anti-inflammatories, rest and icing.

She feels otherwise well without fever and denies any trauma or prior history of joint swelling.

An MRI of the knee showed no meniscal tears and mild synovial thickening.

Last week, an orthopedist aspirated the joint, revealing 18,000 WBC/ml with PMN predominance. No crystals were identified, and cultures were negative.

BR5 – Board Review: Day 5

Moderator: Paul Auwaerter, MD

INFECTIOUS DISEASE BOARD REVIEW AUGUST 20-24 2022 BOARD REVIEW DAY 5

#74 She is a resident of Massachusetts and attends school in South Carolina.

She has no prior past medical history, including sexually transmitted diseases, and doesn't recollect any history of rash consistent with erythema migrans or history of tick bites recently.

Her exam is normal except for her right knee, which has some limited range of motion and a moderate effusion.

INFECTIOUS DISEASE BOARD REVIEW AUGUST 20-24 2022 BOARD REVIEW DAY 5

#74 Which selection below would most support a diagnosis of late Lyme arthritis?

A) A therapeutic trial of antibiotics (doxycycline or ceftriaxone)

B) Synovial fluid *B. burgdorferi* immunoblot (IgM or IgG)

C) Synovial fluid culture for *Borrelia* spp.

D) Two-tiered *B. burgdorferi* serology, including IgG immunoblot

INFECTIOUS DISEASE BOARD REVIEW AUGUST 20-24 2022 BOARD REVIEW DAY 5

#75 A 48-year-old physician presents with complaints of severe fevers, abdominal pain, diarrhea, and back pain for 5 days. The patient returned from a 6-month medical mission to Sudan 2 weeks ago.

The patient took doxycycline daily for malaria prophylaxis while there, but reports she would occasionally forget a dose.

She experienced frequent insect bites, especially when she took hikes along the banks of the White Nile River.

She was usually careful about what she ate, but about once a week would eat home cooked meals prepared by coworkers at the medicine clinic.

INFECTIOUS DISEASE BOARD REVIEW AUGUST 20-24 2022 BOARD REVIEW DAY 5

#75 On exam, her heart rate is 110 bpm, BP is 100/70, respiratory rate is 24/min, and temperature is 38.6°C. Lung sounds are clear to auscultation bilaterally. Abdomen is soft with moderate tenderness in the right upper and right lower quadrants.

Abnormal laboratory values include a white blood cell count of 18,400/mm^3 with 45% neutrophils, 24% lymphocytes, 6% monocytes, 24% eosinophils, and 1% basophils. AST is 158 units/L and ALT is 144 units/L.

Ova and parasite examinations on stool and urine samples, sent by the patient's primary physician three days ago, are negative.

INFECTIOUS DISEASE BOARD REVIEW AUGUST 20-24 2022 BOARD REVIEW DAY 5

#75 Which of the following organisms is most likely causing her illness?

A) Salmonella typhi

B) Plasmodium falciparum

C) Onchocerca volvulus

D) Schistosoma mansoni

E) Ancylostoma duodenale

50

Bone and Joint Infections

Dr. Sandra Nelson

50 – Bone and Joint Infections

Speaker: Sandra Nelson, MD

IDBR INFECTIOUS DISEASE BOARD REVIEW AUGUST 20-24 2022

Bone, Joint and Musculoskeletal Infections

Sandra B. Nelson, MD
Director, Musculoskeletal Infectious Diseases
Division of Infectious Diseases
Massachusetts General Hospital

6/30/2022

INFECTIOUS DISEASE BOARD REVIEW AUGUST 20-24 2022

Disclosures of Financial Relationships with Relevant Commercial Interests

- None

Osteomyelitis:

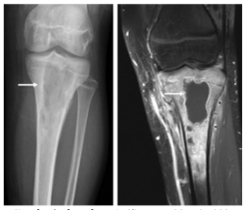
- Hematogenous Osteomyelitis
  - Metaphyseal long bone (more common in children)
  - Vertebral spine (Spondylodiscitis)
  - Usually monomicrobial
- Contiguous Osteomyelitis
  - Trauma / osteofixation
  - Diabetic foot ulceration
  - Infections in decubitus ulcer
  - Often polymicrobial

Osteomyelitis: Unifying Principles

- Radiographic studies:
  - No radiographic study sufficiently specific to confirm diagnosis of osteomyelitis
  - MRI is the most sensitive radiographic study for diagnosis
  - Serial plain films and CT may also be useful in subacute and chronic infection
  - Bone scan has high negative predictive value but lacks specificity
  - No radiographic studies useful as test of cure
- Diagnosis best confirmed by bone histopathology and culture
  - Identification of organism improves outcomes
  - Swab cultures of drainage are of limited value
- Optimal route and duration of therapy an evolving target
  - 6 weeks of IV antimicrobial therapy commonly employed; strong data to support oral therapy
  - Longer oral suppression in setting of retained hardware

Brodie's Abscess (Subacute hematogenous osteomyelitis)

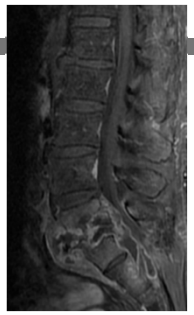
- More common in children and young adults
- Bacteria deposit in medullary canal of metaphyseal bone, become surrounded by rim of sclerotic bone → intraosseous abscess
- "Penumbra sign" on MRI
  - Granulation tissue lining abscess cavity inside bone gives appearance of double line
- *Staph aureus* most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



Simpfendorfer Infect Dis Clin N Am 2017;31:299

Case #1

- 57-year-old male presented with 3 months of progressive lower back pain
- On ROS denied fevers or chills but wife noticed weight loss
- Originally from Cambodia, emigrated as a child.
- Employed at a seafood processing plant
- ESR 84 CRP 16
- MRI with discitis and osteomyelitis at L5-S1
- Blood cultures grew *Staph epidermidis* in 2 of 4 bottles



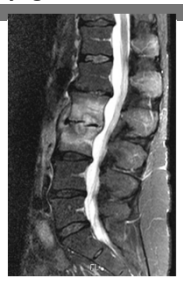
Case #1: Vote

What is the best next step in management?

A. Repeat 2 sets of blood cultures
B. Initiate vancomycin; place PICC for six week treatment course
C. Obtain interferon gamma release assay
D. Percutaneous biopsy of disc space
E. Empiric treatment with rifampin, isoniazid, ethambutol, and pyrazinamide

MASSACHUSETTS GENERAL HOSPITAL HARVARD MEDICAL SCHOOL 7

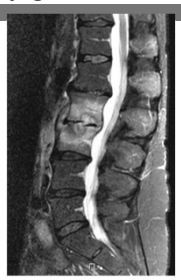
Pyogenic Vertebral Osteomyelitis: diagnosis



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

MASSACHUSETTS GENERAL HOSPITAL HARVARD MEDICAL SCHOOL 9

Pyogenic Vertebral Osteomyelitis: diagnosis



- Blood cultures (positive in 60%)
  - No further diagnostics if *Staph aureus* or *Staph lugdunensis*
- Brucella serologies, PPD/IGRA
  - In appropriate epidemiological setting
- Percutaneous biopsy (paraspinal or bone/disc)
  - When blood cultures and serology negative
  - Yield 36-65%
  - In absence of sepsis and/or neurologic compromise, withhold antibiotics 1-2 weeks if feasible
  - If negative repeat percutaneous or consider open procedure (higher yield)

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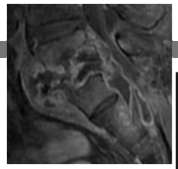
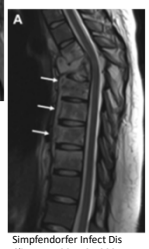
Reference: 2015 IDSA Guidelines
HARVARD MEDICAL SCHOOL 10

Pott's Disease





- Clinically:
  - More indolent than pyogenic osteomyelitis
  - Constitutional symptoms common
  - Anterior collapse may lead to gibbus deformity
- Radiographic:
  - Thoracic>lumbar with anterior involvement
  - Relative sparing of the disc space until later
  - Multi-level disease, large paraspinal abscesses
- Treatment:
  - Conventional TB therapy, 6-12 months
  - Surgery often not necessary

Simpfendorfer Infect Dis Clin N Am 2017;31:299

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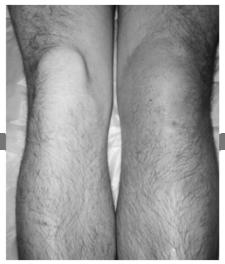
Septic Arthritis



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Septic Arthritis: Clinical Pearls

- Synovial fluid cell counts: No diagnostic threshold
  - Higher probability of SA if WBC >50,000/mm^3
  - Lower cell counts do not exclude septic arthritis
- More subtle presentations in immunocompromised hosts and with indolent organisms
  - Subacute history
  - Lower synovial fluid cell counts
- Negative cultures and/or delayed culture positivity:
  - think Gonococcus, HACEK, Lyme, Mycoplasma
- Surgery indicated for most patients with joint sepsis
  - Type of surgery not standardized

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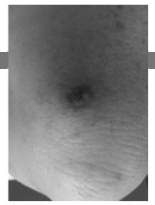
Polyarthritis

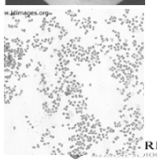
- 10-20 % of septic arthritis is polyarticular:
- Associated with bacteremia/sepsis
  - Staph aureus most common (look for endocarditis)
- Consider also:
  - gonococcal, viral, non-infectious
- Rat bite fever
  - Polyarthritis (usually symmetric), fever, maculopapular and/or pustular rash
  - *Streptobacillus moniliformis* (or if bitten in Asia – *Spirillum minus)*
  - Rx: penicillin

Giorgiutti NEJM 2019: 381:1762

Gonococcal Arthritis

- Tenosynovitis, arthralgias, skin lesions
  - Especially extensor surface tenosynovitis
  - Migratory arthralgias
- Purulent arthritis
  - May be polyarticular; knees most common
  - Lower synovial fluid cell counts more common
- Asymptomatic mucosal phase predisposes
  - Dissemination more common in women
- Highest yield diagnosis: mucosal site sampling (cervical, urethral)
  - Blood (<30%) and synovial fluid (<50%) cultures lower yield
  - Compatible clinical syndrome





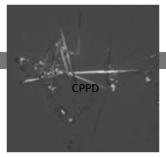
Viral arthritides

- 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

Crystalline arthritis: clinical pearls

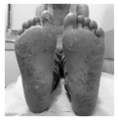
- Acute gout flare mimics septic arthritis
  - Fever common
  - Monoarthritis and polyarthritis forms
  - Clues: rapid onset (hours), history of prior gout, alcohol, CKD, diuretics, elevated uric acid
  - Synovial WBC 10,000-100,000/mm^3
- Crystalline disease and septic arthritis can coexist (esp. CPPD)
  - CPPD rarely has cell count >30,000
  - CPPD rarely associated with high fever



Images: Taljanovic RadioGraphics 2015;35:2026

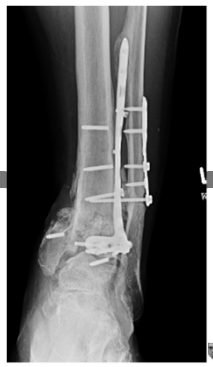
Masquerading as Infection…

- 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….

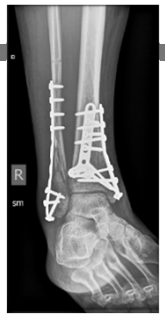


Coelho BMJ Case Reports 2017-222475

Osteofixation Infections



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. Nafcillin followed by long-term trimethoprim- sulfamethoxazole
B. Hardware removal; six weeks of oxacillin
C. Hardware removal; six weeks of oxacillin and rifampin
D. Debridement without hardware removal; six weeks of oxacillin and rifampin
E. Debridement and hardware replacement; six weeks of oxacillin and rifampin

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Osteofixation Infections

Goals: fracture consolidation and infection eradication
Removal of hardware depends upon fracture healing

	Early or delayed infections prior to fracture union	Late nonunion	Late, healed fracture
Microbiology	*Staph aureus* most common Virulent organisms	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 fixation (1 or 2 stage) Or external fixation	Hardware removal
Antimicrobial Management	Pathogen-directed therapy with addition of rifampin if Staph species. Duration not well studied, often 12 weeks or until fracture consolidation	Pathogen-directed therapy Duration not well studied	Pathogen-directed therapy Duration not well studied; two weeks following hardware removal

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Rifampin in orthopedic infections

- Considered a "biofilm active" agent
- Best studied for Staphylococcal PJI in setting of hardware retention
  - Data extrapolated for other hardware infections (osteofixation, spinal implant)
  - Lower treatment failure in PJI with implant retention
- Specifics
  - Never to be used in monotherapy of established infection
  - Should not be used prior to surgical debridement and until partner drug therapeutic
  - Multiple drug interactions (primarily via Cyp 3A4 pathway)

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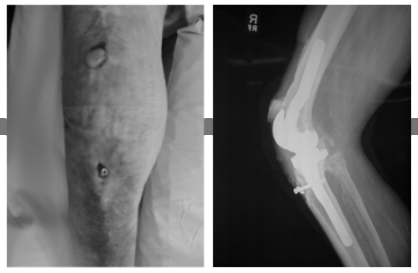
Prosthetic Joint Infection



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Prosthetic Joint Infection (PJI): Clinical presentations

- Early surgical site infection (< 3months)
  - Acute onset of fever, joint pain, swelling
  - Caused by virulent organisms (*Staph aureus*)
- Delayed / Subacute infection (3 – 24 months)
  - Insidious onset of pain; fever is uncommon
  - Less virulent organisms: e.g. Coagulase-negative Staph, Cutibacterium
- Acute hematogenous infection (anytime after arthroplasty)
  - Acute onset fever, joint pain, swelling in previously well joint replacement
  - Hematogenous seeding, virulent organisms (*Staph aureus, Streptococcus)*

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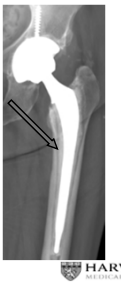
Prosthetic Joint Infection: Diagnostic pearls

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

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



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PJI Management

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

* 2012 IDSA Guidelines

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Case #3

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

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Case #3: Vote

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

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

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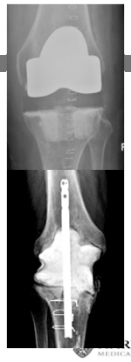
Antimicrobial Cement (PMMA)

- 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 anticipating knee arthroplasty. She takes methotrexate, hydroxychloroquine and low dose prednisone (2.5 mg daily). She has a history of recurrent urinary tract infections. She asks how she might prevent infection after knee replacement.

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Case #4: Vote

What do you advise?

A. Stop methotrexate and prednisone two weeks preoperatively
B. Screen for Staph aureus colonization; decolonize if present
C. Screening UA and urine culture, treat if positive
D. 48 hours perioperative prophylaxis with cefazolin
E. Amoxicillin prior to dental procedures for 2 years postoperatively

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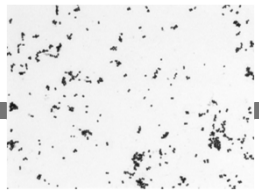
Prevention of PJI

- Immunosuppressives:
  - Stop biologics, no need to stop DMARDs or low dose prednisone
- Surgical antibiotic prophylaxis: one dose prior to surgery
- Urinary tract infections:
  - Diagnose and treat symptomatic UTI
  - Do not screen for asymptomatic bacteriuria
- Dental prophylaxis: no more!
- *Staph aureus* decolonization reduces surgical site infection

MASSACHUSETTS GENERAL HOSPITAL HARVARD MEDICAL SCHOOL 36

Microbiology of Musculoskeletal Infections



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Case #5

56-year-old man presents to ED with a one-week history of atraumatic right knee pain and swelling and low-grade fevers. Weight bearing is now uncomfortable.

- PMHx: poorly controlled diabetes
- One month ago he travelled to the Dominican Republic
  - No illnesses while traveling
- He last saw a dentist six months ago; no tooth pain
- No animal exposures
- No history of injection drug use
- Exam: moderate effusion; pain with passive range of motion
- ESR 68 CRP 17 mg/dL
- Synovial fluid: 45,000 WBCs (82% neutrophils)
  - Negative gram stain

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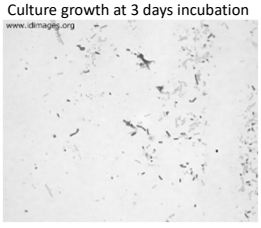
Case #5: Vote

Culture growth at 3 days incubation



What is the most likely organism?

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

MASSACHUSETTS GENERAL HOSPITAL HARVARD MEDICAL SCHOOL 35

Microbiology of Bone and Joint Infections: clinical and epidemiologic clues (1)

Gram-negative Organisms	Clinical Clues	Micro Clues
Pseudomonas aeruginosa and Serratia marcescens	Immunocompromised host, indwelling line, history of injection drug use (IDU)	
HACEK organisms	Human bite wounds (*Eikenella corrodens*) Recent dental procedure or infection	Delayed growth in culture Often culture negative if prior abx
Kingella kingae (K in HACEK)	Common in children <4yo.	Grows poorly in routine culture (diagnose by pcr)
Pasteurella species	Cat or dog bite; rapid onset infection	
Salmonella species	Sickle cell disease, immunocompromise, diabetes. Reptile exposure. Travel to developing world or unsafe food hygiene	
Brucella species	Consumption of unpasteurized dairy; travel to endemic areas (Latin America, Mediterranean Middle East). Sacroiliitis and spondylodiscitis	Delayed growth in culture Can be a biohazard in the laboratory
Streptobacillus moniliformis	Rat bite Fever, rash, polyarthritis	

MASSACHUSETTS GENERAL HOSPITAL HARVARD MEDICAL SCHOOL 41

Microbiology of Bone and Joint Infections: clinical and epidemiologic clues (2)

Other bacteria and mycobacteria	Clinical Clues	Micro Clues
Neisseria gonorrhoeae	Triad of Tenosynovitis, Dermatitis, Arthritis	Requires enriched media (Thayer-Martin) to grow
Mycoplasma species	Humoral immunodeficiency (CVID, XLA) Postpartum women	Difficult to grow in routine culture. "Fried egg" morphology in culture
Borrelia burgdorferi (Lyme)	Northeast and Upper Midwest with tick exposure. Subacute monoarthritis of large joints (knee most common) with large effusions	Does not grow in conventional culture
Tuberculosis	Subacute to chronic infections including vertebral osteomyelitis (Pott's) and septic arthritis	
Non-tuberculous mycobacteria	Environmental water exposure (fishermen, fish tanks). Tenosynovitis of hands	

MASSACHUSETTS GENERAL HOSPITAL HARVARD MEDICAL SCHOOL 42

Microbiology of Bone and Joint Infections: clinical and epidemiologic clues (3)

Fungal Infections	Clinical Clues
Candida species	Seen in immunocompromised hosts, IDU
Molds	Madura Foot (barefoot walking) Environmental contamination (e.g. open fracture with soil contamination) Immunocompromised hosts (neutropenia)
Coccidioides species, Blastomyces dermatitidis (Histoplasma capsulatum less frequent)	Subacute to chronic monoarthritis, long bone osteomyelitis, and vertebral disease. Usually associated with symptomatic or asymptomatic pulmonary findings (esp. cocci). Immunocompromised host

MASSACHUSETTS GENERAL HOSPITAL HARVARD MEDICAL SCHOOL 43

Thank you!

MASSACHUSETTS GENERAL HOSPITAL HARVARD MEDICAL SCHOOL 43

51

Ticks, Mites, Lice, and the Diseases They Transmit

Dr. Paul Auwaerter

51 – Ticks, Mites, Lice and The Diseases They Transmit

Speaker: Paul Auwaerter, MD

IDBR INFECTIOUS DISEASE BOARD REVIEW AUGUST 20-24 2022

Ticks, Mites, Lice, and The Diseases They Transmit

Paul G. Auwaerter, MD
Sherrilyn and Ken Fisher Professor of Medicine
Clinical Director, Division of Infectious Diseases
Johns Hopkins University School of Medicine

7/21/2022

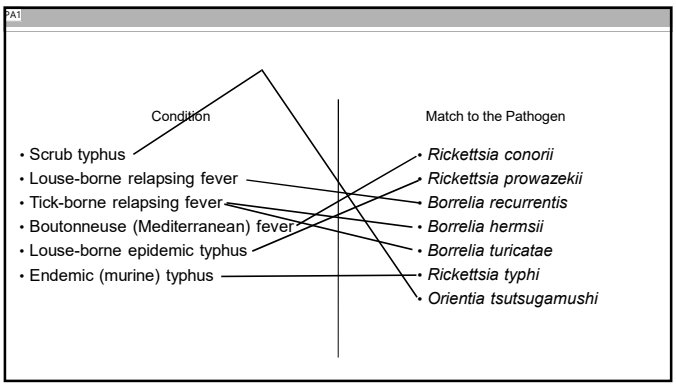
INFECTIOUS DISEASE BOARD REVIEW AUGUST 20-24 2022

Disclosures of Financial Relationships with Relevant Commercial Interests

- **Consultant: EMD Serono, Humanigen**
- **Ownership Interest: Johnson & Johnson, Wellstat**

Why the board exam loves these infections
PLAY THE MATCH GAME

Condition	Pathogen
• Scrub typhus	• *Rickettsia conorii*
• Louse-borne relapsing fever	• *Rickettsia prowazekii*
• Tick-borne relapsing fever	• *Borrelia recurrentis*
• Boutonneuse (Mediterranean) fever	• *Borrelia hermsii*
• Louse-borne epidemic typhus	• *Borrelia turicatae*
• Endemic (murine) typhus	• *Rickettsia typhi*
	• *Orientia tsutsugamushi*



Tick-borne Diseases of North America General Principles I

- Initial, early presentation non-specific:
  - "Flu-like illness" (e.g. fever, headache, myalgia)
- Diagnosis is clinical
  - Treatment is empiric—must start prior to return of diagnostic testing
- Characteristic rash/lesion +/- especially early
- Asymptomatic:symptomatic ratio is high

Ref: Diagnosis and Management of Tickborne Rickettsial Diseases: Rocky Mountain Spotted Fever and Other Spotted Fever Group Rickettsioses, Ehrlichioses, and Anaplasmosis — United States. A Practical Guide for Health Care and Public Health Professionals, MMWR May 13, 2016 / 65(2);1–44

Tick-borne Diseases of North America General Principles II

Seasonal but not always
Geography informs etiology but often changes over time
Lab tip-offs:
- Thrombocytopenia
- Leukocytosis or leukopenia
- Elevated LFTs

Doxycycline is preferred therapy for most
(all ages including children, e.g., Lyme, RMSF, ehrlichiosis…)
Prognosis is worse at age extremes < 10 and > 60 yrs
Convergence in tick vectors
Co-infection probably underestimated

The Major Tick-borne Diseases of North America

- Lyme disease (separate talk)
- Rocky Mountain spotted fever (RMSF)
- Ehrlichioses
- Anaplasmosis
- Relapsing fever (*Borrelia* spp.)
- Babesia spp.

Other Tick-borne Diseases of North America

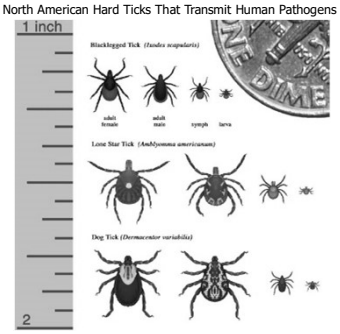
- Tick paralysis
- Southern tick associated rash illness (STARI)
- Viruses:
  - Powassan (Deer Tick Virus Lineage II, flavivirus)
  - Colorado tick fever (coltivirus)
  - Heartland virus (phlebovirus)
  - Bourbon virus (thogotovirus)
- Spotted Fever Group Rickettsia (partial)
  - R. parkeri
  - Rickettsia 364D aka R. philippii (Pacific Coast tick fever)
- Coxiella burnetti
- Tularemia
  - (< 10% tickborne)
- Other Borrelia
  - B. miyamotoi
  - B. mayonii

Ticks: arachnids, not insects

- **Number of species**
  - **896 species or subspecies**
- **Hematophagous arthropods**
  - **parasitize every class vertebrates ≅ entire world**
- **Two major families**
  - **Ixodidae, 702 species (hard ticks, attach & engorge)**
  - **Argasidae, 193 species (soft ticks, bite multiply & briefly)**
- **Four basic life stages**
  - **egg → larva → nymph → adult**
- **Vectors of human disease**
  - **#1 mosquitos**
  - **#2 ticks**

Parola, Raoult CID 2001; 32:897-928
Guglielmone, Zootaxa 2010;2528:1-28

Common North American Hard Ticks That Transmit Human Pathogens (Ixodidae) 1

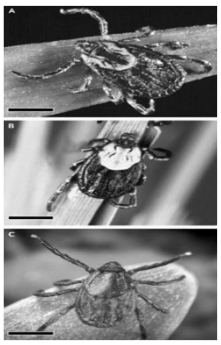


Common North American Hard Ticks (Ixodidae) 2

Amblyomma americanum (Lone star tick)

Common North American Hard Ticks (Ixodidae) 3

Dog ticks

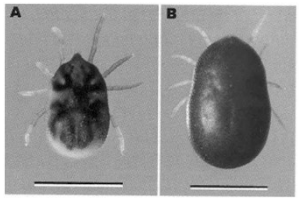


D. variabilis

D. andersoni

R. sanguineus

Ornithodoros Hermsi nymphal Tick
Soft tick (Argasidae)



A: shows the nymph before its infective blood meal (from California)

B: shows it after feeding

These are soft ticks that feed briefly at multiple spots

Scale bars = 2 mm

Question #1:

62M living in an exurb of Phoenix, Arizona presents in early September with a three day history of fever, myalgia, headache and rash.

He works as a lineman for a utility company. He lives with his family in an older adobe home with dogs. He has beginnings of petechial features on the wrists and ankles.

Which of the following is the most likely diagnosis?

A. Human Monocytic Ehrlichiosis (HME)
B. Human Granulocytic Anaplasmosis (HGA)
C. Babesiosis
D. Rocky Mountain Spotted Fever (RMSF)
E. Tularemia

Rickettsial species: two major groups
(not a comprehensive pathogen list)

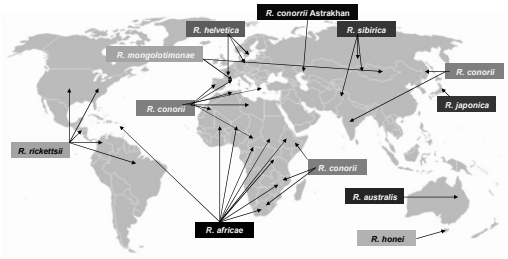
Spotted Fever Group (SFG)

- RMSF (R. rickettsii)
- R. parkeri
- Rickettsia sp. 364D
- Rickettsialpox (R. akari)
- R. conorii
- R. africae
- R. japonica
- R. australis
- …many more

Typhus Group

- Epidemic typhus
  - R. prowazekii
    - Body louse
    - Worldwide
- Murine/endemic typhus
  - R. typhi
    - Rat flea
    - Temperate--tropical, usually

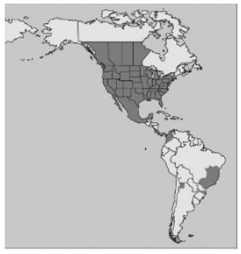
Tick-borne Rickettsia World Wide: many species



- 24 species causing human disease. List continues to grow.

Parola, Clin Microbiol Rev 2013;26(4):657-702

Approximate Geographic Distribution of R. rickettsii in the American Continents



See in all lower 48 states

Mexico

Parts of Canada

Central and South America

Ongoing epidemic in Northern Mexico (2015-present)

Alavarez-Hernandez, Lancet ID 2017;17(6):e189-196
Tinoco-Gracia, EID 2018;24(9):1723-25

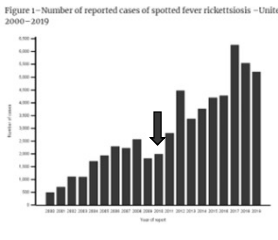


Figure 1–Number of reported cases of spotted fever rickettsiosis –United States, 2000–2019

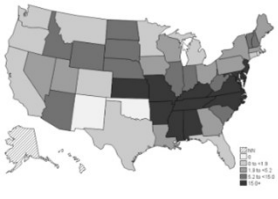


Figure 4.–Annual incidence (per million population) of reported spotted fever rickettsiosis–United States, 2019. (NN= Not notifiable)

Source: CDC (accessed 7/17/22)
Δ category from RMSF to "spotted fever rickettsioses" 2010
Includes RMSF, *R. parkeri*, Pacific Coast tick fever, and Rickettsialpox.

RMSF in the United States

Incidence/Case Fatality 1920-2015

CDC, https://www.cdc.gov/rmsf/stats/index.html (accessed 6/21/21)

Risk Factors for Fatal RMSF ('99-'07)

- Native Americans
- Age extremes: 5-9, 70+
- Use of chloramphenicol (not doxycycline)
- Delay in diagnosis:
  - Treatment after 5 days illness
- Immunosuppression

Am J Trop Med Hyg 2012;86:713-9

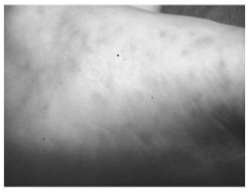
Rocky Mountain Spotted Fever Signs and Symptoms

Fever	99%
Headache	91%
Rash	88% (49% first 3 days)
Myalgia	83%
Nausea/vomiting	60%
Abdominal pain	52%
Conjunctivitis	30%
Stupor	26%
Edema	18%
Meningismus	18%
Coma	9%

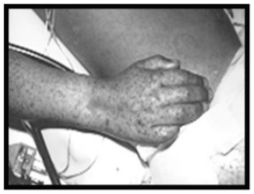
Adapted from Helnick CG et al. *J Infect Dis* 150:480, 1984

Rocky Mountain Spotted Fever

Early: rash absent or maculopapular
Starts on extremities



Later rash: petechial



Fulminant RMSF Gangrenous features (usually seen with multi-organ Failure)

RMSF diagnosis and treatment

- Start treatment upon suspicion: DON'T WAIT
- Labs: leukocytosis, thrombocytopenia, transaminitis
- Dx:
  - Preferred:
    - Skin bxp immunohistochemistry (DFA): timely diagnosis, ~70% sensitive.
    - PCR: *R. rickettsii*-specific
      - Skin bxp or swab (not routinely available, contact local health department → CDC)

RMSF diagnosis and treatment

- Other diagnostics
  - Culture: cell culture-based (BSL3 agent)
  - Serology: obtain acute/convalescent samples
    - Not usually of timely clinical value.
    - IFA : gold standard; cross reacts w/ other SFG species.
      - May be helpful in confusing cases.
    - Caveats: DON'T USE AS SCREENING TEST
      - False positives (especially IgM) common
        - Georgia blood donor study 11.1% IgG > 1:64, but of these only 28% fit case definition for Spotted Fever Group rickettsiosis [Straily A, JID 2020;221:1371]
        - Single IgG titer insufficient for reliable diagnosis
      - Background seroprevalence up to 20% in some regions, e.g., Carolinas
        - Asx infection likely common
      - Both RMSF IgM & IGG can persist
        - May mislead diagnosis, cause necessary treatment

OUTCOME: RMSF ACCORDING TO THE DAY DOXYCYCLINE STARTED

	% mortality
Day 1-5	0
Day 6	33
Day 7-9	27-50

Most lethal of Rickettsial infections: "Black measles"
In US mortality with treatment ~2-5% (higher with delays)

Clin Infect Dis 2015; 60:1659-66

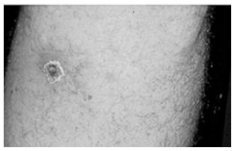
Question #2:

31M from Tidewater region of Virginia presents in June with three days of fever and rash.

Exam: unremarkable but T39.2°C, discrete black eschar on leg, scattered maculopapular rash elsewhere

Which of the following is the most likely etiologic agent?

A. Rickettsia rickettsii
B. Ehrlichia chaffeensis
C. Rickettsia parkeri
D. Anaplasma phagocytophilum
E. Rickettsia akari

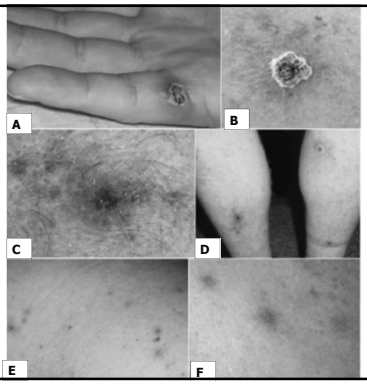


"American Boutonneuse Fever" Rickettsia parkeri

- Transmission: Lone Star or Gulf Coast ticks (*A. maculatum*)
  - Southeastern US, Gulf Coast
- AKA "Maculatum fever"
  - Also seen in Southern South America including Argentina, Uruguay, parts of Brazil
- Symptoms
  - Headache, myalgia
  - Skin
    - Faint salmon-colored rash
    - Single or multiple eschars
- Diagnosis
  - Spotted fever group serology,
  - Immunohistochemistry
  - PCR or culture from skin bxp or swab of eschar

MMWR Morb Mortal Wkly Rep 2016; 65(28): 718-9
Kelman, Infection 2018;46(4):559-563

Examples of R. parkeri-associated rashes



Source: CDC
CID 2008; 47:1188-96

Darker color: Gulf Coast tick range; lighter color: Lone star tick; Red dots: R. parkeri

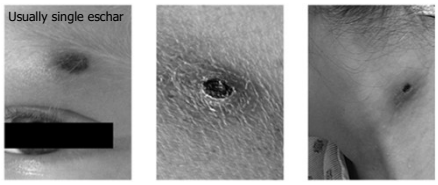
Pacific Coast Tick Fever

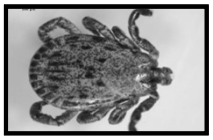
Rickettsia philippii (Rickettsia 364D)
Described in 2008

Transmitted by Pacific Coast tick (*Dermacentor occidentalis*)

Northern Baja → Southern Oregon, Most cases

Common symptoms:
Eschar
Fever
Headache





Dermacentor occidentalis

Pladgett K
PLOS Neg Trop Dis 2016

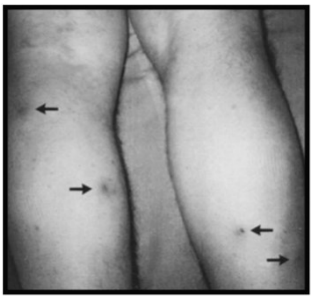
Question 3

28F presents 8d after from a safari in Tanzania
Fever, mild headache, fatigue x 5d
Prior to travel, immunized against yellow fever
Took malaria prophylaxis: atovaquone/proguanil

Temperature is 38.6º, P76, R14, BP 116/70
Exam is unremarkable except for four punctuate eschars on the legs and bilateral inguinal lymph node enlargement

Lab:
Thick and thin blood smears (x 2) negative

Four Inoculation Eschars (Arrows)



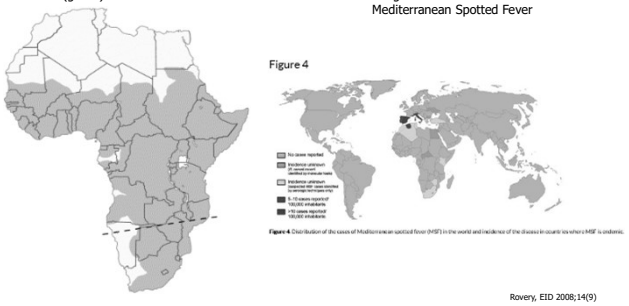
Question #3 Continued:

Which Of The Following Is The Most Likely Etiologic Agent?

A. Rickettsia conorii
B. Rickettsia africae
C. Rickettsia rickettsii
D. Anaplasma phagocytophilum
E. Ehrlichia chaffeensis

Range of R. africae
African Tick Bite Fever
(green)

Range of R. conorii
Mediterranean Spotted Fever



Rovery, EID 2008;14(9)

Clinical Characteristics of R. africae Infection

	%
fever ≥ 38.5º	88
neck muscle myalgia	81
inoculation eschars	95
multiple eschars	54
lymphadenopathy	43
rash (vesicular)	46(45)
death	0

Raoult D, et al. N Engl J Med 2001; 344:1504-10

African Tick Bite Fever

- Seroprevalence:
  - High in residents, R. africae, 30-56%
- Amblyomma ticks (cattle, ungulates)
  - Clusters of cases, multiple eschars
- Incubation period 6-7d
- Dx:
  - Biopsy or swab: PCR or MIFA
  - Serology
- Rx: doxycycline
- Complications unusual

Rickettsioses and The Returning Traveler
Common Cause of Fever After Malaria, Typhoid

Most common
- R. africae (88%)

Others
- Murine typhus (~ 3%)
- Mediterranean spotted fever
- Scrub typhus

Occasional
- RMSF, epidemic typhus, N. Asian or Queensland tick typhus

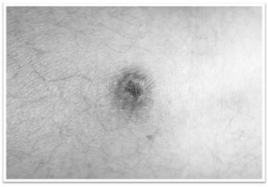
Jensenius M, CID, 2004; 39: 1493-9
Inter J Infect Dis 2004; 8: 139

Question #4:

48M presents in October with fever and rash

Supervisor for apartment bldg in Queens, NY. Lives in cellar apt.

Exam: T 39^{0}C
brown-black 8mm eschar on RLE
~30 papulovesicular lesions on trunk



Question #4:

Which of the following Is the most likely etiologic agent?

A. R. rickettsii
B. R. parkeri
C. R. akari
D. R. conorii
E. Borrelia recurrentis

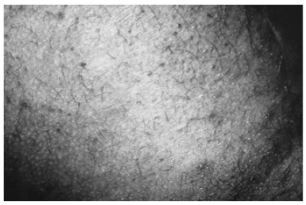
Rickettsialpox

Organism
- R. akari

Reservoir
- House mouse

Vector
- Mouse mites

Clinical
- Single eschar
- Rash: papulovesicular (20-40) or maculopapular
- Diagnosis
  - PCR swab eschar/vesicle
- Treatment: doxycycline



Maculopapular rash due to R. akari (CDC)

Partial DDx of Vesicular Rash

HSV
VZV
Pox viruses
Rickettsialpox
African tick bite fever
Queensland tick typhus

Scrub Typhus

"Scrub typhus is probably the single most prevalent, under-recognized, neglected, and severe but easily treatable disease in the world"

Paris DH et al. Am J Trop Med Hyg 2013;89:301-7

Scrub Typhus

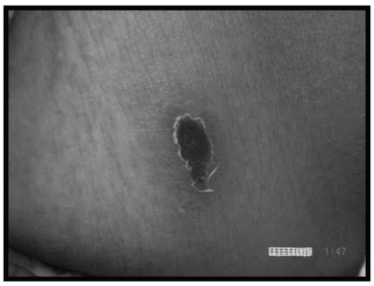
Organism
- O. tsutsugamushi (> 70 strains)

Vector
- Trombiculid mite (chiggers)

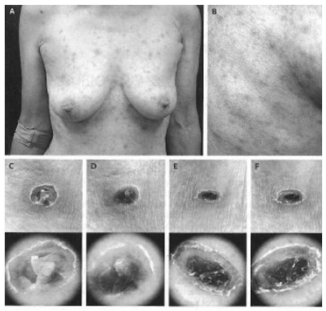
Geography
- Triangle from Japan to Eastern Australia to Southern Russia (rural)
  - Southern China an endemic focus (Yunnan province)

Clinical
- ~1 million cases/yr
- Severe (~ 35%) high fever
- Eschar, painful/draining lymph nodes, rash, delirium
  - Meningitis and meningoencephalitis with progressive infection
  - Development of multiorgan system failure
  - Case fatality rates up to 70%

Treatment
- Doxycycline x 7 days, relapses common
  - Alt: azithromycin (AAC 2014;58:1488-93)



Eschar is often associated with regional lymphadenitis



Question #5:

31M presents in January with 3d fever, HA, malaise, and myalgia.

Works as counselor at wilderness camp in Pennsylvania.

Flying squirrels common at camp including residing in the walls of his cabin.

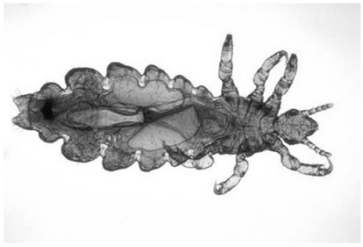
Exam is notable only for fever (39.6^0; no rash), tachycardia (P110)

A diagnostic test for which of the following is most likely to be positive

A. Murine typhus
B. Epidemic typhus
C. RMSF
D. Tularemia
E. Relapsing fever

If I say “flying squirrel”
You say “epidemic typhus” or
“R. prowazekii”

MMWR 2003; 9 (10); Lancet Infec Dis 2008;8(7):417
- Rare infection in US (1976-2001, 39 cases)
- Generally East Coast
- None with louse exposure (the classic vector), so not “epidemic” but sporadic
- Most with flying squirrel exposure (Glaucomys volans)



Body louse: infestation = pediculosis
Pediculus humanus humanus

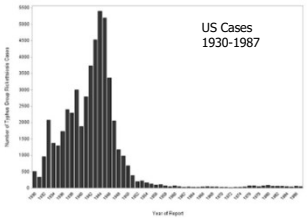
Typhus: Two Forms

	Epidemic	Endemic
Organism	***R. prowazekii***	***R. typhi***
Vector	Louse (body, head)	Flea (rat, cat)
Who	War refugees, crowded conditions/poor hygiene	Worldwide (U.S. Southern California, Texas, Hawaii)
Severity	Lethal	Mild
Treatment	Tetracycline Doxycycline Chloramphenicol	Tetracycline Doxycycline Chloramphenicol
Prevention	Boil clothes, delouse (lindane, malathion, permethrin, DDT)	Flea prevention (cats, domestic animals) Reduce rodent population
Recrudesce	Brill-Zinsser Disease (years-decades)	None known

Murine (or endemic) typhus

- In US, mostly seen in California, Hawaii, and Texas
- Infected flea feces → skin
- Most don't recall fleabite
- Usually non-specific febrile infection
  - Likely quite underdiagnosed
  - ~50% with rash
  - Occasional severe disease:
    - Meningoencephalitis
    - Pneumonitis
    - Shock

Historically, decline w/ better sanitation
No longer reportable since 1987 (Outbreak LA County 2018)



Dittrich, Lancet Global Health 2015;3:e104; Blanton Am J Trop Med 2017;96(1):53

CDC, accessed 7/10/2020 https://www.cdc.gov/typhus/murine/history.html

Murine (or endemic) typhus

- Dx:
  - Serology *R. typhi* (IFA)
    - Acute/convalescent, 4x rise
    - Cross-reacts with R. prowazekii and SFG rickettsia
  - PCR
    - Blood, often negative
- Treatment: No RCTs
  - Doxycycline (preferred)
    - Azithromycin: recent open label trial found azithromycin inferior to doxy
  - Alternatives: limited data
    - Chloramphenicol
    - Levofloxacin
    - Ciprofloxacin

Dittrich, Lancet Global Health 2015;3:e104; Blanton Am J Trop Med 2017;96(1):53

Newton, CID 2019;68(1 March):739

Other location-specific tick-borne Rickettsioses: partial

- Queensland tick typhus, *R. australis*
  - Australia-Queensland, New South Wales, Tasmania, coastal areas of eastern Victoria
- North Asian tick fever, *R. sibeirica*
  - North China; Mongolia; Asiatic areas of Russia
- Tick-borne lymphadenopathy (TIBOLA) or *Dermacentor*-borne necrosis erythema and lymphadenopathy (DEBONEL), ascribed to *R. slovaca* or *R. raoulti:*
  - Europe and Asia.
- Far-Eastern tick-borne rickettsiosis, *R. beilongjiangensis:*
  - Far East Russia and northern China.
- Oriental spotted fever, *R. japonica:*
  - Japan.
- Thai tick typhus, *R. bonei:*
  - Thailand, Australia, Tasmania, Flinders Island
- Australian spotted fever:
  - *R. marmionii*, Australia.

Question #6:

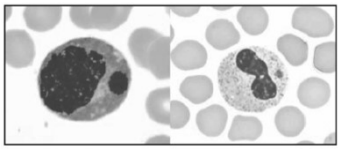
- 43F visited southern Missouri on vacation, returns 7d later with fever, headache and diffuse myalgia x 3d
- Physical examination: no findings
- Laboratory evaluation :
  - WBC: 2.1/mm³ (80% PMNs, 10% lymphocytes, 8% monocytes
  - Hemoglobin: 7.0 g/dL, hematocrit: 24%
  - Platelets: 105,000/mm³
  - AST: 364 U/L, ALT: 289 U/L
  - renal function: normal

Question #6

Which of the following is the most likely etiologic agent?

A. Anaplasma phagocytophilum
B. Ehrlichia chaffeensis
C. Borrelia hermsii
D. Babesia divergens
E. Borrelia burgdorferi

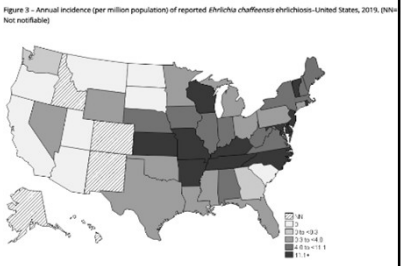
Morulae



HME HGA

Human Monocytic Ehrlichiosis (HME)

- E. chaffeensis
- Vector: Lone star tick
- Rash: ~30%
  - Maculopapular or petechial
- Labs: LFTs ↑, leukopenia, thrombocytopenia
- Mortality 2.7%
- Diagnosis
  - PCR
  - Morulae (2-38%)
  - Serology: acute/convalescent
  - Treatment: doxycycline



Source: CDC (accessed 7/10/22)

Human Granulocytic Anaplasmosis

- Anaplasma phagocytophilum
- Vector: Ixodes scapularis
- Rash rare
- Labs: LFTs, leukopenia, thrombocytopenia
- Mortality 0.3-0.7% (immunosuppressed ↑ 16 x)
- Diagnosis: same as HME (but morulae seen > 25%)

Geography: cross reactivity with HME accounts For most Southern state representation

Source: CDC (accessed 7/10/22)

Other Ehrlichia (less common)

Organism	Vector	Geography	Risk	Mortality
E. ewingii (a canine ehrlichia)	Lone star	Most cases in Southcentral US	Immune compromised	Low
E. muris	*Ixodes persulcatus* *H. flava*	Europe, Russia, Japan, West Coast US	Older patients	Low
Ehrlichia muris eauclairensis (former Ehrlichia muris-like agent)	Deer tick	Wisconsin, Minnesota	Elderly, immune compromised	Low

Question #7:

- 48F c/o headache and fatigue worsening over 2 months since May tick bite
  - PMH: negative
  - SH: Married, works from home, has a dog, resides in suburban eastern PA
  - Treated with doxycycline for Lyme disease, no benefit
- Physical examination: afebrile, normal vital signs, no findings

- Laboratory evaluation :
  - WBC: 7.0 cells/mm³ (70% PMNs, 18% lymphocytes, 12% monocytes
  - Hemoglobin: 11.8 g/dL, hematocrit: 35%
  - Platelets: 145,000/mm³
  - ALT: 22 U/L
  - Babesia IgG 1:128 (positive ≥ 1:64)
  - Blood smear: no parasites

Question #7:

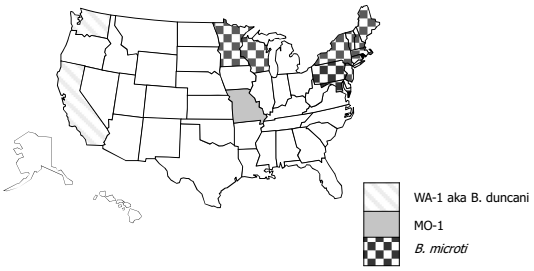
- The best recommended next step:

A. Check Babesia duncani serology
B. Check Babesia PCR
C. Repeat blood smear
D. Azithromycin + atovaquone for 7-10 days
E. None of the above

Babesia spp: Global

Vannier et al, NEJM 2012 366;2397

Babesiosis: USA



Babesia species

- Malaria-like parasite, resides in RBCs
- Geography: Babesia microti (most common in U.S.)
  - Nantucket, Martha's Vineyard, Long Island, Mid-Atlantic/New England, upper Midwest (similar to Lyme disease)
- > 1700 cases per year (2014 data)
  - Range of illness: "flu-like" to fatal
- Reservoir, vector
  - White-footed mouse;
  - Tick transmission: Ixodes scapularis
- Severe disease risks:
  - asplenic, HIV, chemotherapy, age >55, transplant
- Pearl: most common cause of blood transfusion-related infection in US
  - Though decreasing through screening

Severe Babesiosis

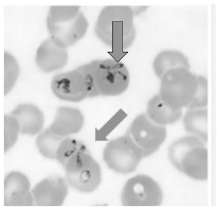
- n=34, Long Island NY
- Clinical manifestations
  - 41% Multi-organ failure
    - ARDS, DIC, CHF, ARF
  - 3 deaths
- Risk factors:
  - age >60
  - splenectomy,
  - immunosuppression (e.g., HIV, rituximab)
- Labs
  - increased LTFs,
  - thrombocytopenia
  - anemia (Hb<10),
  - parasitemia (>10%)

Mortality in immunocompromised > 20%

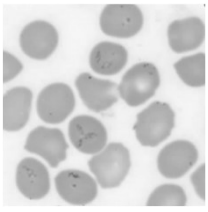
Hatcher JC, et al. Clin Infect Dis 2001; 32:1117-25

Babesiosis: Smear Diagnosis

Maltese Cross Tetrads



Species level identification only by PCR



Diagnosis of Babesiosis

- May observe hemolysis
- Wright-Giemsa stained thin blood smears
  - 1-3μ intraerythrocytic merozoites
    - Parasitemia range: 0-80% (may be confused with malaria)
    - Maltese cross: diagnostic (not seen w/ malaria)
    - Quick, if technical expertise available
- PCR: now widely available
  - Highly specific, but often send-out test = delay
- Serology (IFA)
  - High titer or acute/convalescent c/w active or recent infection
    - Low titer, negative smear: don't treat!

Treatment of Babesiosis

- Severe (2020 IDSA guidelines)
  - Atovaquone 750 mg PO q12h +Azithromycin 500 mg IV q24h
    - Previous: quinine + clindamycin (now an alternative)
  - Duration: 7-10d (may require longer for persistent parasitemia or immunosuppressed)
- Blood exchange transfusion: severe only
  - B. divergens, many require
  - B. microti, some cases
  - Limited evidence for benefit
    - Severe hemolytic anemia or multi-organ failure
- Mild-moderate severity
  - Azithromycin PO plus atovaquone PO

Krause, et al CID 2021; 72 (2) e49-65

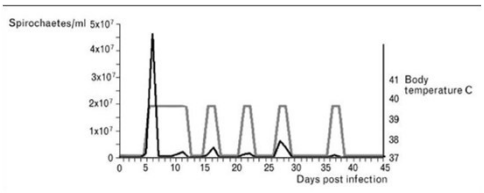
Tickborne Relapsing Fever US

Borrelia spp. (mainly B. hermsii)
- Ornithodorus soft ticks (brief, painless)

Epidemiology
- Western states; 14-45 cases/yr
- Rustic housing and rodents
- Elevation 1500-8000 feet

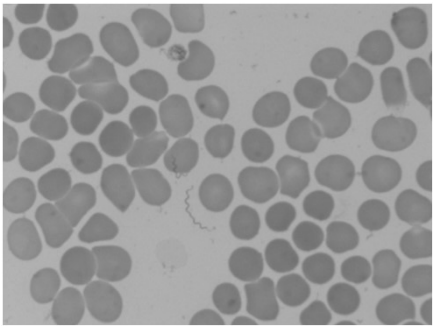
Clinical Manifestations
- Fever (relapsing), HA, myalgia, N/V
  - Can be severe : ARDS
- Laboratory
  - AKI, ↓ platelets,
- **Rx: PCN, doxycycline**
  - Jarisch Herxheimer reaction in 54%

MMWR 2012;61:174-6



Relapsing Fever: recurrent bacteremia (black line) correlates with sudden fever (grey).

After initial bacteremia, relapses are lower and fever duration somewhat shorter.



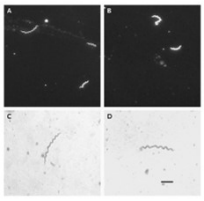
Diagnosis: observation of spirochetes in blood film, PCR

Louse-borne Relapsing Fever (LBRF)

Organism:	Borrelia recurrentis
Vector:	Human body louse
Geography:	Worldwide, but now seen in Sudan, Ethiopia, Somalia, Bolivia… (Refugee camps, famine, natural disasters)
Clinical Illness	More severe than TBRF, (incl. jaundice)
Therapy	Doxycycline

Newer Borrelia species: B. miyamotoi

- Unusual vector: Ixodes ticks (larvae?)
- Epidemiology = Lyme disease
- Appears similar to HGA
  - Meningoencephalitis in immunocompromised
  - ↓ wbc, ↓ plt, ↑ LFTs
- Diagnosis: blood smear (observing spirochetes), PCR, serology
- Treatment: similar to Lyme disease

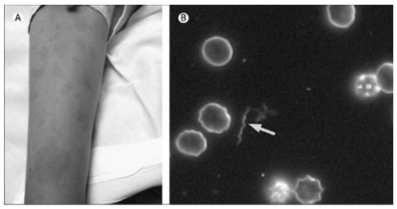


Spirochetes in CSF

Gugliotta, NEJM 2013

Telford, Clin Microbiol Infect 2015

Borrelia mayonii



5 of 6: acute febrile illness with rash (macular)
1 of 6: 1 months knee pain/swelling
To date: only see in in Minnesota and Wisconsin

Pritt et al. Lancet ID 2016;16(5):556

Cluster of Tick Paralysis Cases

- Four cases within 20 miles of each other
  - Ages 6, 58, 78, 86 years
- Ticks on neck or back
  - Usually dog ticks or Rocky Mt wood ticks
- Ascending motor paralysis without sensory loss
- Treatment: remove tick = cure
- Pathogenesis: neurotoxin in tick saliva

MMWR 2006; 55: 933-5

Question #8:

A 59 y.o. man from Missouri presents with fever (39^0), headache, myalgia, anorexia, nausea, one week after removing an engorged tick from his groin. No travel.

Exam: unremarkable except ill appearing, no rash.
Lab: wbc 2300 plt 42,000 ALT 111

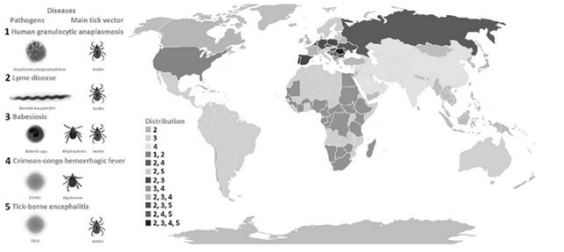
Suspect ehrlichiosis (but no morulae on blood smear)

Question #8:

After sending appropriate diagnostic tests the patient has not improved after three days of doxycycline. Which of the following is the most likely etiologic agent?

A. R. rickettsii
B. B. burgdorferi
C. R. parkeri
D. Heartland virus
E. Severe fever with thrombocytopenia syndrome virus

But wait: There's More (#4) and More (#5)



Front Cell Infect Microbiol, 2017;7:114

Tick-borne infections: some testable points

- Rash: RMSF rash appears after several days of fever and viral-like prodrome
  - Meningococcal rash is earlier
  - No bite site (tache noire)
  - Give doxycycline, even for kids
- Blood smear maybe helpful
  - Morulae: PMN = Anaplasma, Monocyte = Ehrlichia
  - Spirochete: relapsing fever Borrelia or B. miyamotoi
  - Erythrocyte inclusions: Babesia

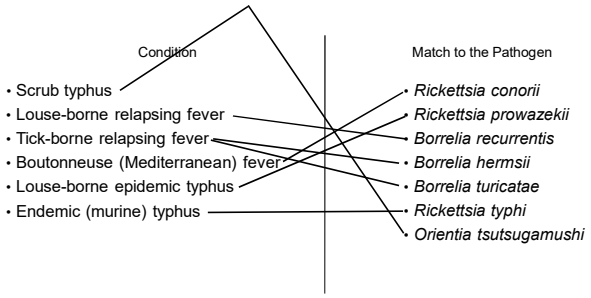
Tick-borne infections: some testable points?

- Babesia:
  - Most common cause of blood transfusion infection in US
  - Splenectomy or immunocompromise = risk severe infection risk
- Co-infections in the US: may complicate some infections especially after black-legged tick (*I. scapularis)* bite
  - Lyme disease + Babesia OR Lyme disease + HGA mostly
- Flying squirrels: epidemic typhus
- Rodent infested urban house: Rickettsialpox
  - Mouse mites. Tache noire first → > dozen papules/vesicles

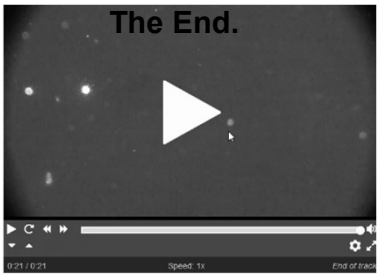
Key features of select tick, louse, and mite-borne diseases

Disease	Usual Organism	Geography	Eschar	Rash	High fever	Comment
TICK-BORNE						
RMSF	R. rickettsii	N,C,S .America	No	Yes	Yes	Serious
STARI	Unknown	S, SC, MA	No	Yes (EM)	No	Mild
R. parkeri	R. parkeri	Gulf, South, Atlantic	Yes (≥1)	Yes	No	
African tick bite fever	R. africae	Sub-Saharan Africa	Yes (≥1)	Yes	No	Mild
HME	E. chaffeensis	S, SC, MA	No	Yes (+/-)	Yes	Cytopenias Transaminitis
HGA	A. phagocytophilum	NE, NY, MA, MW	No	Yes (+/-)	Yes	Cytopenias Transaminitis
Babesiosis	B. microti	NE, NY, MA, MW	No	Yes (+/-)	Yes	
TBRF	B hermsii	W Mountains	No	No	Yes	Spirochetes in blood smear
LOUSE-BORNE						
Epidemic typhus	R. prowazekii	Worldwide	No	Yes	Yes	War, refugee camps serious
MITE-BORNE						
Rickettsialpox	R. akari	Worldwide	Yes (1)	Yes (V)	No	Mouse exposure
Scrub typhus	O. tsutsugamushi	India, Asia, N. Australia	Yes	Yes	Yes	Serious

C	**Central**	**NY**	**New York**
EM	**Erythema Migrans**	**RMSF**	**Rocky Mountain Spotted Fever**
HGA	**Human Granulocytic Anaplasmosis**	**S**	**South**
HME	**Human Monocytic Ehrlichiosis**	**SC**	**South Central**
MA	**MidAtlantic**	**SE**	**Southeast**
MW	**Mid-West**	**STARI**	**Southern Tick Associated Rash Illness**
N	**North**	**TBRF**	**Tick-borne Relapsing Fever**
NE	**New England**	**V**	**Vesicular**
		W	**West**



Thank You! and The End.



B. mayonii Spirochete in Culture

Pritt, Clin Micro and Inf 2022

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Worms and More Worms

Dr. Edward Mitre

INFECTIOUS DISEASE BOARD REVIEW AUGUST 20-24 2022

Worms and More Worms

Edward Mitre, MD
Bethesda, MD

7/25/2022

INFECTIOUS DISEASE BOARD REVIEW AUGUST 20-24 2022

Disclosures of Financial Relationships with Relevant Commercial Interests

- **None**

What are helminths?

What are helminths?

The most complex and fascinating organisms that routinely infect people

Pathogenic Helminths

Eukaryotic, multicellular animals

----- phylum Platyhelminths -----

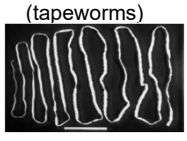
TREMATODES (flukes)

CESTODES (tapeworms)

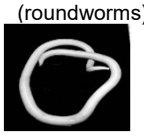
--Its own phylum!!--

NEMATODES (roundworms)

Fasciolopsis



Taenia



Ascaris

Images CDC DPDx

How helminths differ from other pathogens

- **eukaryotic, multicellular organisms**
- **often have complex lifecycles**
- **long lifespans (often for years)**
- **induce Th2 responses with eosinophilia and IgE**
- **with few exceptions*, DO NOT MULTIPLY WITHIN HOST**

(* Strongyloides, Paracapillaria, Hymenolepis)

World Prevalence

Ascaris	> 400 million
Trichuris	> 200 million
Hookworm	> 200 million
Schistosoma	> 150 million

http://ghdx.healthdata.org/gbd-data-tool

But very low ID Boards prevalence

5% of questions are on helminths, protozoa, travel medicine, and ectoparasites

Question #1

28 yo F presents with recurrent crampy abdominal pain for several months. She recently returned to the U.S. after living in Tanzania for two years. Colonoscopy reveals small white papules. Biopsy of a papule reveals an egg with surrounding granulomatous inflammation.

Most likely diagnosis?

A. *Entamoeba histolytica*
B. *Strongyloides stercoralis*
C. *Wuchereria bancrofti*
D. *Schistosoma mansoni*
E. *Paragonimus westermani*

Major Helminth Pathogens

TREMATODES

Blood flukes
- *Schistosoma mansoni*
- *Schistosoma japonicum*
- *Schistosoma haematobium*

Liver flukes
- *Fasciola hepatica*
- *Clonorchis sinensis*
- *Opisthorchis viverrini*

Lung flukes
- *Paragonimus westermani*

Intestinal flukes
- *Fasciolopsis buski*
- *Metagonimus yokagawai*

CESTODES

Intestinal tapeworms
- *Taenia solium*
- *Taenia saginata*
- *Diphyllobothrium latum*
- *Hymenolepis nana*

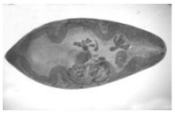
Larval cysts
- *Taenia solium*
- *Echinococcus granulosus*
- *Echinococcus multilocularis*

NEMATODES

Intestinal
- *Ascaris lumbricoides*
- *Ancylostoma duodenale*
- *Necator americanus*
- *Trichuris trichiura*
- *Strongyloides stercoralis*
- *Paracapillaria philippinensis*
- *Enterobius vermicularis*

Tissue Invasive
- *Wuchereria bancrofti*
- *Brugia malayi*
- *Onchocerca volvulus*
- *Loa loa*
- *Trichinella spiralis*
- *Angiostrongylus cantonensis*
- *Anisakis simplex*
- *Toxocara canis/cati*
- *Baylisascaris procyonis*
- *Gnathostoma spinigerum*

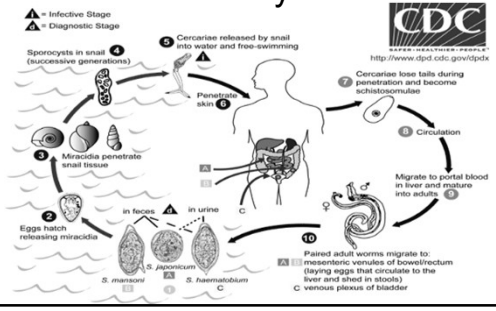
Trematodes (flukes)



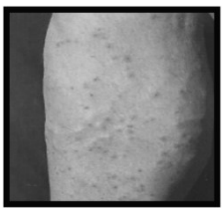
Paragonimus (CDC DpDx)

- flat, fleshy, leaf-shaped worms
- usually have two muscular suckers
- usually hermaphroditic (except Schistosomes)
- require intermediate hosts (usually snails or clams)
- praziquantel treats all (except *Fasciola hepatica*)

Schistosomiasis life cycle



Acute Schistosomiasis (Cercarial dermatitis or Swimmer's Itch)



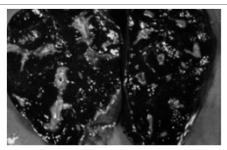
Urticarial plaques and pruritic papules upon reexposure to cercariae penetrating skin in a sensitized individual.

Can occur in response to human or avian schistosomes.

Acute Schistosomiasis: Katayama Fever

- Occurs in previously unexposed hosts.
- Occurs at onset of egg-laying (3-8weeks)
- Symptoms: fever, myalgias, abdominal pain, headache, diarrhea, urticaria
- Eosinophilia, ↑ AST, ↑ alkaline phosphatase
- **No reliable way to confirm the diagnosis acutely as serology and stool O/P frequently negative.**

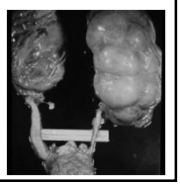
Schistosomiasis



Chronic disease
→ granulomatous colitis (*S. mansoni*)
→ portal hypertension (*S. mansoni*)

→ granulomatous cystitis *(S. haematobium)*
→ bladder fibrosis and cancer *(S. haematobium)*
→ obstructive uropathy (S. haematobium)

→ CNS disease (eggs to brain/spinal cord, esp *S. japonicum*)



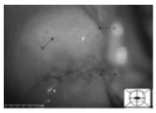
Schistosomiasis

Chronic genital disease
increasingly recognized
primarily due to *S. haematobium*

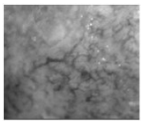
men
- epididymitis
- prostatitis

women (see vaginal and cervical lesions)
- pelvic pain
- dysmenorrhea
- dyspareunia
- post-coital bleeding
- endometritis/salpingitis

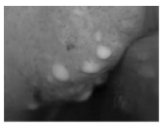
sand grains



sandy yellow patches



abnormal vessels



rubbery papules

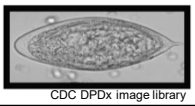
WHO Female Genital Schistosomiasis Pocket Atlas

Schistosome eggs

S. mansoni
(lateral spine)

CDC DPDx image library

S. haematobium
(terminal spine)



CDC DPDx image library

Major Helminth Pathogens

TREMATODES

Blood flukes
Schistosoma mansoni
Schistosoma japonicum
Schistosoma haematobium

Liver flukes
Fasciola hepatica
Clonorchis sinensis
Opisthorchis viverrini

Lung flukes
Paragonimus westermani

Intestinal flukes
Fasciolopsis buski
Metagonimus yokagawai

CESTODES

Intestinal tapeworms
Taenia solium
Taenia saginata
Diphyllobothrium latum
Hymenolepis nana

Larval cysts
Taenia solium
Echinococcus granulosus
Echinococcus multilocularis

NEMATODES

Intestinal
Ascaris lumbricoides
Ancylostoma duodenale
Necator americanus
Trichuris trichiura
Strongyloides stercoralis
Paracapillaria philippinensis
Enterobius vermicularis

Tissue Invasive
Wuchereria bancrofti
Brugia malayi
Onchocerca volvulus
Loa loa
Trichinella spiralis
Angiostrongylus cantonensis
Anisakis simplex
Toxocara canis/cati
Baylisascaris procyonis
Gnathostoma spinigerum

Fasciola hepatica (a liver fluke)

→acquired by eating encysted larvae on aquatic vegetation (e.g. water chestnuts)

→fluke migration through the liver: RUQ pain and hepatitis

→arrive at biliary ducts in liver and mature over 3-4 months

→can induce biliary obstruction

Dx: eggs in stool exam (low sensitivity), serology

Rx: triclabendazole (FDA approved in 2019!)
(***note: the only trematode that don't respond well to praziquantel)

Clonorchis sinensis

"Chinese Liver Fluke"

- eggs→snails→freshwater fish
- Acquisition by ingestion of undercooked fish
- Flukes develop in duodenum then migrate to liver bile ducts
- Can live for 50 years, making 2000 eggs/day

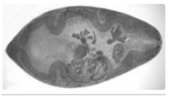
Opisthorchis viverrini

"Southeast Asian Liver Fluke"

- similar lifecycle
- also acquired by eating fish

Both can cause
biliary obstruction
cholelithiasis
cholangiocarcinoma

Paragonimus westermani
"lung fluke"



CDC

eggs→snails→freshwater crabs and crayfish
Ingestion of undercooked seafood
Adults migrate to LUNGS, frequent EOSINOPHILIA
Symptoms:

- *fever, cough, diarrhea during acute migration*
- *later, may have chest pain as worms migrate through lungs*
- *can develop chronic pulmonary symptoms*

Dx: Sputum and/or stool exam for eggs.

NOTE: Cases of Paragonimus kellicotti acquired in U.S. by ingestion of raw crayfish in rivers in Missouri

CID 2009 Sep 15;49(6):e55-61.
Clin Microbiol Rev 2013 Jul;26(3):493-504

Question #2

A 25 yo Peace Corps worker in Madagascar reports passing thin, white, flat tissue fragments in her stool. The microbiology lab reports the tissue fragments are proglottid segments of *Taenia solium*.

A long-term complication that can occur as a result of infection with the larval form of this parasite is:

A. HTLV-1 infection
B. bladder cancer
C. appendicitis
D. liver abscess
E. seizures

Major Helminth Pathogens

TREMATODES

Blood flukes
- *Schistosoma mansoni*
- *Schistosoma japonicum*
- *Schistosoma haematobium*

Liver flukes
- *Fasciola hepatica*
- *Clonorchis sinensis*
- *Opisthorchis viverrini*

Lung flukes
- *Paragonimus westermani*

Intestinal flukes
- *Fasciolopsis buski*
- *Metagonimus yokagawai*

CESTODES

Intestinal tapeworms
- *Taenia solium*
- *Taenia saginata*
- *Diphyllobothrium latum*
- *Hymenolepis nana*

Larval cysts
- *Taenia solium*
- *Echinococcus granulosus*
- *Echinococcus multilocularis*

NEMATODES

Intestinal
- *Ascaris lumbricoides*
- *Ancylostoma duodenale*
- *Necator americanus*
- *Trichuris trichiura*
- *Strongyloides stercoralis*
- *Paracapillaria philippinensis*
- *Enterobius vermicularis*

Tissue Invasive
- *Wuchereria bancrofti*
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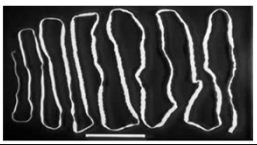
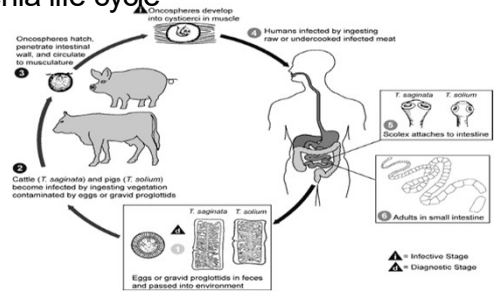
- *Onchocerca volvulus*
- *Loa loa*
- *Trichinella spiralis*
- *Angiostrongylus cantonensis*
- *Anisakis simplex*
- *Toxocara canis/cati*
- *Baylisascaris procyonis*
- *Gnathostoma spinigerum*

Cestodes (tapeworms)

- all except *D. latum* have suckers with surrounding hooklets on the scolex (head) to attach to intestinal lining
- have flat, ribbon-like bodies composed of proglottid segments which contain reproductive organs
- have no digestive systems (food absorbed through soft body wall of worm)



Taenia life cycle



INTESTINAL TAPEWORMS

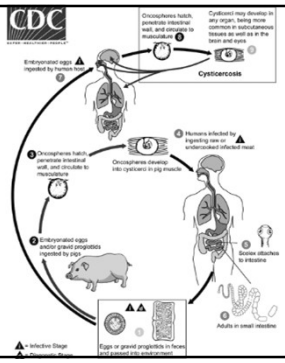
Taenia solium
tapeworm is acquired by eating larvae in pork
adult tapeworm causes few symptoms

Taenia saginatum
acquired by eating larvae in undercooked beef
causes few symptoms
can grow to 10 m

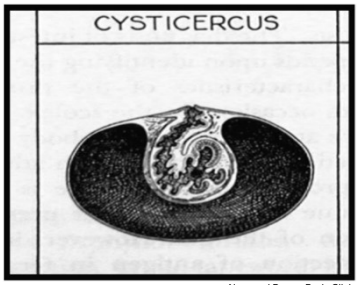
Diphyllobothrium latum *(can grow > 10 m)*
acquired by ingesting fish with larvae
***B12 deficiency in up to 40% of patients**

Dx: eggs/proglottids in stool **Rx**: praziquantel (not FDA-approved)

For some cestodes, humans can be infected by the larval stages and this can cause severe pathology.

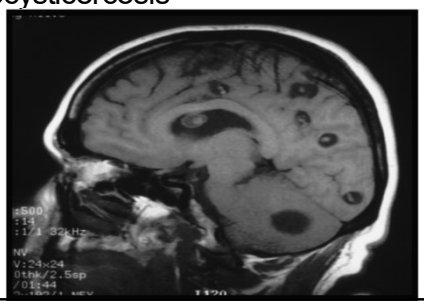


Cysticercus: a fluid filled bladder containing the invaginated head (scolex) of the larval form of a tapeworm.



Neva and Brown, Basic Clinical Parasitology 6th Edition

Neurocysticercosis



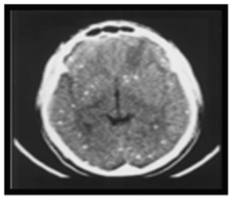
Neurocysticercosis

Can cause:

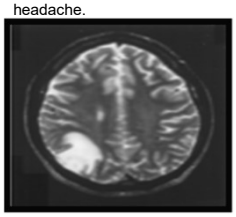
- seizures
- hydrocephalus
- headaches
- focal neurologic deficits

Neurocysticerosis

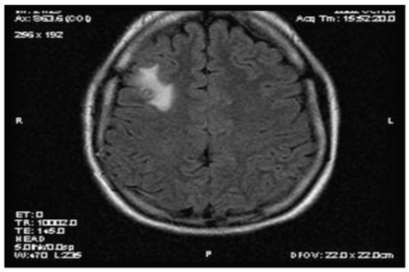
Multiple old calcifications



Perilesional edema – typically occurs around dying cysts and is a frequent finding on initial presentation of seizure or terrible headache.



Cysticercosis – single lesion disease is diagnostic challenge



Neurocysticercosis

Diagnosis:

Definitive = tissue biopsy
- multiple cystic lesions each with scolex on imaging
- retinal cysticercus seen on fundoscopic exam

Presumptive = suggestive lesions on imaging

Cysticercosis serology → supportive (sensitive if high burden of disease)

Treatment: *Medical therapy decreases risk of future seizures, but has immediate risk of increasing seizures/brain inflammation*

If hydrocephalus or diffuse cerebral edema, treat with steroids and/or surgery, not anti-parasitic therapy

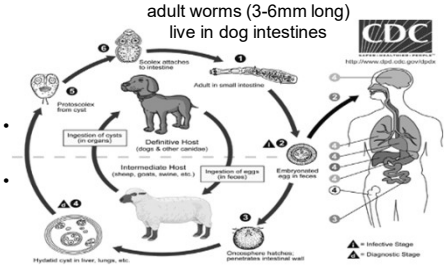
If no increased ICP:
- 1-2 viable cysts → albendazole for 1-2 viable cysts
- > 2 viable cysts → albendazole + praziquantel

AND corticosteroids started before anti-parasitic therapy

****2017 IDSA Guidelines for Diagnosis and Treatment of Cysticercosis****

Echinococcus granulosus

adult worms (3-6mm long) live in dog intestines



humans = accidental hosts

infected by ingestion of eggs in dog feces

Echinococcus granulosus

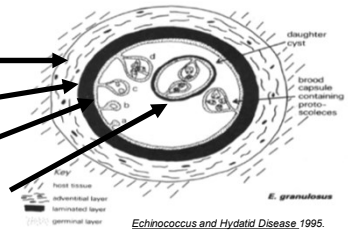
hydatic cyst = "watery vessel"

surrounding inflammatory response of fibrosis and chronic inflammation

outer acellular laminated layer

inner, nucleated germinal layer (PLURIPOTENTIAL TISSUE!)

internal cystic fluid and daughter cysts



Echinococcus and Hydatid Disease 1995.

Echinococcus granulosus - presentation

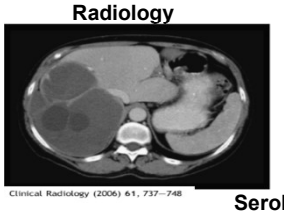
Most cysts (65%) in the liver
25% in the lung, usually in the right lower lobe
Rest occur practically everywhere else in the body

Common presentations
- allergic symptoms/anaphylaxis due to cyst rupture after trauma
- cholangitis and biliary obstruction due to rupture into biliary tree
- peritonitis b/c intraperitoneal rupture
- pneumonia symptoms due to rupture into the bronchial tree

Uncommon presentations
- bone fracture due to bone cysts
- mechanical rupture of heart with pericardial tampanode
- hematuria or flank pain due to renal cysts

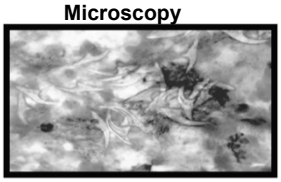
Echinococcus granulosus - diagnosis

Radiology



Clinical Radiology (2006) 61, 737–748

Microscopy



Serology

IgG ELISA about 85% sensitive for liver cysts of E. granulosus

only 50% sensitive in cases of single pulmonary cyst

Echinococcus granulosus – treatment

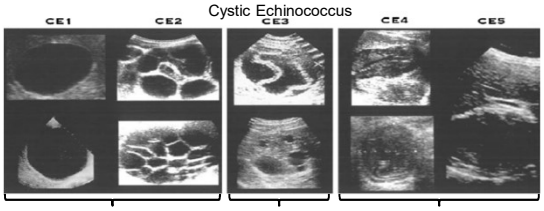
Reasons for not spilling cyst contents

1. Anaphylaxis may occur
2. Spilled protoscoleces can reestablish infection

Typically treat with albendazole for several days before surgery or PAIR (usually 2d-1wk before, and 1-3 months after)

Treatment – WHO Guidelines 2010

Cystic Echinococcus



Acta Tropica 114 (2010) 1–16

ACTIVE		TRANSITIONAL	INACTIVE
Unilocular Simply cyst Cyst wall visible	Multivesicular Multiseptated cysts	Anechoic content Detached membrane Solid matrix	Heterogenous, hypoechoic or hyperechoic No daughter cysts CE5 with thick calfied wall
---PAIR or SURGERY---	---SURGERY---	---SURGERY--- ---PAIR if no solid matrix---	---NO TREATMENT---

Question #3

A 25 yo F from rural Peru presents with shortness of breath, bilateral interstitial infiltrates, fever, loose stools, hypotension, and *E. coli* bacteremia. She has received > 4weeks of high dose corticosteroids and cyclophosphamide for a recent diagnosis of lupus nephritis. Which of the following anthelmintic agents should be included in her treatment regimen:

A. *Albendazole*
B. *Ivermectin*
C. *Praziquantel*
D. *Pyrantel pamoate*
E. *Diethylcarbamazine*

Major Helminth Pathogens

TREMATODES

Blood flukes
- *Schistosoma mansoni*
- *Schistosoma japonicum*
- *Schistosoma haematobium*

Liver flukes
- *Fasciola hepatica*
- *Clonorchis sinensis*
- *Opisthorchis viverrini*

Lung flukes
- *Paragonimus westermani*

Intestinal flukes
- *Fasciolopsis buski*
- *Metagonimus yokagawai*

CESTODES

Intestinal tapeworms
- *Taenia solium*
- *Taenia saginata*
- *Diphyllobothrium latum*
- *Hymenolepis nana*

Larval cysts
- *Taenia solium*
- *Echinococcus granulosus*
- *Echinococcus multilocularis*

NEMATODES

Intestinal
- *Ascaris lumbricoides*
- *Ancylostoma duodenale*
- *Necator americanus*
- *Trichuris trichiura*
- *Strongyloides stercoralis*
- *Paracapillaria philippinensis*
- *Enterobius vermicularis*

Tissue Invasive
- *Wuchereria bancrofti*
- *Brugia malayi*
- *Onchocerca volvulus*
- *Loa loa*
- *Trichinella spiralis*
- *Angiostrongylus cantonensis*
- *Anisakis simplex*
- *Toxocara canis/cati*
- *Baylisascaris procyonis*
- *Gnathostoma spinigerum*

Nematodes (roundworms)

→ Nonsegmented round worms

→ Flexible outer coating (cuticle)

→ Muscular layer under the cuticle

→ Nervous, digestive, secretory, and reproductive systems

How do people get infected with nematodes?

1. Eating eggs in fecally contaminated food or soil
   Ascaris, Trichuris, Enterobius, and Toxocara
2. Direct penetration of larvae through skin
   Hookworms, Strongyloides
3. Eating food containing infectious larvae
   Trichinella, Angiostrongylus, Anisakis
4. Vector transmission
   Wuchereria, Brugia, Oncho, Loa

Intestinal Helminths - Lifecycles

Strongyloides and Hookworms

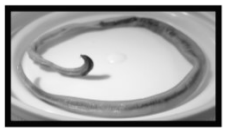
SKIN → LUNGS → GUT

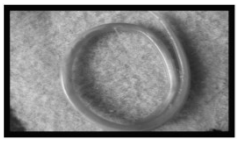
Ascaris

GUT → LIVER → LUNGS → GUT

Ascaris lumbricoides

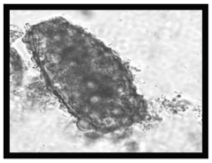
- Large numbers of worms can cause abdominal distention and pain or intestinal obstruction
- can cause "Loeffler's syndrome" - an eosinophilic pneumonitis with transient pulmonary infiltrates
- cholangitis and/or pancreatitis b/c aberrant migration



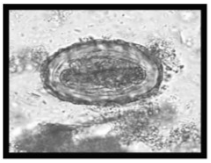


Ascaris lumbricoides - Diagnosis

Will not find eggs until 2-3 months after pulmonary symptoms occur
After 2-3 months, easy to find eggs since females make 200,000/day



Unfertilized



Fertilized CDC DPDx

Rx: albendazole or mebendazole

HOOKWORMS

Ancylostoma duodenale and Necator americanus
also Ancylostoma ceylanicum (zoonotic from dogs/cats in Asia)

- MAJOR cause of ANEMIA and protein loss (b/c plasma loss)
- pneumonitis associated with wheezing, dsypnea, dry cough (usually a few days to weeks after infection)
- urticarial rash
- mild abdominal pain

If sensitized → papulovesicular dermatitis at entry site "ground itch"

If worms migrate laterally → **cutaneous larvae migrans**
(especially dog and cat hookworms, as late as 2-8 wks after exposure to A. braziliense)

Still endemic in the U.S. → 35% of individuals from a rural community in Alabama had *N. americanus* in their stool samples
Am. J. Trop. Med. Hyg., 97(5), 2017, pp. 1623–1628

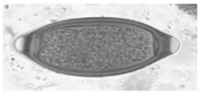
Trichuris trichiura (whipworm)

4cm long nematode

Life cycle: Fecal-oral

In heavy infections:
- loose and frequent stools
- tenesmus
- occ blood to frank blood
- in heavily infected children: rectal prolapse

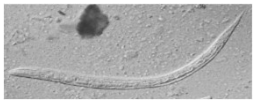
Dx: eggs are football shaped with two polar plugs



CDC DPDx

Strongyloides stercoralis

(can complete lifecycle in host!)



Usual manifestations
GI: mild abdominal/epigastric 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.

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*

Major Helminth Pathogens

TREMATODES	CESTODES	NEMATODES
Blood flukes *Schistosoma mansoni* *Schistosoma japonicum* *Schistosoma haematobium*	Intestinal tapeworms *Taenia solium* *Taenia saginata* *Diphyllobothrium latum* *Hymenolepis nana*	Intestinal *Ascaris lumbricoides* *Ancylostoma duodenale* *Necator americanus* *Trichuris trichiura* *Strongyloides stercoralis* *Paracapillaria philippinensis* *Enterobius vermicularis*
Liver flukes *Fasciola hepatica* *Clonorchis sinensis* *Opisthorchis viverrini*	Larval cysts *Taenia solium* *Echinococcus granulosus* *Echinococcus multilocularis*	Tissue Invasive *Wuchereria bancrofti* *Brugia malayi* *Onchocerca volvulus* *Loa loa* *Trichinella spiralis* *Angiostrongylus cantonensis* *Anisakis simplex* *Toxocara canis/cati* *Baylisascaris procyonis* *Gnathostoma spinigerum*
Lung flukes *Paragonimus westermani*		
Intestinal flukes *Fasciolopsis buski* *Metagonimus yokagawai*		

Filariae: tissue-invasive, thread-like nematodes, transmitted by arthropod vectors

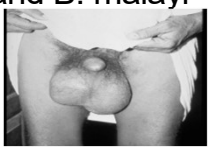
	Adults	Microfilariae
Wuchereria bancrofti *Brugia malayi* (lymphatic filariasis) --mosquitoes--	lymphatics	blood (night)
Loa loa (eyeworm) --Chrysops flies--	SQ tissues (moving)	blood (day)
Onchocerciasis (river blindness) --blackflies--	SQ tissues (nodules)	skin

Treatment of Filariasis

	Treatment	Avoid
Lymphatic filariasis	**DEC**	**-----**
Loa Loa	**DEC**	**DEC and Ivermectin if high microfilaria level**
Onchocerciasis	**ivermectin**	**DEC**

ADVERSE EFFECTS
Loa with high microfilaremia → encephalopathy and death
Onchocerciasis → severe skin inflammation and blindness

W. bancrofti and B. malayi

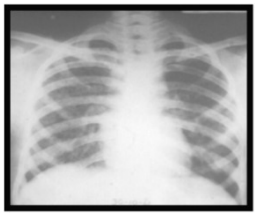




- Asymptomatic microfilaremia
- Lymphangitis
  - retrograde (filarial lymphangitis)
  - bacterial skin/soft tissue infections (dermatolymphangioadenitis)
- Lymphatic dysfunction
  - Lymphedema, elephantiasis, hydrocele, chyluria

Tropical pulmonary eosinophilia

- Paroxysmal nocturnal asthma
- Pulmonary infiltrates
- Peripheral blood eosinophilia (>3,000/mm^3)
- Elevated serum IgE
- Rapid response to anti-filarial therapy

Likely due to excessive immune response to microfilariae in lung vasculature



Lymphatic filariasis: diagnosis

Definitive diagnosis

- Identification of microfilariae in nighttime blood
- Detection of circulating antigen in blood (only Wb)
- Identification of adult worm (by tissue biopsy or ultrasound "filaria dance sign")

Presumptive diagnosis

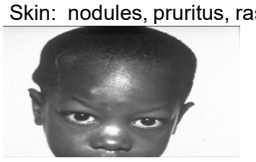
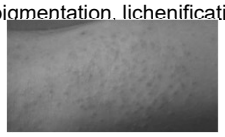
- Compatible clinical picture + positive antifilarial antibodies

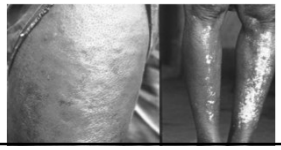
Treatment

- DEC, doxycycline
- NOTE: Triple drug single dose therapy (DEC/albendazole/ivermectin) is now recommended by W.H.O. for mass drug administration eradication campaigns in areas that are NOT co-endemic for Loa loa or Onchocerca

Manifestations of Onchocerciasis

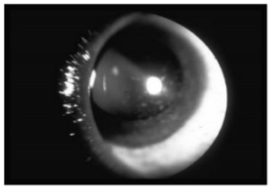
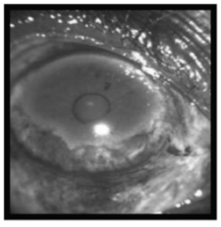
Skin: nodules, pruritus, rash, depigmentation, lichenification



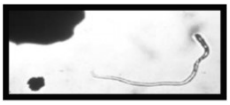
Manifestations of Onchocerciasis

- Eye: punctate keratitis, sclerosing keratitis, chorioretinitis

Onchocerciasis

Diagnosis
- Serology
  - anti-filarial
  - onchocerca-specific
- Parasitologic: skin snips, nodulectomy



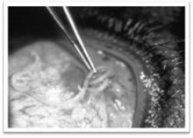
Treatment

Ivermectin

Moxidectin (FDA approved in 2018…has much longer half-life)
→ both are primarily microfilaricidal
→ therefore need repeated treatments for many years

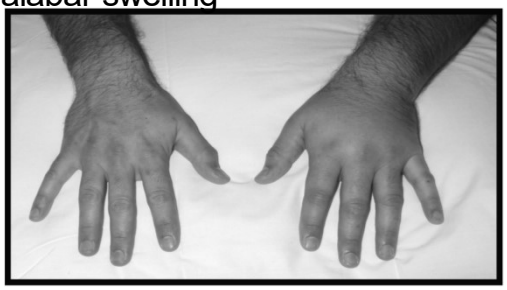
(alternative: **doxycycline** for 6 weeks, which kills endosymbiotic *Wolbachia* bacteria, kills adult worms)

Loiasis: clinical manifestations

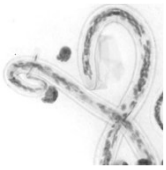


- Asymptomatic microfilaremia
- Non-specific symptoms
  - fatigue, urticaria, arthralgias, myalgias
- Calabar swellings
- Eyeworm
- End organ complications (rare)
  - endomyocardial fibrosis, encephalopathy, renal failure

Calabar swelling



Loiasis: Diagnosis



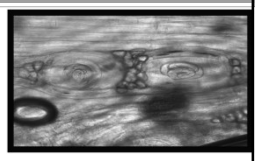
CDC DpDx

Definitive diagnosis
- Identification of adult worm in subconjunctiva
- Detection of Loa microfilaria in **noon blood**

Presumptive diagnosis

Compatible clinical picture + positive antifilarial antibodies

Trichinellosis



CDC DPDx

1. Eat meat containing cysts (pork, boar, horse, wild game)
2. Larvae released from cysts by gastric acid.
3. Adults invade small bowel,
   - mature into adults over 1-2wks.
   --> ABDOMINAL CRAMPS and DIARRHEA IF HEAVY INFXN
4. Adults (who only live for about a month) make larvae.
5. Larvae migrate to striated muscle, encyst, and live in "nurse cells"
   → **SEVERE MUSCLE PAIN**
   → **PERIORBITAL EDEMA**
   → **EOSINOPHILIA**
   +/- fever and urticaria

Diagnosis: serologies are supportive, + biopsy is definitive
Treatment: albendazole + steroids

Angiostrongylus cantonensis summary
(the rat lungworm)

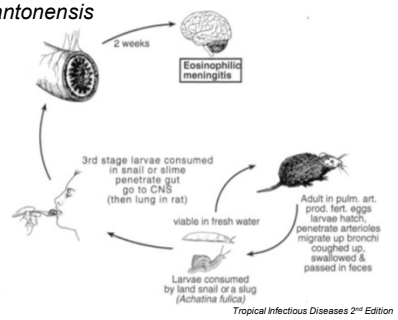
- The most common parasitic cause of eosinophilic meningitis worldwide
- SE Asia, Pacific basin, Caribbean (Jamaica)
- Caused by
  - ingestion of parasites in snail or slugs (often on vegetables!!)
  - OR
  - ingestion of paratenic hosts (prawns, shrimps, crabs, frogs)
- In rats, develop to adults in 2-3 weeks and migrate from surface of brain through venous system to the pulmonary arteries
- In humans, develop to young adults and cause meningitis 1-2 weeks after infection

Rx: primarily supportive
corticosteroids often given…benefit unclear but some data suggests they may be helpful
anthelmintic therapy controversial as may cause exacerbation of meningitis

Angiostrongylus cantonensis

Human acquisition by eating

- Snails or slugs (often on vegetables!!)
- Paratenic hosts (Freshwater shrimps or crabs, frogs)



Nice CDC movie on angiostrongylus:

https://www.youtube.com/watch?v=V_f1lK93ZtE

Tropical Infectious Diseases 2nd Edition

Angiostrongylus cantonensis

→ *Case reports in Hawaii past few years*

Anisakis

CDC DPDx

Ingestion of larvae in raw or undercooked seafood (found worldwide)

In humans, parasite buries its head into gastric mucosa. Eosinophilia common.

Symptoms
1) due to invasion of worm (pain, vomiting)
2) due to allergic rxn to worm
(mild urticaria, itchy sensation back of throat, naphylactic shock)

Treatment
→ usually simple endoscopic removal
→ for allergic symptoms, avoid contaminated fish

Possible question hints

Freshwater exposure + eosinophilia → Schistosomiasis
Crab/crayfish + pulmonary sxs + eosinophilia → Paragonimus
Cysticercosis → ANY food contaminated with tapeworm eggs
Allergic symptoms after trauma → Echinococcus
itchy feet return to tropics → ground itch due to hookworms
Gram- sepsis after corticosteroids or TNF inhibitor → Strongyloides hyperinfection
Subcutaneous nodules → Onchocerca volvulus
Blood microfilaria night → lymphatic filariasis (day = Loa loa, skin = Ov)
Muscle pain + eosinophilia → Trichinella
Eosinophilic meningitis → Angiostrongylus
Abdominal pain after sushi → Anisakis
Eosinophilia + F + ↑ AST/ALT in child → visceral larva migrans

Caveat to today's talk – a bit simplistic
Multiple parasites can cause similar diseases

Eosinophilic meningitis

Nematodes:
- Angiostrongylus cantonensis
- Baylisascaris procyonis
- Gnathostoma species
- Toxocara canis & T. cati
- Trichinella spiralis
- Strongyloides stercoralis
- Loa loa
- Meningonema peruzzi

Trematodes:
- Schistosoma species (larvae or eggs)
- Paragonimus westermani
- Fascioliasis

Cestodes:
- Neurocysticercosis
- Echinococcus

Good Luck!

Ed Mitre
edwardmitre@gmail.com

53

Lyme Disease

Dr. Paul Auwaerter

53 – Lyme Disease
Speaker: Paul Auwaerter, MD

INFECTIOUS DISEASE BOARD REVIEW AUGUST 20-24 2022

Lyme Disease

Paul G. Auwaerter, MD
Sherrilyn and Ken Fisher Professor of Medicine
Clinical Director, Division of Infectious Diseases
Johns Hopkins University School of Medicine

7/18/2022

INFECTIOUS DISEASE BOARD REVIEW AUGUST 20-24 2022

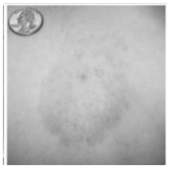
Disclosures of Financial Relationships with Relevant Commercial Interests

- **Consulting –Pfizer, medical-legal**
- **Research –Pfizer**

Question # 1

A 56 y.o man from southern Missouri
Onset in July:
Myalgia and malaise
Rash of two days duration
Tick bite 1 week ago

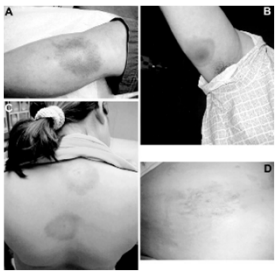
Exam: T 37.0°C
Annular "bulls-eye" ~6 cm
(same area that engorged tick was removed earlier in the week)



Question # 1

Which of the following is the most likely diagnosis?

A. Lyme disease (*Borrelia burgdorferi* infection)
B. Human Monocytic Ehrlichiosis (*Ehrlichia chaffeensis)*
C. *Borrelia mayonii*
D. Southern tick-associated rash illness (STARI)
E. B. lonestarii infection



STARI

Rash variable

Usually single lesion

Multiple described

Maybe Bull's eye-like

Expanding range of Lone Star Tick
(name may be obsolete?)

STARI

No infection yet convincingly documented *B. lonestarii* (single case)

Appears to occur after bite of Lone star tick

B. burgdorferi tests including serology negative

Likely accounts for some reported Lyme disease cases in non-endemic states

Unclear if doxycycline needed, typically given

No sequelae

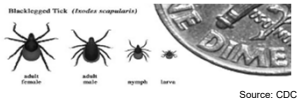
James AM, J Infect Dis 2001;183:1810

CDC, https://www.cdc.gov/stari/geo/index.html (accessed 7/18/22, last updated 11/19/18)

53 – Lyme Disease
Speaker: Paul Auwaerter, MD

B. burgdorferi: Vector-borne Infection

- Spirochetal infection due to *Borrelia burgdorferi* (Bb)
- Tick-borne disease
  - *Ixodes* species
  - In North America
    - *Ixodes scapularis* (mostly)
      - Black legged tick
    - *Ixodes pacificus*
      - Western black legged tick
- Not known as STD or blood-borne infection



Source: CDC

Commonly called the "deer tick"

Small-sized tick, unengorged
- Adults: sesame seed
- Nymphs: poppy seed

Bacterial reservoir:
- Mice, other small mammals
- Not: deer, humans

Most common vector-borne infection in US: A mostly regional disease

Reported Cases of Lyme Disease — United States, 2019

Source: CDC accessed 7/18/22

Lyme Borreliosis

USA

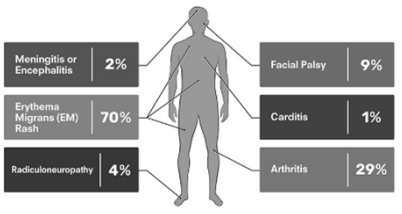
- *Borrelia burgdorferi*
  - Geographically localized
    - ~20-30,000 cases reported annually in US
      - Actual >10x more than reported
    - 95% cases in 14 states
    - Coastal, lake and river environs
      - New England
      - Mid-Atlantic
      - Upper Midwest

Europe

- *Borrelia afzelii & Borrelia garinii >> Borrelia burgdorferi*
- Occasionally others
- Genus name: changing to *Borreliella?*
  (to distinguish from relapsing fever Borrelia spp.)

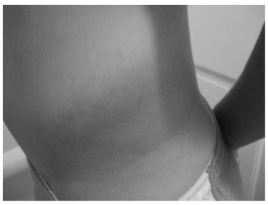
Lyme Disease Presentations

- Early, localized
  - Rash: erythema migrans
- Early, disseminated
  - Rash: multiple erythema migrans
  - Cardiac
  - Neurologic
- Late
  - Lyme arthritis
  - Neurologic (rare)
  - Dermatologic (Europe)
- Overlapping presentations possible



(based on 62% of 311,561 confirmed cases reported--probably favoring later presentations, Source CDC: accessed 6/21/21)
http://www.cdc.gov/lyme/stats/chartstables/casesbysymptom.html

Question # 2



July, 18M living in suburban Maryland, with this rash growing to ~12 cm, first noted 4d, ago, asymptomatic. Landscaper, had tick bite 10d ago. PCP gave cephalexin 2d ago.

Which of the following is true

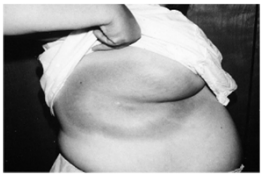
A. Lack of response to cephalexin is consistent with erythema migrans
B. Lack of systemic symptoms makes this unlikely to be Lyme disease
C. Ordering *B. burgdorferi* 2-tier serology will likely confirm Lyme disease
D. Whole blood *B. burgdorferi* PCR is superior to serology in early infection
E. Tick should be submitted for detection of *B. burgdorferi* by PCR

53 – Lyme Disease

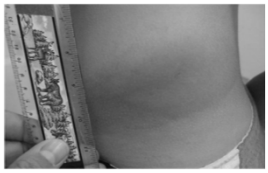
Speaker: Paul Auwaerter, MD

Early, localized LD: Erythema migrans

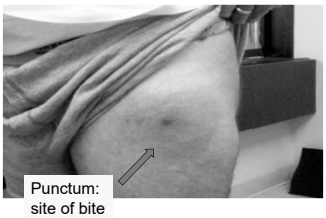
Classic: "bull's eye"
with central clearing upon expansion



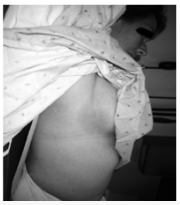
Most common: homogeneous, pink-red ovoid



Typical Erythema Migrans

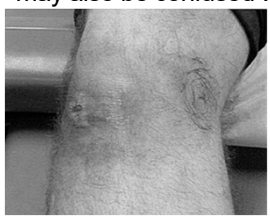


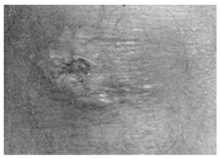
Punctum:
site of bite



Lesions: occur typically below neck and above knees & elbows

Spider bite?: differential diagnosis may also be confused with MRSA, cellulitis



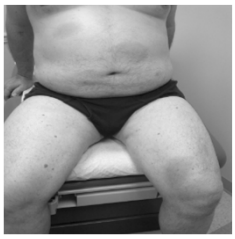


Less typical erythema migrans:
skin punch biopsy *B. burgdorferi* culture positive (research labs only)

Erythema migrans

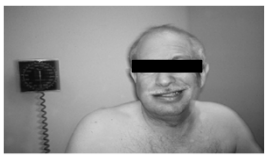
- Primary lesion: occurs 3-30d [7-14d average] @ site tick bite site
  - > 5cm = more secure diagnosis
    - Ddx: includes cellulitis, tinea, erythema marginatum, tick hypersensitivity reaction (smaller)
  - Diagnosis: characteristic rash + epidemiology
    - Serologic testing not recommended, rash sufficient
    - Acute serology negative 40-70% in early Lyme disease
- Most lesions with minimal local symptoms
  - ~70% experience flu-like problems (fever, HA, myalgia)

Early, Disseminated Lyme disease (1)



- Multiple Erythema Migrans
  - Often smaller and less red than primary lesion
  - Always ill:
    - Fever
    - Flu-like symptoms
    - Headache

Early, Disseminated Lyme disease (2)



- Neuroborreliosis
  - Aseptic meningitis
    - Lymphocytic predominance
  - Cranial nerve palsy
    - CN VII (facial)
      - Most common
      - Bilateral CN VII may occur
      - Other CN palsies: seen less
        - e.g., III, VI, VIII
  - Radiculoneuritis
  - Mononeuritis multiplex

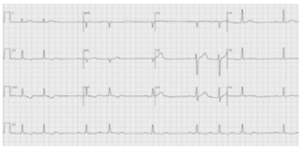
Diagnosis – Facial Palsy

- Facial Palsy: up to 25% due to *B. burgdorferi* (Long Island NY)[1]
- Serology may take 4-6 wks turn positive
  - (if untreated, recheck if negative and suspicious)
- Lumbar puncture
  - Not required
- Most would recover without antibiotic therapy[2]
  - Main role of abx: prevent later disease manifestations

[1]Neurology 1992; 41:1268.
[2]Laryngoscope 1985; 95:1341. Clin Infect Dis. 2006 Nov 1;43(9):1089

Early, Disseminated Lyme disease (3)

- 19M collapsed outside VT college cafeteria
  - Lacrosse athlete, not well for ~ 1 month



- Lyme carditis
  - 1°, 2° or 3° block
    - May be variable
    - 3° most identified since symptomatic
      - May need temporary pacer
      - Complete heart block usually resolves within several days of antibiotic, lesser block may take weeks

PA2

Question # 3

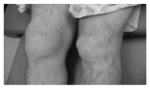
56M Long Island, NY with R knee pain and swelling x 3 weeks. Thought this was a wrenched knee from yardwork.

No fever, rash, tick bite or Lyme disease history

PMH: HTN, hyperlipidemia

PE: afebrile, mildly warm knee, moderate effusion, reduced ROM

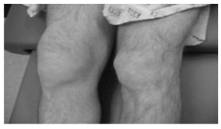
Labs: nl CBC



Which of the following is usually true for Lyme arthritis?

A. If untreated, the knee swelling will not remit
B. *B. burgdorferi* PCR synovial fluid ~ 100% sensitivity
C. Synovial fluid WBCs >50,000 cells/mL
D. Synovial fluid *B. burgdorferi* culture ~100% sensitivity
E. Serum *B. burgdorferi* 2-tier testing ~100% sensitivity

Late Lyme disease (1): Lyme arthritis



- Recurrent mono- or oligo-arthritis
  - Knee most common
    - Large, cool effusions
    - Baker's cysts may develop
  - Other large joints possible + TMJ
- Afflicts ~30% untreated patients (historically 50-60%)
- May remit, recur in different joints over period of wks to mos w/o abx Rx

Ann Int Med 1987; 107:725
Lantos, CID Nov 30, 2020

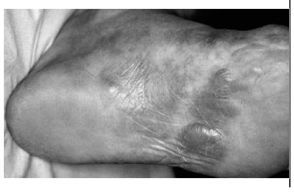
Late Lyme disease (2): Neurologic

- Encephalopathy:
  - Cognitive dysfunction, objective
  - Due to systemic illness, rather than true CNS infection
- Encephalitis: rare
  - Objective neurological or cognitive dysfunction
  - White matter changes on MRI or abnormal CSF
  - CSF: (+) lymphocytic pleocytosis, Bb antibody
- Peripheral neuropathy: rare (controversial)
  - Pain or paresthesia
  - Diffuse axonal changes on EMG/NCV

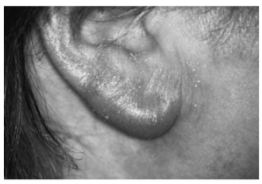
Late Lyme disease (3): Dermatologic

Europe only

Acrodermitis chronica atrophicans (Europe)



Borrelia Lymphocytoma (Europe)



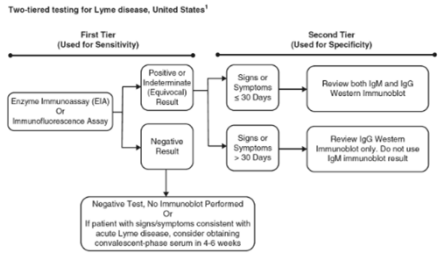
Question # 4

- 49F complains of four years of fatigue, headache, poor sleep and joint aches since trip to London UK
  - PMH: TAH/BSO
  - Medications: hormone replacement
  - SH: Married, accountant. Lives in central Pennsylvania. Two dogs, often sleep in bed.
  - PE: normal
  - Labs: normal CBC, ESR, TSH
    - *B. burgdorferi* serology: EIA (not done), IgM WB 3/3 bands, IgG 1/10

Question # 4

- What is the best recommendation at this time?

A. Doxycycline 100 mg twice daily x 14 days
B. Doxycycline 100 mg twice daily x 28 days
C. Repeat Lyme serology (two tier: EIA w/ reflex WB)
D. Lyme C6 antibody assay
E. Neither additional Lyme disease testing nor treatment



Laboratory testing

- Two tier serology: not needed for erythema migrans
  - First: total Ab screen – ELISA or EIA
  - If positive, second tier reflexes to immunoblots (IB)
    - IgM: ≥ 2/3 bands, use only if < 4 wks of symptoms
      - High rates false (+)
    - IgG: ≥ 5/10 bands, more reliable
      - Alternative criteria (different bands): less specific
  - Often negative in early infection (first 2-3 weeks)
  - May need acute/convalescent for confusing rashes or neuroborreliosis
  - Serology: may remain (+) for decades including IgM

MMWR 1995;44:590
Clin Infect Dis 2001;33(6):780-5

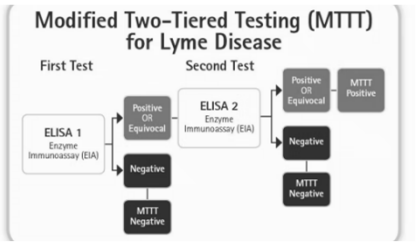
Modified Two-tier (2-EIA) vs. STTT

- Technically easy, quick
- Less cost
- Appears to provide similar sensitivity/specificity
- Better in early disease

Pooled LD USA	Standard 2-tier	Modified 2-tier	C6 only
Specificity (%)	98.3-100	98.3-100	96.5-100
Sensitivity (%) --Early LD	28-54	38-61	64-68
--Late LD	96-100	98-100	98-100

Branda et al. Clin Infec Dis 2018;66(7):1133-1139

MTTT: Faster, Cheaper, Better?



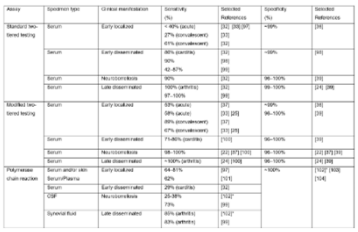
Diagnostics: Lyme arthritis

- Arthrocentesis
  - Synovial fluid: inflammatory
    - 10,000-25,000 WBC average (range: 500 – 100,000)
    - PMN predominant
  - Bb PCR –non standardized
    - Sensitivity 40-96% if prior to antibiotic therapy
    - Specificity 99%
- Serology: ~100% (+) in blood
  - High titer, Bb IgG immunoblot
- Culture: rarely (+)

Arvikar, Steere: Inf Dis Clin N Am 2015;29(2):269-280

FYI: Stats on Lyme disease presentations and routine diagnostics

Table1: Sensitivity and specificity of assays for the diagnosis of Lyme disease



Kobayashi, Auwaerter. Inf Dis Clinics N Am Sept 2022

Common Clinical Scenarios: Improper Use of Serology

1) EIA/ELISA only, no Western blot (WB aka immunoblot)
2) Ordering just WB -- w/o EIA/ELISA (total ab)
   - >50% population reactive to 1 or more antigens
3) Using the IgM WB alone for symptoms > 1 month
4) Serology at time of erythema migrans
5) Treating tests that "stay positive [IgM or IgG]"
6) Testing samples by WB other than serum
   --CSF or synovial fluid

Other tests

- Second generation Ab assays: C6 or VlsE (variable major protein-like sequence expressed)
- C6 Ab: more specific than first tier screen
  - Less specific than full two tier test
  - Positive, earlier in infection
  - Helpful to discriminate false (+) IgM IB
  - Better at detecting *B. garinii, B. afzelli* (Europe)
- Beware of "Lyme" specialty labs with unvalidated or poorly validated testing

Clin Infect Dis 2013;57(3):333-343.

Lyme disease: Initial Regimens

Treatment

Disease Manifestation	Route	Medication[a]	Duration (days)[b]
Lyme disease			
Erythema migrans	Oral	Doxycycline or Amoxicillin or Cefuroxime axetil	10 14 14
Meningitis/radiculopathy	Oral	Doxycycline	14-21
	IV[c]	Ceftriaxone	14-21
Cranial nerve palsy	Oral	Doxycycline	14-21
Encephalomyelitis	IV[c]	Ceftriaxone	14-28
Carditis	Oral	Doxycycline or Amoxicillin or Cefuroxime axetil	14-21
	IV[c]	Ceftriaxone	14-21
Arthritis	Oral	Doxycycline or Amoxicillin or Cefuroxime axetil	28

[a]Further details regarding adult and pediatric dosing can be found in the 2021 Guideline.
[b]Ranges are given if available studies are insufficient to determine the optimal duration.
[c]Cefotaxime and penicillin G are alternative IV options.
[d]Parenteral therapy is used for hospitalized patients, who, with improvement, may transition to oral antibiotics to complete the treatment course.

Lantos et al, IDSA/AAN/ACR Lyme GL, CID 2021; 72(1)e1-e48

Treatment: Late Lyme arthritis

- Initial treatment: amoxicillin or doxycycline PO x 28d
  - If lack of response: second course orals or ceftriaxone IV x 14-28d
- ~10% do not respond to repeated antibiotic therapy
  - Abx-refractory Lyme arthritis
    - Bb culture/PCR (-), no viable organisms
    - Autoimmune phenomenon, associated with certain HLA DR alleles binding to OspA → strong Th1 response
  - Treatment: DMARDs, intra-articular corticosteroids, synovectomy

53 – Lyme Disease
Speaker: Paul Auwaerter, MD

Lyme Disease: Expectations Regarding Resolution

- Subjective problems, post-treatment
  - Prospective studies, treated erythema migrans

Time	Symptomatic
Erythema migrans (d0)	73%
3 months	24%
≥ 6 months	11.5% [0-40.8%]
15 years	Equivalent to general US population

Need to manage expectations,

No benefit from additional antibiotics

Post-infectious syndromes not unique to LD

Wormser, et al. Ann Intern Med 2003;138:697 Wormser, et al. Clin Infect Dis 2015;61(2):244
Cerar, et al. Am J Med 2010;123:79

Randomized, placebo-controlled trial scorecard for persistent symptoms attributed to Lyme disease after initial treatment

Longer-term abx v. placebo Subjective sx OR Encephalopathy after initial treatment	Antibiotics with Durable Effect and Clinically Significant Benefit	Antibiotics Not Effective
7 trials	0	7

Placebo effect: noted in up to 36%
No study yielded evidence of *B. burgdorferi* by culture or PCR in these patients

1. Klempner M, et al. NEJM 2001; 345:85 (2 studies)
2. Krupp LB, et al. Neurology 2003;60:1923
3. Oksi J, et al. Eur J Clin Micro 2007;26(8):571
4. Fallon BA, et al. Neurology 2008; 70:992
5. Sjöwall, BMC Infectious Diseases 2012; 12:186
6. Berende A, et al. NEJM 2016;375(13):1209-20 (PLEASE trial)

"Chronic Lyme disease"

- What is it? Originally, late Lyme disease
  - Now: vague term, often used by some to encompass broad range of symptoms
    - Objective evidence of LD not needed.
      - Lack of good clinical history
      - Often no reliable evidence of LD by laboratory testing
  - Offered as explanation for
    - Chronic—fatigue, pain, headaches, brain fog, sleep problems, depression
    - Legitimate diseases: multiple sclerosis, ALS, Alzheimer's, autism, Parkinson's

PA2

Question # 5

42M went camping with his son on Cape Cod, MA

Didn't use DEET, no tick bites known

About 4d after returning home, fever, chills, myalgia. Noted rash on thigh

PMH: none

PE: Appears ill, non-toxic, 104/60, P96 T101.7°F

Exam only notable for 3 pink ovoid rashes over trunk, R thigh (largest ~7cm)

Labs: WBC 2.2 Hg 9.6 plt 110K
ALT 80 AST 58 Tot Bili 2.4

Doxycycline is prescribed. What should also be performed as part of the plan?

A. PCR for *E. chaffeensis*
B. Serology for spotted fever rickettsia (RMSF)
C. Blood smear
D. Serology for *B. burgdorferi*
E. Nothing additional

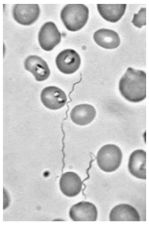
Lyme disease: co-infections

- Incidence depends on geographic acquisition
  - *B. microti:* 2-40%
  - HGA: *2-11.7%*
  - Uncommon to rare
    - *B. miyamotoi*
    - *B. mayonii*
    - *Ehrlichia eauclairensis*
    - Powassan virus (Deer Tick virus)
- Disease severity
  - Lyme + HGA:
    - Data mixed on effect
  - Lyme + Babesia:
    - Increases severity of Lyme disease presentation
    - Converse: Lyme doesn't appear to affect Babesia presentations

IDSA/AAN/ACR Lyme disease Guideline 2020

B. miyamotoi--Ixodes spp. vector

Neither Lyme disease nor Relapsing Fever

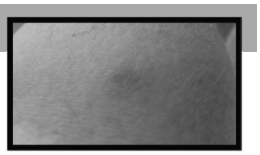


Telford, et al. Clin Lab Med 2015; 35(4):867

- Serosurvey New England: 0.8-4.0%
- Likely underdiagnosed
- Sx: HA, fever, chills, myalgia
- Not like relapsing fever:
  - No rigor, ↓ BP
  - May resemble HGA
    - Leukopenia, thrombocytopenia, LFT abnl
  - Opportunistic pathogen?
- Dx: not widely available
  - rGlpQ EIA
  - PCR
  - Spirochetes on fluid H&E
  - Doesn't appear to frequently cross-react with B burgdorferi Ab
- Treatment: likely identical as for LD

PA2

Question # 5



42M just returned from a hiking trip Colorado, a tick on his arm removed 2d earlier. Now heading out of town for a beach vacation.

Today, intense itching and redness at the site he thinks may be larger (~1cm) than yesterday. He is otherwise well.

The best course of action would be:

A. Doxycycline 200mg x single dose
B. Doxycycline x 14d
C. Doxycycline x 30d
D. Cefuroxime x 14d
E. Observation

I. scapularis tick bite prophylaxis

B. burgdorferi transmittal

- Tick attachment time
  - < 24 h: 0/58 (0%)
  - < 48 h: 4/50 (8%)
  - < 72 h: 36/52 (69%)

JID 2001; 183:773-8

Infection risk in highly endemic areas

Intervention	Risk	95% CI
No tick found	20%	
Removing tick	2.2%	[1.2-3.9%]
Single 200mg dose doxycycline*	0.4%	[0.02-2.1%]
10d doxy	0%	[0-0.97%]

*200 mg given with 72h of tick bite

J Antimicrob Chemother 2010;65:1137-1144
N Engl J Med 2001; 345:79-84

Lyme disease: some pearls

- No need for serology if diagnosing erythema migrans
- *B. burgdorferi* IgM immunoblot most common cause of misdiagnosis
- Late Lyme arthritis: always seropositive
  - No evidence that seronegative Lyme exists in patients with long-term symptoms
- Lab evidence of LD essential unless hx of EM exists
- Prolonged antibiotic treatment doesn't improve resolution of subjective symptoms

54

Penicillin Allergies

Dr. Sandra Nelson

54 - Penicillin Allergies

Speaker: Sandra Nelson, MD

IDBR INFECTIOUS DISEASE BOARD REVIEW AUGUST 20-24 2022

Penicillin Allergies

Sandra B. Nelson, MD
Director, Musculoskeletal Infectious Diseases
Division of Infectious Diseases
Massachusetts General Hospital

6/30/2022

INFECTIOUS DISEASE BOARD REVIEW AUGUST 20-24 2022

Disclosures of Financial Relationships with Relevant Commercial Interests

- None

Penicillin (PCN) Allergy: Premise

- 10% of the US population have reported penicillin allergy
  - Rash most common adverse drug reaction (ADR)
  - Others include "unknown", angioedema, GI symptoms, itching
  - More common in older adults and hospitalized patients
- Vast majority of patients with PCN allergy can safely receive penicillins (with appropriate evaluation and testing)
  - Reactions are mild drug rashes that do not always recur
  - True allergies often wane with time
  - Some reactions are not allergic

MASSACHUSETTS GENERAL HOSPITAL 3

PCN Allergy: Consequences

- Alternative antimicrobial use
  - Less effective, more toxic, higher cost, broader spectrum
- Associated with:
  - increased risk of MRSA infection and VRE colonization
  - increased risk of *C. difficile* colitis
  - increased risk of surgical site infection
  - increased mortality
- An important target of stewardship efforts

MASSACHUSETTS GENERAL HOSPITAL HARVARD MEDICAL SCHOOL 4

Case #1

A 73-year-old woman undergoing chemotherapy for cholangiocarcinoma is hospitalized with bacteremia and sepsis due to ampicillin-susceptible *Enterococcus faecalis*. She has a history of allergy to penicillin that is listed in the records as rash; the family recalls that she went to the ED when the rash occurred several years earlier. She is delirious and not able to corroborate the history; no additional documentation of the reaction is available. Two of her daughters have allergies to penicillin.

MASSACHUSETTS GENERAL HOSPITAL HARVARD MEDICAL SCHOOL 5

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. Administer vancomycin

MASSACHUSETTS GENERAL HOSPITAL HARVARD MEDICAL SCHOOL 6

54 - Penicillin Allergies
Speaker: Sandra Nelson, MD

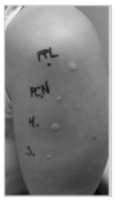
Classification of Drug Allergy (Gell and Coombs)

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

MASSACHUSETTS GENERAL HOSPITAL HARVARD MEDICAL SCHOOL 8

Options for Approaching PCN Allergy

- Monitored oral challenge
  - Useful for outpatients with low-risk reactions (remote rash, pruritus) without imminent need of beta-lactam therapy
- Penicillin skin testing
  - Epicutaneous and intradermal administration of PPL (penicilloyl polylysine, Pre-Pen) and penicillin G
  - Useful for inpatients and outpatients with a history of IgE mediated reaction
  - Useful for inpatients and outpatients with unknown reaction or vague history
  - Followed by test dose of implicated drug or desired drug



Shenoy JAMA 2019;321:188

MASSACHUSETTS GENERAL HOSPITAL HARVARD MEDICAL SCHOOL 9

Options for Approaching PCN Allergy

- Graded Challenge (oral of IV drugs)
  - $1/4^{th}$ to $1/10^{th}$ dose, followed by full dose 30-60 minutes later
  - As a first step if suspicion for immediate reaction is low
  - After negative PCN skin testing
- Desensitization
  - Sequential administration of increasing dilutions of PCN every 15-30 minutes until therapeutic dose is reached
  - Positive skin test and/or confirmed immediate reaction, when a penicillin is the best therapy for an important infection
  - Desensitization wanes with missed doses (3 half-lives)
- Use of alternate therapy

MASSACHUSETTS GENERAL HOSPITAL HARVARD MEDICAL SCHOOL 10

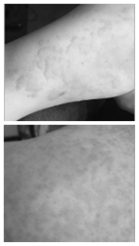
Classification of Drug Allergy, revisited (Gell and Coombs)

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

MASSACHUSETTS GENERAL HOSPITAL HARVARD MEDICAL SCHOOL 11

Deciphering Cutaneous Reactions

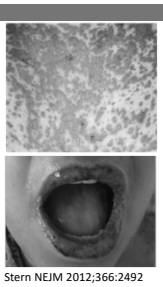
- IgE Mediated Reactions (hives)
  - Occur within minutes to hours, resolve within 24 hours
    - ➡ skin testing appropriate
  - if positive – desensitize or use alternate therapy
  - If negative – graded challenge
- Benign T-cell mediated
  - morbilliform or maculopapular
  - Usual onset days to weeks;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


Shenoy JAMA 2019;321:188

MASSACHUSETTS GENERAL HOSPITAL HARVARD MEDICAL SCHOOL 12

Deciphering Cutaneous Reactions

- Severe cutaneous reactions
  - DRESS and SJS/TEN
  - Usual onset days to weeks
  - Blistering, mucosal involvement, severe skin desquamation, organ involvement
    - ➡ avoid any beta-lactam
- Vague or unknown skin reaction
  - Evaluate risk of severe cutaneous reaction
  - Assume possibly IgE mediated
    - ➡ skin test then test dose


Stern NEJM 2012;366:2492
Shenoy JAMA 2019;321:188

MASSACHUSETTS GENERAL HOSPITAL HARVARD MEDICAL SCHOOL 13

Case #2

A 43-year-old man with diabetes is hospitalized with a closed tibial fracture. Three years ago when he was being treated for a foot infection with piperacillin-tazobactam he developed a very itchy rash after several weeks of treatment. The anesthesiologist calls to ask advice about surgical antibiotic prophylaxis prior to operative fixation.

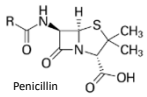
Case #2: Vote

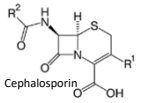
What do you do counsel?

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

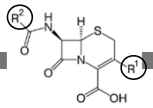
PCN Allergy and other beta-lactams

- Cephalosporins:
  - Significant cross reactivity 2%
  - Higher risk with earlier generation cephalosporins
  - If suggestive type I PCN allergy:
    - use 3rd/4th gen (graded challenge preferred)
    - use 1st/2nd after PCN skin testing
  - If mild type IV reaction:
    - any cephalosporin OK
  - Avoid if severe reaction to PCN
- Carbapenems <1%
- Aztreonam: no cross reactivity in PCN-allergic





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

A few more testable points

- A patient that tolerates penicillins may still be allergic to aminopenicillins, while 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 save ceftazidime

Thank you and good luck!

55

Kitchen Sink: Syndromes Not Covered Elsewhere

Dr. Stacey Rose

55 – Kitchen Sink: Syndromes Not Covered Elsewhere

Speaker: Stacey Rose, MD

IDBR INFECTIOUS DISEASE BOARD REVIEW AUGUST 20-24 2022

Kitchen Sink: Syndromes Not Covered Elsewhere

Stacey R. Rose, MD, FACP, FIDSA
Associate Dean of Curriculum, School of Medicine
Associate Professor, Infectious Diseases Section
Baylor College of Medicine

6/30/2022

INFECTIOUS DISEASE BOARD REVIEW AUGUST 20-24 2022

Disclosures of Financial Relationships with Relevant Commercial Interests

- **None**

Session plan

- Case-based discussions of topics not extensively covered in other sessions
- Highlight points likely to be assessed on ID Boards (rather than comprehensive overview)

3

Question 1

- **A 51-year old male with past medical history significant for insulin dependent diabetes presents with a six-month history of progressive athralgias, abdominal pain, diarrhea, weight loss, and low grade fevers.**
- **Work up thus far:**

Negative blood cultures x 2
Negative Rheumatoid factor
Normal metabolic panels
Mild normocytic anemia

4

Question 1

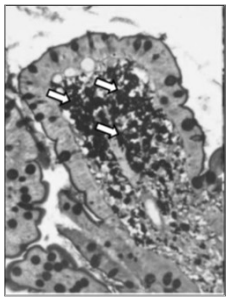
- **Which of the following tests will most likely yield the diagnosis?**

a) **Anti-streptolysin O Antibody**
b) **Anti-nuclear Antibody**
c) **Stool ova and parasite**
d) **Duodenal biopsy**

5

Whipple's disease

- **Caused by *Trophyrema whipplei* (gram variable bacterium, difficult to cultivate)**
- **More common in middle aged, Caucasian men**
- **Diagnosis often delayed due to indolent clinical presentation**
- **Most commonly diagnosed via duodenal biopsy, stained with PAS**
- **PCR increasingly used**



Periodic acid-Schiff-diastase (PAS-D)-stained duodenal biopsy specimens with PAS-D-positive granules in the foamy macrophages (arrows).

Dolmans RAV, Boel CHE, Lacle MM, Kusters JG. 2017. Clinical manifestations, treatment, and diagnosis of Tropheryma whipplei infections. Clin Microbiol Rev 30:529–555. https://doi.org/10.1128/CMR.00033-16.

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)		

[a]See text for references.
[b]Values for relative incidence are unknown.

Dolmans RAV, Boel CHE, Lacle MM, Kusters JG. 2017. Clinical manifestations, treatment, and diagnosis of Tropheryma whipplei infections. Clin Microbiol Rev 30:529 –555. https://doi.org/10.1128/CMR.00033-16.

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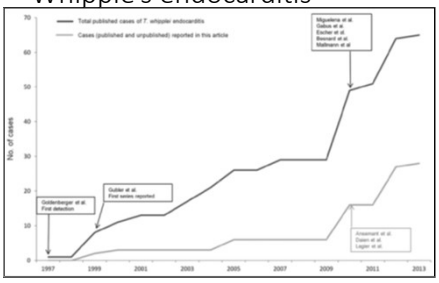
Whipple's endocarditis



- **Increasingly recognized (PCR on heart valves)**
- **Analysis of > 1000 cardiac valves in Germany concluded that *T. whipplei* was the most common pathogen associated with *culture negative endocarditis***

Fenollar F, Célard M, Lagier JC, Lepidi H, Fournier PE, Raoult D. Tropheryma whipplei endocarditis. Emerg Infect Dis. 2013;19(11):1721-1730. doi:10.3201/eid1911.121356
Geissdörfer W, Moos V, Moter A, et al. High frequency of Tropheryma whipplei in culture-negative endocarditis. *J Clin Microbiol*. 2012;50(2):216-222. doi:10.1128/JCM.05531-11

8

Whipple's: treatment

No gold standard

Options:

- Ceftriaxone or meropenem plus prolonged co-trimoxazole (~1 year)

OR

- Doxycycline plus hydroxychloroquine (12-18 mos)

Symptoms improve, but relapse is common without prolonged treatment / suppression

Dolmans RAV, Boel CHE, Lacle MM, Kusters JG. 2017. Clinical manifestations, treatment, and diagnosis of Tropheryma whipplei infections. Clin Microbiol Rev 30:529 –555. https://doi.org/10.1128/CMR.00033-16.
Principles and Practice of Infectious Diseases, 9th ed

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- **Cause: *Trophyrema Whipplei***
- **Epidemiology: middle aged, Caucasian males**
- **Clinical presentation: classic – *arthralgia, diarrhea, weight loss***
- **Localized infection including *endocarditis* (increasingly recognized)**
- **Diagnosis with *duodenal biopsy* (*PAS* stain; foamy macrophages) or *PCR* of infected tissue**
- **Prolonged treatment needed to prevent relapse**

Whipple's disease

Take home points

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Question 2

- **A 20 year-old female school teacher presents to her primary care doctor with fever and pain / swelling in multiple joints (knees, elbows and wrists). The pain seems to move from joint to joint.**
- **She is generally healthy, but reports being ill ~3 weeks prior with sore throat and headache which resolved without specific treatment. She has no skin rash and no lymphadenopathy.**
- **She denies travel. She is sexually active with one male partner, using barrier protection (condoms).**
- **Labs are notable for elevated ESR and CRP and + ASO titer; pregnancy and HIV tests (4th generation Ag/Ab) are negative.**

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**

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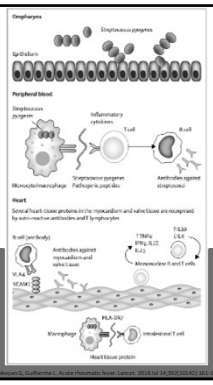
55 – Kitchen Sink: Syndromes Not Covered Elsewhere

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.

13



Acute Rheumatic Fever

- Rare in US (0.5 per 100K per year), but remains common worldwide (0.5 million per year)
- Affects ***children / young adults***
- Recurrence common
- *Pathogenesis*: immune responses following *Streptococcus pyogenes* pharyngitis; leads to systemic manifestations (**arthritis, carditis, chorea, skin – subcutaneous nodules; erythema marginatum**)

Karthikeyan G, Guilherme L. Acute rheumatic fever. Lancet. 2018 Jul 14;392(10142):161-174. doi: 10.1016/S0140-6736(18)30999-1. Epub 2018 Jun 29.

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REVISED JONES CRITERIA

For patients with evidence of prior GAS infection*,

Acute Rheumatic fever =

2 MAJOR

OR

1 MAJOR plus 2 MINOR

Major	Minor
Arthritis (usually migratory polyarthritis)	Arthralgia
Carditis (clinical or subclinical)	Fever
Chorea	Elevated ESR or CRP
Erythema marginatum	Prolonged PR interval (unless carditis is a major criterion)
Subcutaneous nodules	

***e.g. rapid strep test; culture; anti-streptolysin-O titer (ASO**

Revision of the Jones Criteria for the diagnosis of acute rheumatic fever in the era of Doppler echocardiography: a scientific statement from the American Heart Association. Circulation.

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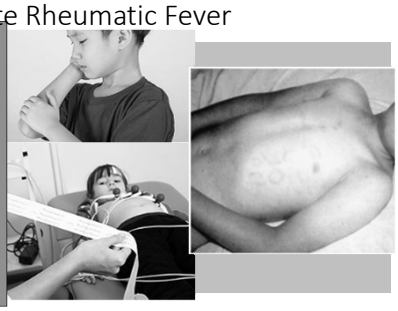
Revision of the Jones Criteria for the diagnosis of acute rheumatic fever in the era of Doppler echocardiography: a scientific statement from the American Heart Association. Circulation.

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 Jul 14;392(10142):161-174. doi: 10.1016/S0140-6736(18)30999-1. Epub 2018 Jun 29.
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.

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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 pharyngitis***
- **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, elevated ESR/CRP; PR prolongation***
- **Diagnosis based on Jones criteria = 2 major OR 1 major + 2 minor (plus e/o prior GAS infection e.g. ASO titer)**
- **Treatment and secondary ppx with IM Penicillin; duration based on carditis (10 yr or to age 40 if carditis + residual valvular disease)**

Acute Rheumatic Fever

Take home points

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Question 3

- **A 34 year old male with a history of injection drug use presents to the emergency room with a 2 day history of progressive muscle weakness and blurry vision. He also notices some difficulty swallowing.**
- **On examination, vital signs are normal, but the patient is noted to have ptosis and sluggish pupillary responses as well as slurred speech.**

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Question 3

- **Which of the following treatment(s) are recommended?**

A. Plasmapheresis
B. Naloxone
C. Tetanus antitoxin
D. Botulinum antitoxin

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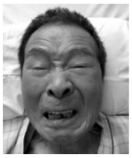
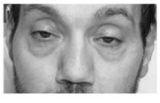
Explanation



Tetanus: sardonic smile



Botulism: ptosis

- **Plasmapheresis – for Lambert-Eaton syndrome, immune attack of neuromuscular junction (chronic; associated with lung cancer)**
- **Naloxone – for opioid intoxication (respiratory suppression, *constricted* pupils)**
- **Tetanus antitoxin – for tetanus (rigid paralysis)**
- **Botulinum antitoxin – for botulism**

https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(19)31137-7/fulltex
https://www.nejm.org/doi/pdf/10.1056/NEJMcm1003352

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https://phil.cdc.gov/details.aspx?pid=2107

Botulism

- **Caused by **Clostridium botulinum* (gram positive, strict anaerobe with subterminal spore; found in soil)**
- **Symptoms due to TOXINS which prevent release of acetylcholine in neuromuscular junction**
- **Leads to flaccid paralysis of motor and autonomic nerves, beginning with the cranial nerves (*descending* weakness)**
- **DX: culture or detection of toxin**

**other neurotoxin producing species of Clostridium: C. butyricum, or C. baratii*

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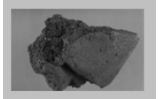
Botulism

Foodborne

Infant



Wound (black-tar heroin)

Iatrogenic

Peak CM, Rosen H, Kamali A, et al. Wound Botulism Outbreak Among Persons Who Use Black Tar Heroin — San Diego County, California, 2017–2018. MMWR Morb Mortal Wkly Rep 2019
https://www.cdc.gov/botulism/
Principles and Practice of Infectious Diseases, 9th ed.

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Botulism treatment

Supportive care	Antitoxin
• Ventilatory support for respiratory compromise • Wound debridement	• Botulinum anti-toxin (adults) Or • Botulinum immune globulin (infants)

https://www.cdc.gov/botulism/
Principles and Practice of Infectious Diseases, 9th ed.

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- **Cause: *Clostridium botulinum* toxin impedes acetylcholine release from neuromuscular junction**
- **Epidemiology: food (home canned veggies / fruits / fish); infant (honey); wound (black-tar heroin); iatrogenic (rare)**
- **Clinical presentation: *descending flaccid paralysis*, starting with *cranial nerves* (ptosis, blurred vision, slurred speech)**
- **Diagnosis: clinical; confirmed by culture or ID of toxin**
- **Treatment: *antitoxin* plus supportive care; wound debridement**

Botulism

Take home points

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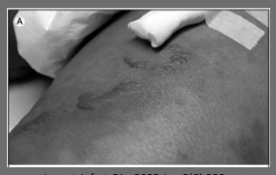
Question 4



Lancet Infect Dis. 2008 Jun;8(6):399.

- **A 44 year-old male with a history of cirrhosis due to Hepatitis B and alcoholism presents with fever, lethargy and leg swelling. On exam, he is febrile, hypotensive and tachycardic. Skin exam is as pictured.**

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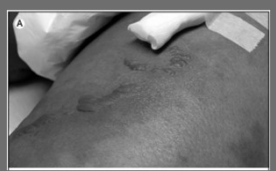
Question 4



Lancet Infect Dis. 2008 Jun;8(6):399.

- **The patient's clinical syndrome was most likely caused by which of the following exposures?**

A. Rat bite
B. Tick bite
C. Consumption of raw oysters
D. Consumption of raw egg

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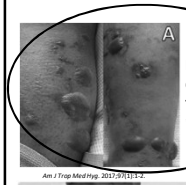
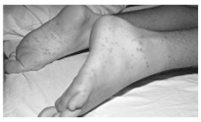
Explanation



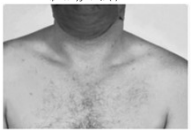
Hemorrhagic bullae from *Vibrio vulnificus*

Am J Trop Med Hyg. 2017;97(1):12.

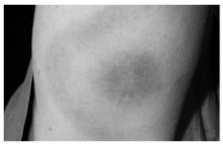


Petechial rash from *Streptobacillus moniliformis* (rat bite fever); fever, rash, migratory arthritis

CMAJ. 2006 Aug 15;175(4):354.



Rose spots from *Salmonella typhi*



Erythema migrans due to *Borrelia burgdorferi* (tick borne)

https://www.cdc.gov/vaccines/vpd/typhoid/public/photos.html

https://www.cdc.gov/lyme/signs_symptoms/rashes.html

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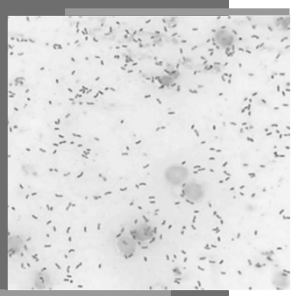
55 – Kitchen Sink: Syndromes Not Covered Elsewhere

Speaker: Stacey Rose, MD



Vibrio vulnificus

- **Gram-negative, curved bacillus**
- **Halophilic (salt loving) – ***brackish water***
- **Cause: ***consumption of raw seafood (oysters) or contamination of open wound***
- **At risk: ***liver disease* **(cirrhosis); iron overload; renal disease; immunosuppression**
- **High mortality**

Beatty NL, Marquez J, Al Mohajer M. Skin Manifestations of Primary *Vibrio vulnificus* Septicemia. *Am J Trop Med Hyg*. 2017;97(1):1-2.

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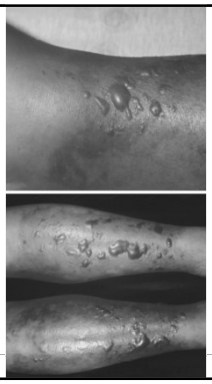
Clinical presentation and treatment



- Abrupt onset
- Fever, hypotension
- Rapidly progressive skin lesions: erythema → ***hemorrhagic bullae*** → necrosis
- Bacteremia common
- Treatment:
  - Fluoroquinolone plus 3rd generation cephaloporin
  - Debridement

Principles and Practice of Infectious Diseases, 9th ed.

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- **Epidemiology: consumption of raw seafood; contamination of wound (organism lives in warm, brackish water)**
- **At risk: liver disease, iron overload (also renal; immune suppression)**
- **Clinical presentation: rapidly progressive skin lesions with *hemorrhagic bullae; fever, hypotension, sepsis***
- **Diagnosis: clinical; blood cultures usually positive**
- **Treatment: fluoroquinolone plus 3rd generation cephalosporin; debridement**

Vibrio vulnificus

Take home points

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Question 5

- **A 23-year-old otherwise healthy college student presents to the university clinic with a non-productive, intermittent cough for 3 weeks. She describes spells during which she coughs repeatedly for several minutes. On two occasions she vomited after coughing.**
- **She reports episodes of sweating but has had no fever or other constitutional symptoms.**
- **She has tried several cough medicines, but nothing seems to help. She knows several other students who have been "coughing for weeks," and says the showers in her dorm are "covered with mold."**

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Question 5

- **She is afebrile and has a completely normal exam.**
- **Her CBC is normal; chest x-ray is normal.**
- **Specific nasopharyngeal culture for *Bordetella pertussis* is negative.**

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Question 5

- **Which one of the following is the most likely cause of her illness?**

A. Bordetella pertussis

B. Chlamydophila pneumoniae

C. Respiratory syncytial virus

D. Mycoplasma pneumoniae

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55 – Kitchen Sink: Syndromes Not Covered Elsewhere

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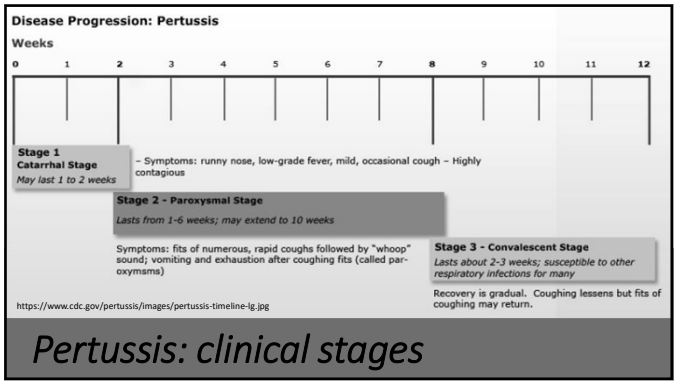

Pertussis: clinical stages

Pertussis diagnosis – no perfect test

Clinical case criteria (in absence of alternate dx):

- cough illness lasting ≥2 weeks, with at least one of the following:
  - Paroxysms of coughing; **OR**
  - Inspiratory whoop; **OR**
  - Post-tussive vomiting; **OR**
  - Apnea (with or without cyanosis)

Test	*Sensitivity (%)*	*Specificity (%)*	*Advantages*	*Disadvantages*
Culture	15	100	Specific; confirms diagnosis; most useful in first two weeks	Fastidious growth requirements; delayed results; inaccurate in late stages of disease
Polymerase chain reaction	45	85	Confirms diagnosis; rapid results; most accurate in early stages of disease	Sensitivity declines in late stages of disease
Serology	65	89	Accurate in late stages of disease	Cannot confirm acute infection (can be positive because of past infection or immunization); testing method not standardized

https://www.cdc.gov/nndss/conditions/pertussis/case-definition/2020/
Am Fam Physician. 2013 Oct 15;88(8):507-514.

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/

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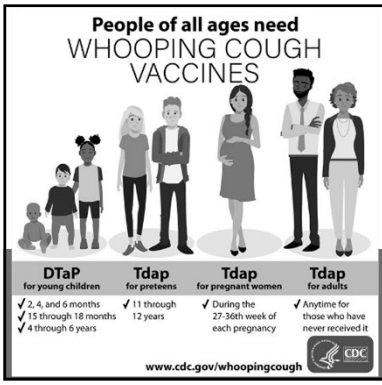

Pertussis Vaccination

for adults:
-wound mgmt.
-*each* pregnancy
-booster q 10 yrs

- **Epidemiology: in past infants / kids; now young adults (waning immunity?)**
- ***Severe disease: infants, pregnant women*, lung disease**
- **Clinical presentation: *cough* lasting 2+ weeks plus *paroxysmal cough*, *inspiratory whoop*, *post-tussive vomiting or apnea***
  - **Stages:**
    - ***catarrhal*: URI**
    - ***paroxysmal*: coughing fits / whoop**
    - ***convalescent*: gradual lessening of cough**
- **Diagnosis: clinical; culture (insensitive), PCR, serology (late)**
- **Treat with *macrolide within 3 wks* of onset**
- ***PEP* for household contacts / at risk of severe dz *within 3 wks* of exposure**

Bordatella pertussis

Take home points

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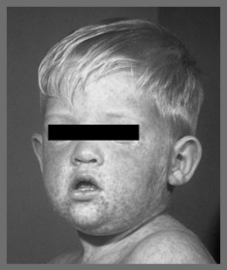
Question 6



- **A 25-month old child is brought to the emergency room for *fever, rash and fussiness*. The rash *started on the face and spread to trunk* and extremities within 1-2 days.**
- **10 days ago, the family returned to the United States following a 1-month trip to Tanzania (where the parents conduct research as university professors).**
- **The child's 4-year old sibling is also ill, with cough and watery eyes, but does not have a rash.**
- **The parents do not believe in vaccination for their children due to fear of adverse effects (autism).**

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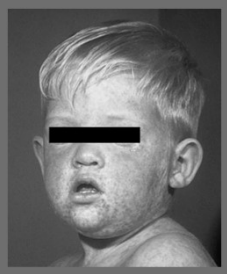
Question 6



- **Which of the following could have prevented the development of the patient's illness?**

A. **Varicella zoster virus vaccination**
B. **Measles, mumps, rubella vaccination**
C. **Mefloquine prophylaxis**
D. **Influenza vaccination**

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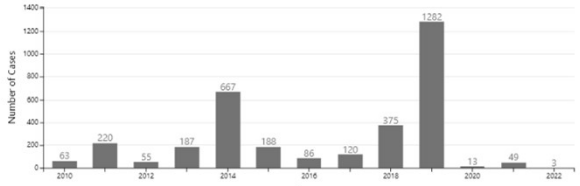
Measles (Rubeola) in the US

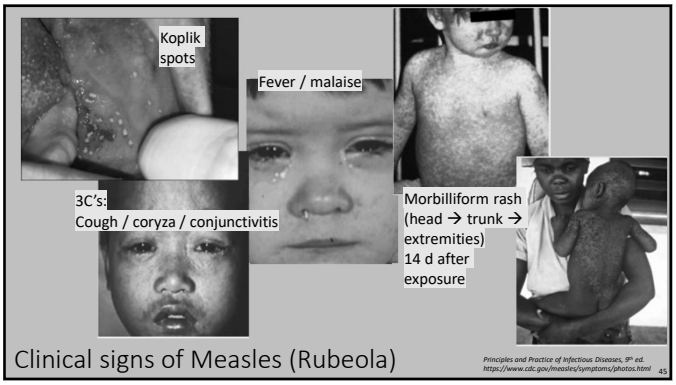
Mostly in <u>unvaccinated</u> individuals, related to international travel or an imported case

Number of measles cases reported by year

2010-2022* (as of June 3, 2022)



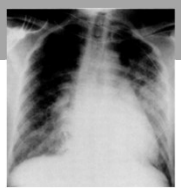
https://www.cdc.gov/measles/cases-outbreaks.html44



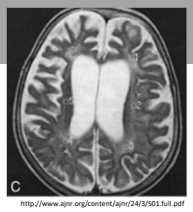
Clinical signs of Measles (Rubeola)

Principles and Practice of Infectious Diseases, 9th ed. https://www.cdc.gov/measles/symptoms/photos.html 45

Complications of measles



Chest. 1993 May;103(5):1625-6



http://www.ajnr.org/content/ajnr/24/3/501.full.pdf

Acute

- 1 of 1000 children – death from respiratory / neurologic complications

Delayed

- rare but fatal - Subacute Sclerosing Pan-Encephalitis (SSPE)
- 7 yrs after infection; degenerative disease, seizures

Principles and Practice of Infectious Diseases, 9th ed. https://www.cdc.gov/measles/ 46

Diagnosis

Don't wait for confirmation: isolate patients with suspected infection (airborne)

Clinical – high suspicion in unvaccinated individuals

Serum: measles-specific IgM antibody

*Respiratory specimen (nasopharyngeal swab): measles RNA by real-time polymerase chain reaction (RT-PCR)

https://www.cdc.gov/measles/

*may also be detected in urine

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Prevention: Measles-mumps-rubella (MMR) Vaccination

CHILDREN
1st dose: 12-15 mos
2nd dose: 4-6 years

ADULTS born after 1957 without evidence of immunity (at least one dose)

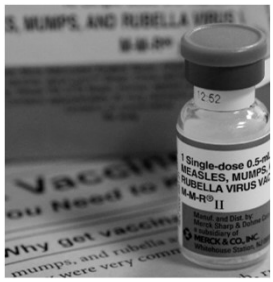
COLLEGE STUDENTS without evidence of immunity
(two doses, 28 d apart)

INTERNATIONAL TRAVELERS (6 mos and older) without evidence of immunity

Principles and Practice of Infectious Diseases, 9th ed. https://www.cdc.gov/measles/ 48

Immunity and post exposure prophylaxis

Who is immune to measles?	What is the recommendation for PEP?
• written documentation of adequate vaccination • Lab evidence of immunity • Lab confirmation of measles infection • Born before 1957	• Non-immune persons with measles exposure should receive ***either*** **MMR vaccine** (within 72 hours of exposure) **or Immune globulin (IG)** within 6 days of exposure • **Do not co-administer** MMR vaccine and IG (invalidates vaccine)



Principles and Practice of Infectious Diseases, 9th ed.
https://www.cdc.gov/measles/
https://www.washingtonpost.com/health/2019/04/09/how-does-measles-spread-other-frequently-asked-questions-about-measles/

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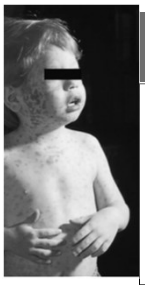
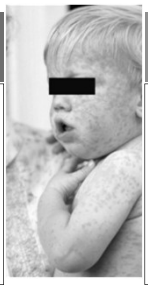
"German measles" (Rubella) vs. Measles (Rubeola)



German Measles (Rubella)	Measles (Rubeola)
• Caused by RNA virus of *Togaviridae* family • Often **mild** / asymptomatic • Viral prodrome → maculopapular rash which spreads from head to extremities, +/- **arthritis** • Transmitted in utero (**congenital** rubella): deafness, cataracts, glaucoma, heart disease, cognitive defects	• Caused by RNA virus of Paromyxovirus family • **Severe** disease with complications including death • Viral prodrome → **cough / coryza / conjunctivitis, fever, Koplik spots** → maculopapular rash which spreads from head to extremities



50

- **Cause: Rubeola (RNA virus of Paramyxovirus family)**
- **Epidemiology: worldwide distribution; *in US, seen in unvaccinated persons due to travel or exposure to imported case***
- **Clinical presentation: three C's (*cough, coryza, conjunctivitis*), Koplik spots, morbilliform rash spreading from head → trunk → extremities (14 d after exposure)**
- **Diagnosis: clinical; serum IgM; PCR on respiratory swab (or urine)**
- **Treatment: supportive care, Vit A for severe cases in children**
- **Post-exposure ppx: vaccination (within 72 h) or IG (within 6 days)**

Measles (Rubeola)

Take home points

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Question 7

- **A 19 year old male, previously healthy, complained of abdominal pain and nausea after eating leftovers from a restaurant.**
- **Within several hours, his symptom progressed to include weakness, headache and neck stiffness.**
- **Five hours later, he had developed purplish skin discolorations and a friend brought him to the emergency room for evaluation.**

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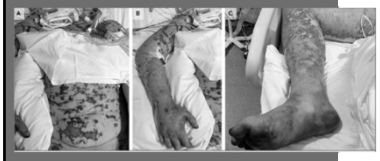
Question 7



- **Upon arrival to the hospital, he was noted to be febrile (40.4 degrees Celsius), tachycardic (HR 166), and tachypneic (RR 28), with BP 120/53, and with rapidly progressive reticular, purpuric rash.**
- **Within 24 hours, gram stain of blood cultures showed gram-negative diplococci.**

N Engl J Med. 2021 Mar 11;384(10):953-963.

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Question 7

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

A. **Meningococcemia**
B. **Disseminated *Streptococcus pneumonia***
C. **Disseminated gonorrhea**
D. **Secondary syphilis**

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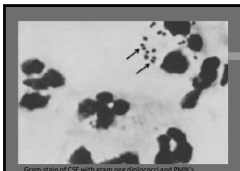
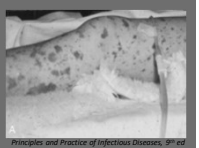
55 – Kitchen Sink: Syndromes Not Covered Elsewhere

Speaker: Stacey Rose, MD



Gram stain of CSF with gram neg diplococci and PMN's
https://www.cdc.gov/meningitis/lab-manual/chpt06-culture-id.html



Principles and Practice of Infectious Diseases, 9th ed

Invasive meningococcal disease (*N. meningitidis*)

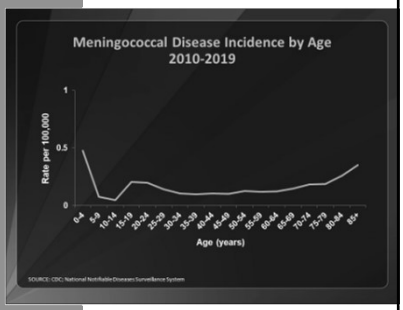
- Main manifestations:
  - *meningococcemia*
  - *acute meningitis*
- **Petechial or purpuric rash** in 40-80% of meningococcemia cases
- Fulminant disease **can progress to death within hours**
- Treat with 3rd generation cephalosporin (**ceftriaxone or cefotaxime**) and supportive care

Principles and Practice of Infectious Diseases, 9th ed.
https://www.cdc.gov/meningococcal/clinical-info.html

55

Epidemiology

In the US, infants, young adults, and adults >80 years of age have the highest rates of meningococcal disease



https://www.cdc.gov/meningococcal/surveillance/index.html

Transmission and risk factors

Transmission: person to person (respiratory droplets, oral secretions) from asymptomatic carriage or invasive disease

HOST / IMMUNE factors: asplenia; terminal complement deficiencies (native or acquired, such as use of complement inhibitors: eculizumab or ravulizumab); HIV

BEHAVIORAL / ENVIRONMENTAL factors: crowded conditions (college dorms, military barracks; Hajj and Umrah pilgrimages); daycare / preschool facilities; microbiologists; men who have sex with men (MSM)

https://www.cdc.gov/meningococcal/about/risk-community.html

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Detection of Ciprofloxacin-resistant, β-lactamase-producing *Neisseria meningitidis* Serogroup Y Isolates, United States, 2019–2020

HAN HEALTH ALERT NETWORK

This is an official CDC HEALTH ADVISORY

Treatment

First line: 3rd generation cephalosporin

Susceptibility testing recommended before changing to penicillin or ampicillin to complete course of therapy

https://emergency.cdc.gov/han/2020/han00433.asp

ANTIBIOTIC	CONSIDERATIONS
Rifampin	Drug interactions
Ceftriaxone	Recommended in pregnancy
Ciprofloxacin	Not generally recommended for persons < 18 yrs
Azithromycin	Limited data

https://www.cdc.gov/vaccines/pubs/surv-manual/chpt08-mening.html

Chemoprophylaxis for:

Household members
Childcare center contacts
Anyone directly exposed to an infected person's oral secretions (kissing; mouth to mouth resuscitation; intubation) within 7 d before symptom onset
HCW with exposure to respiratory secretions of infected patient

Meningococcal Immunization

- Recommendations revised in 2020

Summary:

- **MenACWY for all adolescents (11-12 yrs) plus persons at increased risk** due to host or environmental factors
- **MenB for those at increased risk** due to host or environmental factors; shared decision making for others

https://www.cdc.gov/vaccines/vpd/mening/public/index.html

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- **Epidemiology:**
  - **Host (*asplenia*; *complement deficiencies*; *complement inhibitors* – eculizumab or ravulizumab)**
  - **Environmental (crowded conditions – dorms, barracks, day care)**
  - **Person to person transmission from oral / respiratory droplets**
- **Clinical presentation: *acute meningitis* or *meningococcemia*; rapidly progressive, *petechial / purpural rash***
- **Treatment: ceftriaxone or cefotaxime; immunize for prevention and during outbreaks**
- **Chemoprophylaxis for close contacts within 7 d of exposure: *rifampin*, *ceftriaxone* (pregnancy), or *ciprofloxacin* (adults)**

Invasive meningococcal disease (*Neisseria meningitidis)*

Take home points

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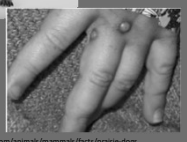
Question 8



https://www.nationalgeographic.com/animals/mammals/facts/prairie-dogs
PMID 14720564

- **A 4 year-old boy develops a new rash two weeks after adopting a new pet prairie dog.**
- **He also has fever and malaise.**
- **He is up to date on vaccinations and has no recent travel.**
- **His parents and older brother remain well.**

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Question 8

https://www.nationalgeographic.com/animals/mammals/facts/prairie-dogs

- **To prevent spread of this illness to other household members, which of the following would be recommended?**

A. **Avoid contact with the pet**
B. **Avoid contact with the child's skin lesions or bedding**
C. **Smallpox vaccination**
D. **All of the above**

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Monkeypox (MPV) then and now

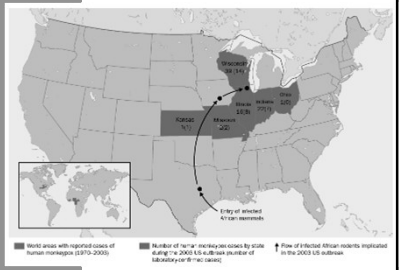
MPV – orthopoxvirus (same family as variola = smallpox)

Incubation: 5 d – 3 weeks

Papular / vesicular / pustular / crusting lesions

Usually self-limited 2-4 weeks

US outbreak: 2003 related to imported rodents



Di Giulio, D. B., & Eckburg, P. B. (2004). Human monkeypox: an emerging zoonosis. *The Lancet. Infectious diseases*, *4*(1), 15-25. https://doi.org/10.1016/s1473-3099(03)00856-9

Viewpoint ONLINE FIRST FREE

June 13, 2022

Monkeypox in 2022—What Clinicians Need to Know

Jeannette Guarner, MD[1]; Carlos del Rio, MD[2,3]; Preeti N. Malani, MD, MS[4,5]

Author Affiliations | Article Information

JAMA. Published online June 13, 2022. doi:10.1001/jama.2022.10802

- ***Diagnosis*: PCR of swab from a lesion**
- ***Post-exposure ppx*: smallpox vaccination**
- ***Antivirals*: tecorvirimat; brincidofovir**
- ***Intravenous vaccinia immune globulin* (VIGIV) if T cell immune deficiency**

- 2022 outbreak:
  as of June 9, 2022,:
  > 1350 lab-confirmed cases
  > 30 countries
  suspected sexual transmission (inoculation to skin / mucosal surfaces by direct contact)

Kitchen Sink summary

55 – Kitchen Sink: Syndromes Not Covered Elsewhere

Speaker: Stacey Rose, MD

Kitchen Sink summary - 1

Whipple's:

- Classic: arthralgia, diarrhea, weight loss
- Dx with duodenal bx (PAS+, foamy macrophages)
- or PCR of tissue (heart valve for endocarditis)

Acute Rheumatic fever:

- Kids / young adults with migratory polyarthritis, carditis, chorea, subcutaneous nodules, erythema marginatum following GAS pharyngitis
- Monthly IM penicillin prophylaxis for10 years or to age 40 if carditis + residual valvular disease

https://www.cdc.gov/groupastrep/diseases-public/rheumatic-fever.html

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Kitchen Sink summary - 2

Botulism:

- Due to *C. botulinum* toxin
- Food; infant; wound (black-tar heroin); iatrogenic
- Descending flaccid paralysis (starts with cranial nerves)
- Antitoxin / supportive care

***Vibrio vulnificans*:**

- Liver disease at risk
- Exposure to raw seafood or contaminated wound (brackish water)
- Rapidly progressive, hemorrhagic bullae / sepsis
- Fluoroquinolone, ceftriaxone, debridement

https://www.cdc.gov/vibrio/wounds.html

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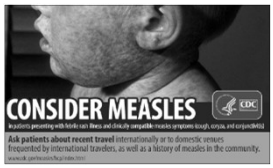
Kitchen Sink summary - 3

Pertussis

- Clinical diagnosis: >2 weeks of cough plus paroxysms, inspiratory whoop, post-tussive emesis, apnea
- Macrolide if within 3 weeks of onset or as PEP for contacts at risk of severe disease

Measles

- unvaccinated + travel history
- 3 C's – coryza, cough, conjunctivitis
- Koplik spots
- Rash spreads from head to trunk to extremities
- Contagious and severe
- Later – SSPE (degenerative neurologic dz / seizures)



https://www.cdc.gov/measles/consider-measles-infographic.html

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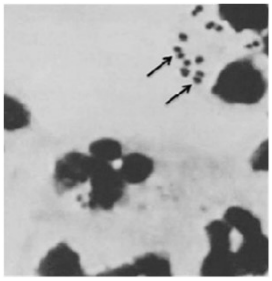
Kitchen Sink summary - 4

Monkeypoxvirus

- Orthopoxvirus; same family as variola virus (smallpox); vaccine cross-protective
- Incubation 5d-3 weeks
- Usually self-limited, lesions crust and scar
- Spread by direct contact (sexual); past outbreak in US due to exposure to infected rodents

Invasive meningococcal disease

- Host (asplenia/ complement deficiency or inhibitor); environmental (crowded conditions) risks
- Rapidly progressive; meningitis; purpuric rash
- Rx: 3rd gen cephalosporin
- Ppx for close contacts within 7 d: *rifampin*, *ceftriaxone* (pregnancy), or *ciprofloxacin* (adults)
- No rx for asx carriage



https://www.cdc.gov/meningitis/lab-manual/chpt06-culture-id.html

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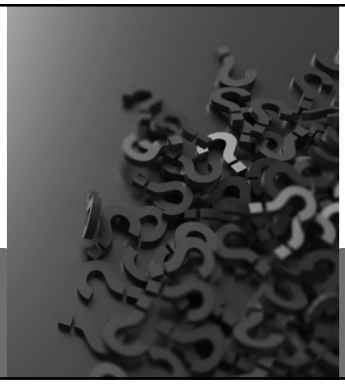


Questions?

Stacey Rose, MD, FACP, FIDSA
srrose@bcm.edu

Online Only Lectures			
#	Duration	Title	Faculty
OL - 1	45 Mins	Encephalitis including West Nile and Rabies	Allan Tunkel, MD
OL – 2	45 Mins	Management of AIDS-Related Opportunistic Infections II	Henry Masur, MD
OL – 3	45 Mins	Epididymitis, Orchitis, and Prostatitis	Barbara Trautner, MD
OL - 4	56 Mins	Management of AIDS-Related Opportunistic Infections III	Henry Masur, MD
OL - 5	40 Mins	ID Bootcamp: HIV	Roy Gulick, MD
OL - 6	50 Mins	ID Bootcamp: Transplant	Camille Kotton, MD
OL - 7	33 Mins	Other Antibacterial Drugs (Macrolides, TMP, SMX, etc)	David Gilbert, MD
OL – 8	25 Mins	Statistics	Khalil Ghanem, MD
OL – 9	60 Mins	Infections in Solid Organ Transplant Recipients	Barbara Alexander, MD
OL – 10	30 Mins	Even More Worms	Edward Mitre, MD

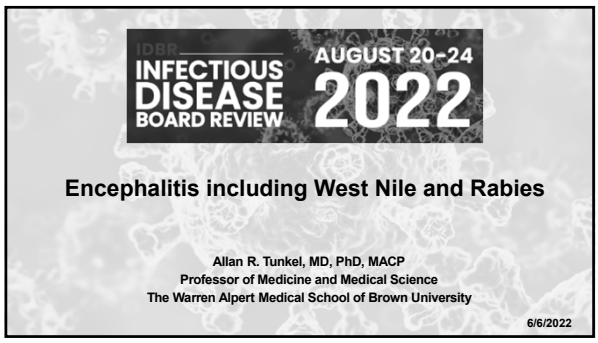
OL1

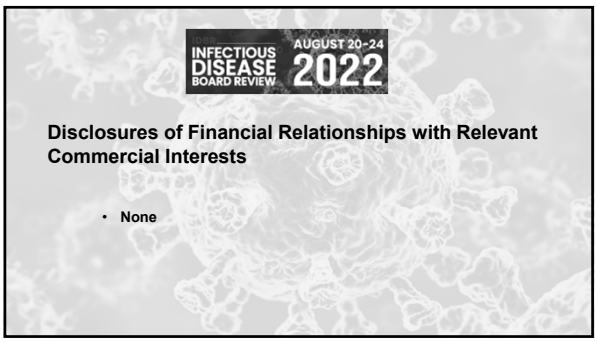
Encephalitis Including West Nile and Rabies

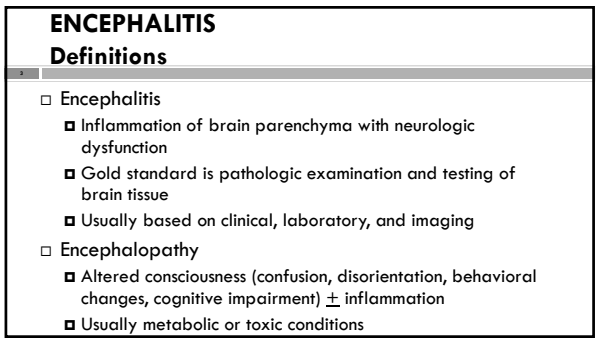
Dr. Allan Tunkel

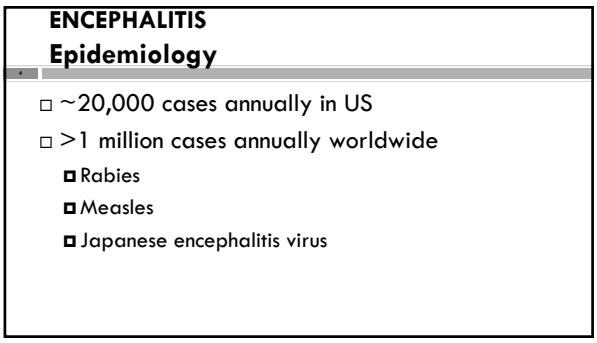
Online Only Lectures - Encephalitis including West Nile and Rabies

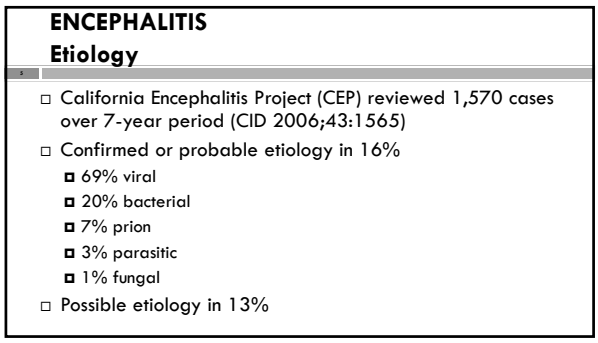
Speaker: Allan Tunkel, MD

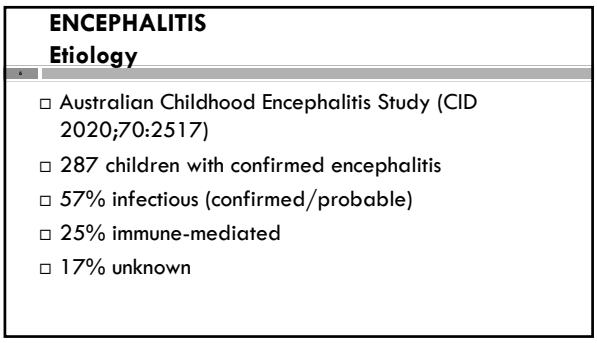












Reasons Etiology not Identified

7

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

General Approach

8

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

Tunkel et al. Clin Infect Dis 2008;47:303
Venkatesan et al. Clin Infect Dis 2013;57:1114

CASE #1

9

- 80-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

CASE #1

10

- 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

11

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

ANSWER #1

12

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

Herpes Simplex Encephalitis

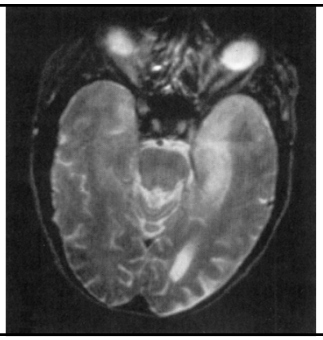
13

- Epidemiology
  - Among the most severe of all human viral infections of brain; >70% mortality with no or ineffective therapy
  - Accounts for10-20% of encephalitis viral infections
  - Occurs throughout the year and in patients of all ages
  - Increased risk in those with defects in TLR3 pathway?
  - Majority in adults caused by HSV-1
- Clinical features
  - Fever, personality change, dysphasia, autonomic dysfunction

Herpes Simplex Encephalitis

14

- 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

16

- 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

17

- 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

18

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

Other Herpesviruses

19

- Human herpesvirus 6
  - Immunocompromised patients, but seen in children
  - CSF PCR (sensitivity >95%); high rate of detection in healthy adults (PPV only 30%)
  - Ganciclovir or foscarnet
- B virus
  - Bite or scratch from old world primates (macaques)
  - Vesicular eruption at site; neurologic disease in 3-7 days
  - Culture and PCR at site of bite; CSF PCR
  - Prophylactic valacyclovir
  - Therapy: acyclovir, valacyclovir, or ganciclovir

Other Herpesviruses

20

- 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

21

- 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

22

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

QUESTION #2

23

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

ANSWER #2

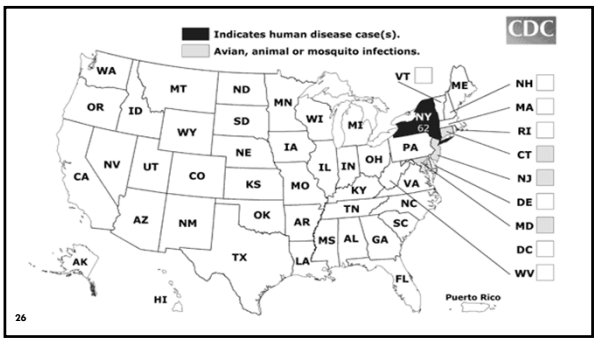
24

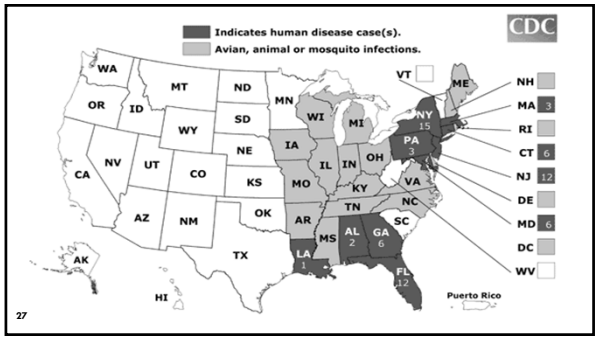
Which of the following tests is most likely to establish the etiology of this patient's encephalitis?

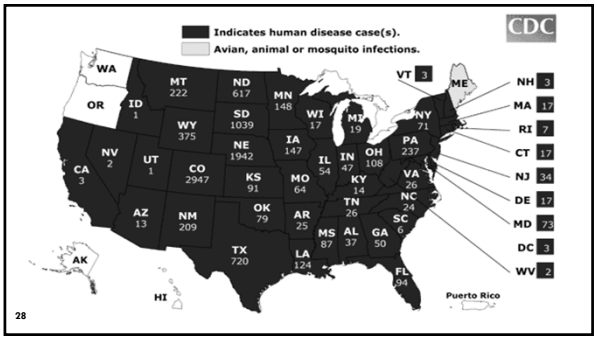
A. Serum IgM
B. Serum polymerase chain reaction
C. Cerebrospinal fluid IgM
D. Cerebrospinal fluid polymerase chain reaction
E. Brain MRI

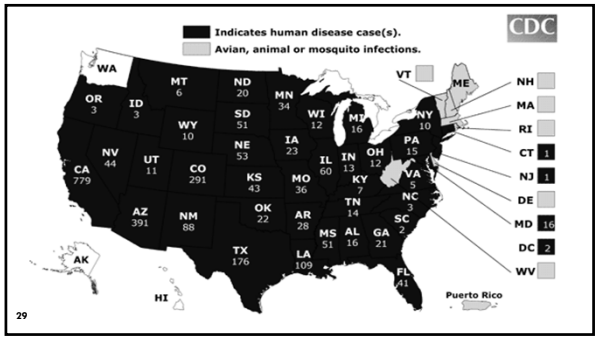
West Nile Virus (WNV) Encephalitis

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



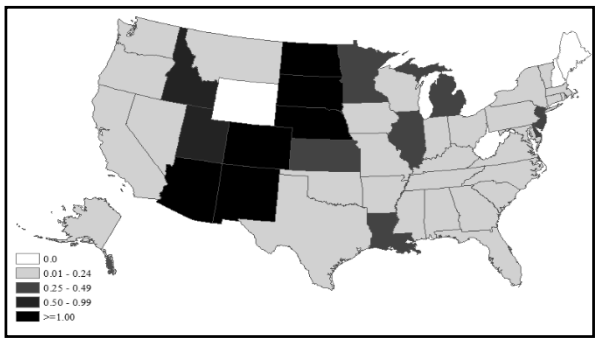






WNV Human Cases Reported To CDC

Year	Total 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 (1/11/22)	2695	1855	191

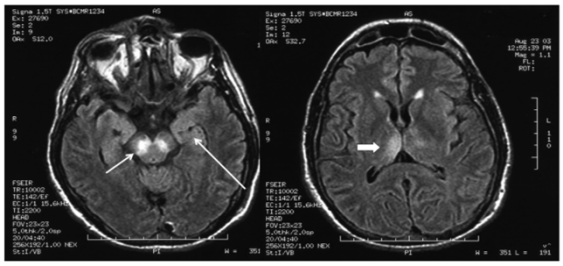


West Nile Virus Clinical Syndromes

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

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

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

Other Arboviruses

- 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

Other Arboviruses

37

- 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

38

- 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

39

- Acute disseminated encephalomyelitis
  - Usually 1-2 weeks after the rash; 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

40

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).
- Role in testing of enigmatic cases

CASE #3

42

- 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

43

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

ANSWER #3

44

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

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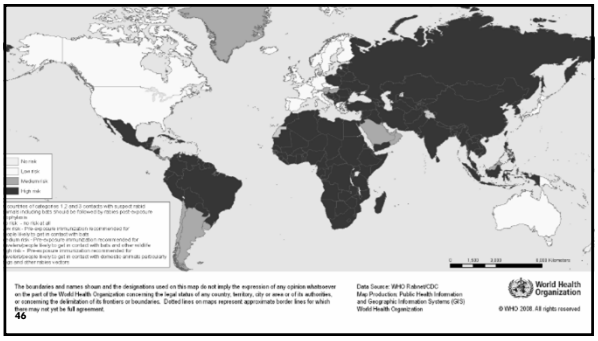
B. Rabies immune globulin in the deltoid muscle
C. Rabies immune globulin in the buttocks
D. Rabies immune globulin intraperitoneally
E. Nothing further is indicated

Rabies

45

- 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



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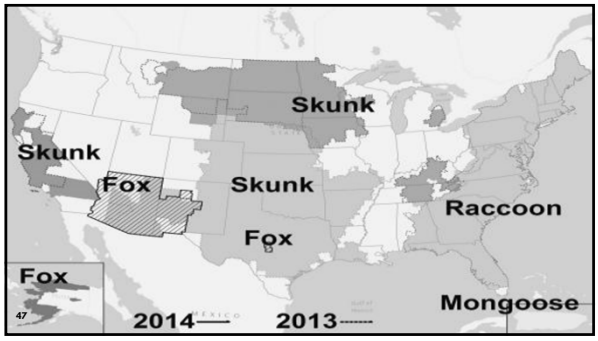

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Rabies

48

- 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

49

- 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

50

- 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

51

- 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

52

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

ANSWER #4

53

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

54

- 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

55

- 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

56

- 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

57

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

Anti-NMDAR Encephalitis

58

- 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

59

- 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%

60 QUESTIONS

Allan R. Tunkel, MD, PhD, MACP
Email: allan_tunkel@brown.edu

OL2

Management of AIDS-Related Opportunistic Infections II

Dr. Henry Masur

INFECTIOUS DISEASE BOARD REVIEW AUGUST 20-24 2022

Management of AIDS-Related Opportunistic Infections II

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

6/27/2022

INFECTIOUS DISEASE BOARD REVIEW AUGUST 20-24 2022

Disclosures of Financial Relationships with Relevant Commercial Interests

- None

Question #1

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

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

The pharmacy cannot obtain sulfadiazine or pyrimethamine.

The best option for therapy of the toxoplasmosis would be:

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

Answer #1

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

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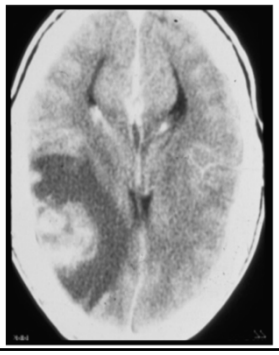
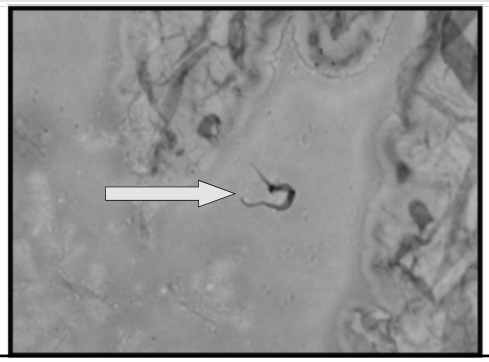
The best option for therapy of the toxoplasmosis would be:

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

Question #2

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





Question #2

What is the most likely diagnosis?

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

Answer #2

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

- **What is the most likely diagnosis?**

A. Toxoplasmosis
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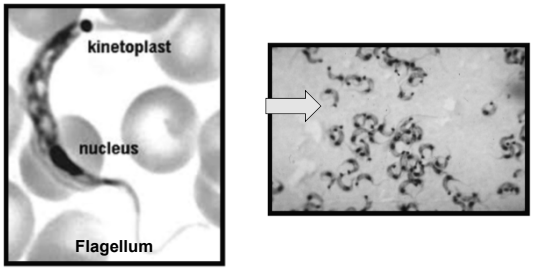
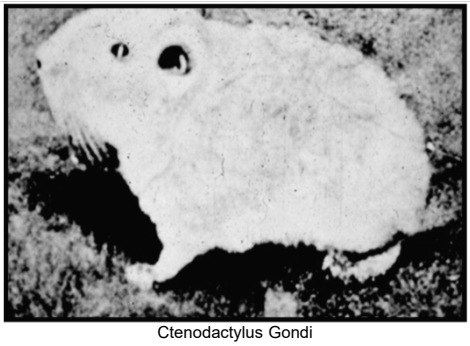
Trypanosoma cruzi
Blood Smear and CSF

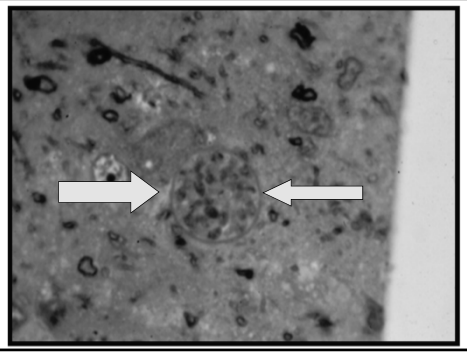


Badero et al, AIDS THERAPY, 4th Ed

Toxoplasmosis



Ctenodactylus Gondi



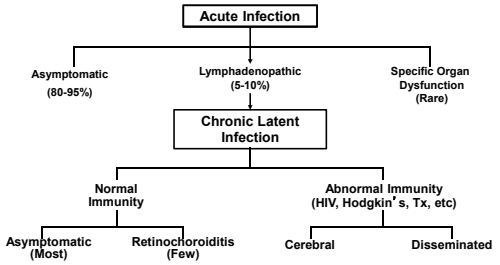
Incidence of Toxoplasmosis

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

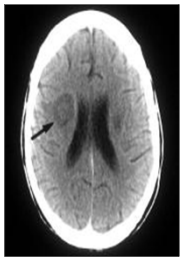
Transmission of Toxoplasma

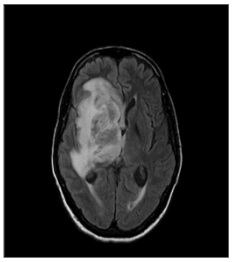
- **Feline feces (cats, but also lions etc)**
  - Oocysts begin to be excreted 20 - 24 days post infection
  - Excretion persists 7 - 21 days
- **Rare Meat (Lamb>Beef>Pork)**
- **Unusual**
  - Raw shellfish, goat milk (reported 2009-2010)
  - Iatrogenic
    - Transfusion/Needle injury/transplant
- **Congenital**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

Clinical Manifestations of Toxoplasmosis when Acquired Post-Partum



CNS Toxoplasmosis


Non Contrast CT


Flair MRI

Evaluation of CNS Mass Lesions in Patients with HIV/AIDS

Toxoplasmosis
Lymphoma
Tuberculosis
Fungus
Nocardia
Bacterial
Syphilis
Kaposi
Chagoma
Glioblastoma

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

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

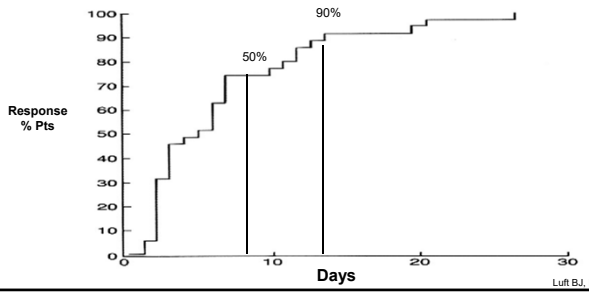
Response to Empiric Therapy

Empiric Diagnosis of CNS Toxo

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

Time to Neurologic Response for CNS Toxo

35 CNS Toxo Patients Treated with Clindamycin - Pyrimethamine



Luft BJ, NEJM 1993

Definitive Diagnosis of Cerebral Toxoplasmosis

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

Therapy for Cerebral Toxoplasmosis

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

Note: Sulfadiazine and Pyrimethamine may be unavailable or unrealistically expensive

Adjunctive Therapies for CNS Toxoplasmosis

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

Primary Prevention of Toxoplasmosis in Patients with HIV

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

Primary Prevention of Toxoplasmosis in PLWH

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

Mycobacteria Species

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

Question #3

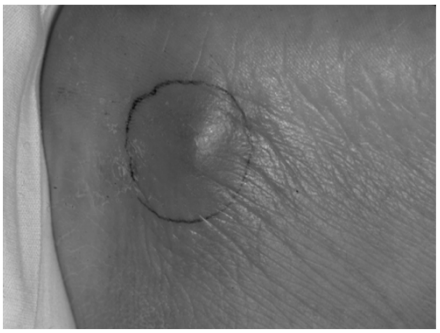
A 45-year-old male with HIV (CD4<10 cells/cc3, VL> 100k) has been taking TMP-SMX and Efavirenz-Tenofovir-Emtricitabine only intermittently.

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

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

The lesion is to be aspirated again.

See next slide



Question #3

What advice do you give the lab and hospital epi?

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

Answer #3

What advice do you give the lab and hospital epi?

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D. This is treatable with trimethoprim-sulfamethoxazole
E. This can be cultured only at 32°C with iron enriched medium

TB Prophylaxis in PWH

- **There are TWO indications for PWH**
  - Positive screening test for LTBI, and
    - No evidence of active TB disease, and no prior history of treatment for active disease or latent TB infection
  - Close contact with a person with infectious TB is given prophylaxis for TB
    - Regardless of screening test result
- **For persons without HIV**
  - Close contact with a person with infectious TB is given prophylaxis
    - Only if IGRA or ppd pos with 5mm

Prevention of TB in Persons With HIV

- **Preferred**
  - 3HP: Weekly INH/Pyr plus Rifapentine x 12w
  - 3HR: Daily INH/Pyr plus rifampin x 3 months (but only with efavirenz!!)
    - Recommend by NIH OI guidelines but not CDC
- **Alternate**
  - INH: Daily x 6-9 months
  - 4R: Daily rifampin x 4 months
  - 1HP: Daily INH/Pyr plus Rifapentine x 12 w
    - (with efavirenz or soon to be assessed-dolutegravir)

Therapy for HIV Positive Patients With Active TB

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

Active TB disease: Treatment Durations Regardless of HIV Status

Review from Susan Dorman

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

Active TB disease: Treatment Durations Regardless of HIV Status

Review from Susan Dorman

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

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

- INH + Rifapentine + Moxifloxacin + Pyrazinamide Months 1+2
- INH + Rifapentine + Moxifloxacin Months 3+4

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

(Drug shortages not testable!)

Pulmonary (including pleural)	Rifampin + INH + PZA + EMB	Rifampin + INH	
Pulmonary that is cavitary plus cultures still pos at completion of 2 months of tx		Rifampin + INH	
Bone and Joint (6 to 9 months)		Rifampin + INH	Consider extending to 9 mos
CNS (9 to 12)		Rifampin + INH	Consider extending to 12 months

Non Tuberculous Mycobacterial Infections in HIV Infected Patients

You Need Microbiologic or Epidemiologic Clue on Exam!

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

Mycobacterium Avium Complex

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

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

Question #4

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

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

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

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

What type of isolation is appropriate?

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

Question #4

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

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

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What type of isolation is appropriate?

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

Mycobacterium Avium Intracellulare Complex

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

Mycobacterium Avium Intracellulare

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

Mycobacterium Avium Intracellulare Diagnosis

- **Source of isolates**
  - **Blood**
    - Bactec (7-14 days)
  - **Sputum/stool/urine**
    - Low predictive value
- **Lab identification**
  - Specific DNA Probes for specimens/ cultures
  - MALDI-TOF

MAC: Susceptibility Testing

Recommended for primary isolates

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

Treatment for MAC

- **Antiretroviral therapy**
  - **Start within 2 weeks of anti mac therapy**
- **Specific therapy**
  - **Clarithro (or Azithro) + Ethambutol**
    - Rifabutin optional 3rd drug: use if severe disease ("high burden of organisms")
    - Beware drug interactions with clari or rifabutin

Treatment for MAC

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

Salvage Therapy for MAC Not For Boards

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

~~Primary MAC Prophylaxis 2021~~

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

What Is This?

Immune Reconstitution Inflammatory Syndrome

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

Immune Reconstitution Inflammatory Syndrome

- **Predictors**
  - Pre therapy low CD4 or high VL
  - Prior OI or short therapy for OI
  - High pathogen load
- **Outcome – morbidity can be severe**
  - Obstructed bowel, biliary tract, ureter, bronchus
  - Myocarditis, meningeal inflammation/increased ICP, serositis (pleura, peritoneum, pericardium)

Pathogens Commonly Associated with IRIS

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

Examples of IRIS

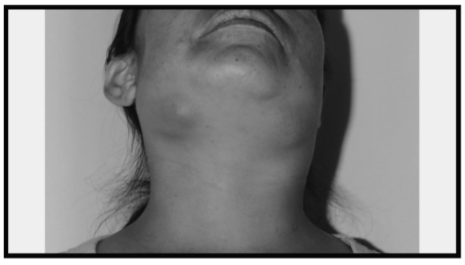
PATHOGEN	NOMENCLATURE	TYPICAL/CHARACTERISTICS OF THE DISEASE
Mycobacterium tuberculosis	TB-IRIS	Paradoxical exacerbation of TB
Nontuberculous mycobacteria (NTM)	NTM-IRIS	Mainly lymphadenitis, also pulmonary and abdominal diseases
Bacille Calmette-Guérin (BCG)	BCG-IRIS	Necrotizing regional lymphadenitis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

Cecil Textbook French and Meintjes)

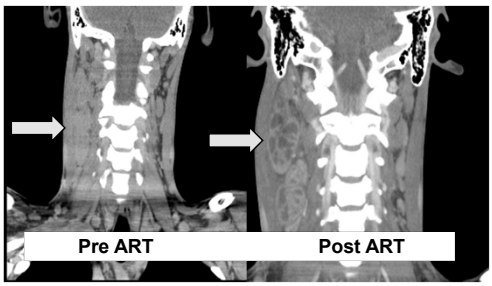
Management of IRIS

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

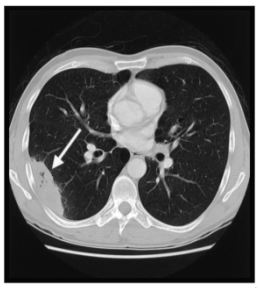
Immune Reconstitution Inflammatory Syndrome (Mycobacterium avium complex)



MAC IRIS in Patient with HIV



CT Scan: Pleural-Based MAC



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

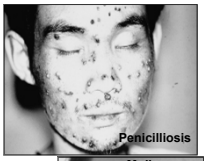
Life Threatening IRIS –How Would They Test for These?

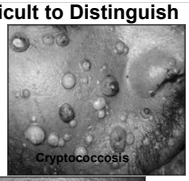
- **Unmasking**
  - Unrecognized lymphadenitis due to TB, MAC, Fungi
  - Unrecognized cryptococcal meningitis
  - Unrecognized CMV retinitis
  - Inflammation of Kaposi sarcoma skin lesion
  - Pulmonary infiltrates due to PCP, fungi, TB
- **Exacerbation of crypt meningitis – increased intracranial pressure**
  - New focal findings
- **Transaminase flair in patient with untreated HBsAg or HBcoreAb**
  - Transaminase flair due to HBV
- **Exacerbation of previously treated CMV retinitis, PCP, TB**

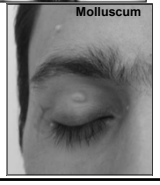
Fungal Diseases in HIV-Infected Persons

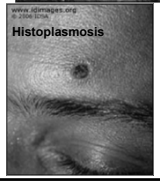
- **Candidiasis**
- **Cryptococcosis**
- **Histoplasmosis**
- **Coccidiomycosis**
- **Talaromyces**

Skin Lesions HIV-Difficult to Distinguish









Importance of HIV Associated Cryptococcosis

- **Prevalence**
  - **Pre ART in United States: 5 – 8% of patients**
  - **More common in Sub-Saharan Africa**
    - 15% of AIDS related deaths
  - **Less common in current era in US**
- **CD4 Count at Onset**
  - **<100 cells/uL in 90% of patients**

HIV-Related Cryptococcal Meningitis

- **Clinical Presentation**
  - **CNS manifestations are usually subacute (median 2 weeks)**
    - Classic neck stiffness and photophobia only occur in 25%
    - Many cases are disseminated when initially diagnosed-any organ
      - e.g., May mimic PCP or present as lobar consolidation
    - Crypt IRIS is typically more acute than active infection
  - **Meningeal involvement may initially be asymptomatic**
    - Encephalopathic manifestations usually due to high ICP

Diagnosis of Cryptococcal Disease

- **CSF**
  - Often minimal abnormalities with lymphocyte pleocytosis
  - Opening pressure >20-25cm H20 in 60-80% of patients
- **Crypt Antigen**
  - Highly sensitive in serum and CSF
  - CSF crypt ag can be positive months before symptomatic disease
  - Both blood and CSF should be tested
- **Culture positive**
  - Blood: 60% of patients with clinical meningitis
  - CSF: 80% in patients with clinical meningitis
  - Growth in < 7 days

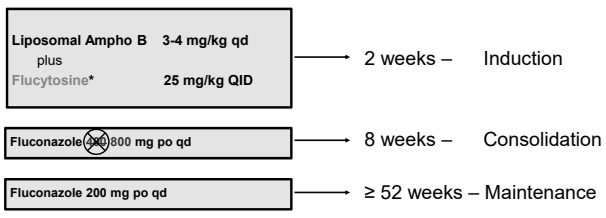
Antigen Tests for Cryptococcal Disease

- **Blood, Serum, Plasma, CSF:**
  - **Antigen Latex Agglutination or**
  - **Enzyme Linked Immunoassay (EIA) or**
  - **Cryptococcal Lateral Flow Assay (IMMY LFA)**
    - Dipstick test for whole blood/serum/plasma and CSF
    - Four-fold higher titers than Latex Aggl or EIA
    - High titers suggest (1:160) or highly suggest (1:640) dissemination

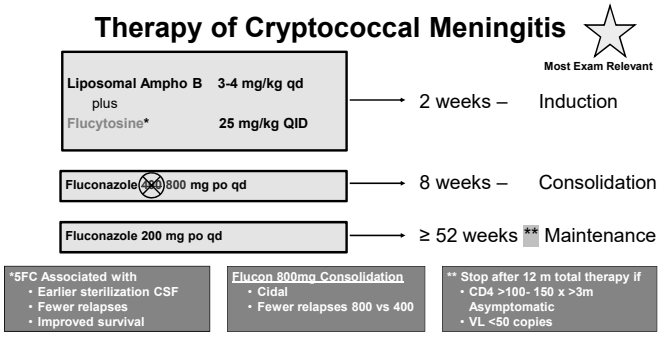
PCR Tests for Cryptococcal Disease C. neoformans and C. gatti

- **PCR for CSF**
  - **Screening test available in multiplex assays**
    - False positives and false negatives (!!) reported
    - Simultaneous antigen test should be performed if cryptococcal meningitis is suspected and PCR is negative
  - **May be useful for distinguishing**
    - **IRIS (PCR neg) and clinically acute**
    - **Relapse (PCR positive) and more subacute**

Therapy of Cryptococcal Meningitis and Extrapulmonary Disease



Therapy of Cryptococcal Meningitis



Therapy of HIV Related Cryptococcal Meningitis

- **Regimens with Liposomal ampho B <2 weeks**
  - 1 week of liposomal Ampho or 1 Day regimens followed by Fluc +/- 5FC
  - **NOT FOR EXAM 2022 and probably not for US**

Question #5

Patient presents with cryptococcal meningitis, severe headache, and opening pressure >25 cm H20 on day 1 of therapy

Which of the following would you initiate if the CNS symptoms persist on day 2:

A. Dexamethasone
B. Acetazolamide
C. Mannitol
D. Lumbar puncture to remove fluid
E. Lumbar puncture for repeat diagnostic studies and MRI to assess for a second, concurrent infectious or neoplastic process

Answer #5

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E. Lumbar puncture for repeat diagnostic studies and MRI to assess for a second, concurrent infectious or neoplastic process

Elevated CSF Pressure

Most Exam Relevant

- **75% of patients have Opening Pressure >20 cm CSF**
  - Abnormal ≥25 cm CSF
  - Left lateral decubitus, flat position
- **Symptoms**
  - Blurred vision, confusion, obtundation
- **Management: IF symptomatic and >25cm**
  - Remove volume to reduce pressure by half or <20cm H20 or remove 20-25 ml if no manometer
  - Continue LPs daily for symptomatic patients until stable for at least 2 days
  - Shunt if regular LPs required for "many" days
- **Not routinely recommended**
  - Corticosteroids, Mannitol, Acetazolamide

Consolidation Therapy

(Duration of Therapy: ≥8 Weeks)
Followed by Maintenance Therapy

- **Perform LP and repeat CSF culture at 2 Weeks**
  - Success = Substantial clinical improvement AND negative CSF culture
  - Need not wait for culture if patient symptomatically improved
  - Persistent CSF crypt ag is not indicative of failure
- **Preferred Regimen**
  - Fluconazole 800 mg PO once daily
    - For clinically stable patients with negative CSF cultures, dose can be reduced to 400 mg PO once daily
    - If CSF remains positive (but clinically stable) after 2 weeks of induction therapy, increase fluconazole dose to 1,200mg and perform LP 2 weeks later
    - Duration of consolidation therapy should be 8 weeks from the time of negative CSF culture

Maintenance Therapy

- **Preferred regimen**
  - Fluconazole 200 mg PO once daily
- **Stop if all the following criteria are fulfilled:**
  - At least 1 year from initiation of antifungal therapy, and
  - Patient remains asymptomatic from cryptococcal infection, and
  - CD4 count ≥100 cells/mm^3, and
  - Suppressed HIV RNA in response to effective ART

Monitoring Therapy for Cryptococcal Meningitis

- **During Therapy**
  - **"Monitoring serum or CSF CrAg titers is of no value in determining initial response to therapy and is not recommended" --NIH CDC IDSA Guideline**
  - **Monitor 5FC levels after dose 3 or 5**
  - **Negative serum or CSF Ag is NOT required for termination of therapy**
    - Exam: Use crypt ag for diagnosis, NOT for monitoring

Commonly Asked Questions About Crypt Meningitis

- **Liposomal Amphotericin B Induction for < 14 days**
  - Not recommended in US and not for boards
- **Fluconazole based regimens in US as initial Rx**
  - No
- **Amphotericin plus Fluconazole induction**
  - Not for boards and not recommended in US

When To Start ART

- **4-6 weeks after initiation of antifungal therapy for meningitis**
  - May have to defer for patients with severe disease
  - When to start for non CNS disease less clear
- **Monitor for IRIS**
  - 10-30% of crypt meningitis patients experience IRIS
  - Distinguishing IRIS from treatment failure is challenging
    - IRIS
      - CSF culture negative
      - Negative CSF Biofire is useful early indicator of IRIS

HIV Related Focal Pulmonary Cryptococcosis

- **If Serum LFA Titer ≤1:320**
- **Fluconazole 400-800mg qd x 10 weeks and then**
- **Fluconazole 200mg daily for 6 months**

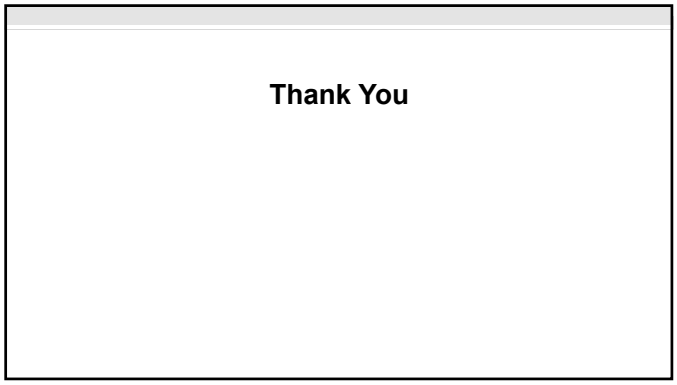
Asymptomatic Cryptococcal Antigenemia

- **Recommendation:**
  - **Screen patients with CD4< 100**
    - Frequency: 2.9% if CD4 <100, 4.3% if CD4 < 50
  - **Positive serum ag predicts development of active disease**
- **If Positive Serum Crypt Ag**
  - **Perform LP and blood cultures to determine Rx**
  - **If CSF positive or serum LFA is >=640**
    - Treat like crypt meningitis/disseminated (Ampho/5FC)
  - **If CSF negative and low Crag titer or LFA <= 1:320**
    - Treat with fluconazole 400mg or 800mg x6 months

IDSA OI Guidelines for Crypt 2021

Flucytosine

- **Oral only form available in US**
  - 25mg/kg po q6h
- **Toxicities**
  - Marrow suppression, hepatitis, diarrhea
- **Monitoring**
  - Serum level drawn after 3-5 doses
  - Renal elimination
    - monitor renal function
  - Maintain 2 hr peak at 30-100mg/ml



OL3

Epididymitis, Orchitis, and Prostatitis

Dr. Barbara Trautner

Online Only Lectures - Epididymitis, Orchitis, and Prostatitis

Speaker: Barbara Trautner, MD

IDBR INFECTIOUS DISEASE BOARD REVIEW AUGUST 20-24 2022

Epididymitis, Orchitis, and Prostatitis

Barbara W. Trautner, MD, PhD
Professor of Medicine
Baylor College of Medicine

6/21/2022

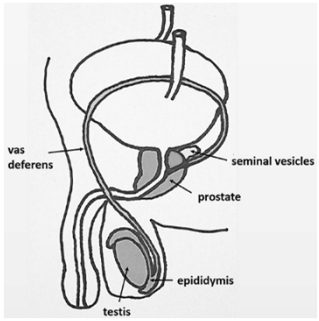
INFECTIOUS DISEASE BOARD REVIEW AUGUST 20-24 2022

Disclosures of Financial Relationships with Relevant Commercial Interests

- Genentech for COVID-related research

Overview

- Epididymitis
- Prostatitis
  - Acute
  - Chronic
- Orchitis



Case #1

72 year-old man presented to ER with fever, urinary retention. No culture sent. Sent home with transurethral catheter and ciprofloxacin. Walks into ID clinic one month later with the urinary catheter is still in place. Temp 102.5, costovertebral angle tenderness present on exam. Admitted and started on ciprofloxacin.

Blood cultures: *Serratia marcescens (sensitive to cipro)*

Urine cultures: *Serratia marcescens and Klebsiella pneumoniae (both sensitive to cipro)*

On hospital day 3, he is still febrile to 102.3, and he reports right testicular pain/swelling.

Case #1 continued

Given his fevers on 3 days of ciprofloxacin, and the new development of right testicular pain and swelling, your next step is to:

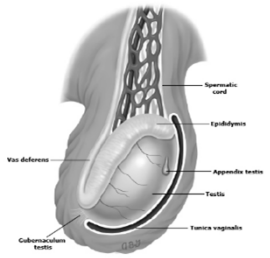
A. Change antibiotics to ertapenem
B. Consult urology
C. Order a scrotal ultrasound
D. Add doxycycline

Case #1 continued

Given his fevers on 3 days of ciprofloxacin, and the new development of right testicular pain and swelling, your next step is to:

A. Change antibiotics to ertapenem—no, organisms are sensitive to cipro
B. Consult urology—no, not concerning for torsion and he can urinate
C. Order a scrotal ultrasound—yes, will let you see structures in GU tract
D. Add doxycycline—no, because we are not worried about STI here; we know he is bacteremic from a urinary source

Normal testicular anatomy



The testicle is vertical and its anterior portion is surrounded by the tunica vaginalis.

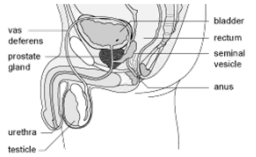
UpToDate

Epididymitis: Clinical Presentation

- Testicular pain, swelling, and tenderness
- Scrotal erythema
- Fever
- Dysuria or other urinary irritative symptoms
- Urethral discharge
- Reactive hydrocele can occur
- Epididymo-orchitis if testes also inflamed
- Gradual onset (if sudden, consider testicular torsion)
- Cremasteric reflex is preserved

Risk factors for epididymitis

- Insertive anal intercourse
- Urinary outlet obstruction
- Prostate biopsy
- Urinary tract instrumentation
- Immunosuppression



Workowski et al, Sexually Transmitted Infections Treatment Guidelines, 2021
Recommendations and Reports / Vol. 70 / No. 4
UpToDate Acute Scrotal Pain in Adults

Etiologic agents of epididymitis

>14 and < 35 years of age: typically sexually transmitted

- *Neisseria gonorrheae*
- *Chlamydia trachomatis*
- *Mycoplasma genitalium*

Chronic or atypical

- *Mycobacterium tuberculosis*
- *Brucellosis*
- *Nocardia*
- *Blastomycosis*

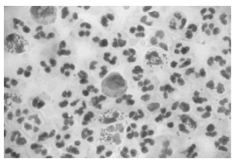
> 35 years of age: enteric flora or spread from urine

- *Escherichia coli*
- *Klebsiella*
- *Proteus*
- *Pseudomonas*
- Enterococci

McGowan, Chapter 110, in Mandell, Douglas, and Bennett's Principles and Practice of Infectious Diseases, 9th edition

Workup of epididymitis

- Physical exam
  - Intact cremasteric reflex
  - Testes in normal location
  - No draining sinus
- Gram stain of urethral secretions
- Urinalysis and urine culture
- Nucleic acid amplification test (NAAT) of urine
  - *N. gonorrhoeae*
  - *C. trachomatis*
- Consider blood cultures
- Failure to improve within 48-72 hours
  - Scrotal ultrasound
- Call urology if concern for torsion



https://en.wikipedia.org/wiki/Neisseria_gonorrhoeae

Gram stain of urethral discharge

Differentiating epididymitis from torsion

Table 1. Selected Differential Diagnosis of Acute Scrotum

Condition	*Typical presentation*	*Examination findings*	*Ultrasound findings*
Epididymitis	Gradual onset of pain that occasionally radiates to the lower abdomen; symptoms of lower urinary tract infection	Localized epididymal tenderness that progresses to testicular swelling and tenderness; normal cremasteric reflex; pain relief with testicular elevation (Prehn sign)	Enlarged, thickened epididymis with increased blood flow on color Doppler
Orchitis	Abrupt onset of testicular pain	Testicular swelling and tenderness; normal cremasteric reflex	Testicular masses or swollen testicles with hypoechoic and hypervascular areas
Testicular torsion	Acute onset of pain, usually severe	High-riding transversely oriented testis; abnormal cremasteric reflex; pain with testicular elevation	Normal-appearing testis with decreased blood flow on color Doppler

Trojian, American Family Physician, 2009

Online Only Lectures - Epididymitis, Orchitis, and Prostatitis

Speaker: Barbara Trautner, MD

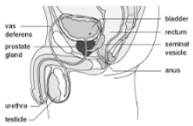
Treatment of epididymitis

- If patient is low risk for sexually transmitted infection
  - Levofloxacin or trimethoprim-sulfamethoxazole—for enterics
- If risk for sexually transmitted infection
  - And NO insertive anal intercourse
    - Ceftriaxone—for *N. gonorrhoeae*
    - Doxycycline (azithro as alternative)—for *C. trachomatis*
  - And YES insertive anal intercourse
    - Ceftriaxone—for *N. gonorrhoeae*
    - Fluoroquinolone (can cover for chlamydia)—for enterics
- For all: scrotal elevation and cold packs

UpToDate Acute Scrotal Pain in Adults
MMWR Vol. 70, No. 4,2021
Trojian, American Family Physician, 2009

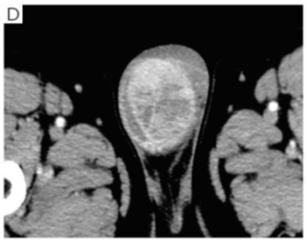
Epididymitis: Management

- Medical management
  - Antibiotics
  - Scrotal elevation and ice packs
- Complications
  - Testicular infarction
  - Scrotal abscess
  - Epididymo-orchitis



Case #2

- 63 year-old man currently living homeless in Houston presented with a gradually enlarging, painful right testicle over the past 4 months
- Afebrile and he has thickened right scrotal skin but no fistula on exam
- WBC 15,000; negative HIV, AFP, RPR, and beta-HCG
- CT with contrast shows uneven enhancement of right testes and epididymis; the left epididymis was also enlarged with diffuse enhancement
- What test would you NOT do next?
  - A. TB spot
  - B. Urine culture for AFB
  - C. Testicular biopsy
  - D. Urine PCR for TB



Li, Chen, Fang et al, Quant Imaging Med Surg 2021; 11(6)

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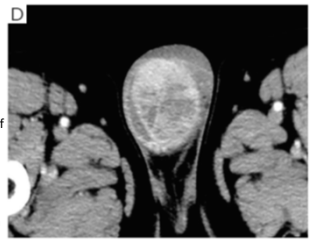
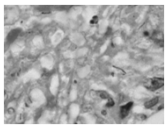
- What test would you NOT do next?
  - A. TB spot
  - B. Urine culture for AFB
  - **C. Testicular biopsy-contraindicated in germ cell tumor, also can be insensitive/false negative**
  - D. Urine PCR for TB



Li, Chen, Fang et al, Quant Imaging Med Surg 2021; 11(6)

Tuberculous epididymo-orchitis

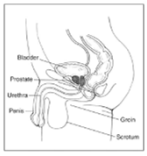
- Genitourinary TB typically starts in the epididymis
- Hematogenous or contiguous spread (direct from sexual contact)
- Presents as painful scrotal mass
- Imaging may reveal bilateral involvement
- TB testing often positive
- Diagnosis: AFB stain, culture, and PCR of urine
  - Consider also prostatic secretions
- Avoid fine needle biopsy if any concern for germ cell tumor
- Fistulas, abscesses, and infertility can result if untreated



Yadav et al, Transl Androl Urol 2017
Liu et al, Surgical Infections 2021
Li et al, Quant Imaging Med Surg 2021

Prostatitis NIH Consensus Categories

- I Acute bacterial* prostatitis
- II Chronic bacterial* prostatitis
- III Chronic prostatitis/chronic pelvic pain syndrome
  - IIIA Inflammatory
  - IIIB non-inflammatory
- IV Asymptomatic inflammatory prostatitis
  - Incidental finding, no need to treat



*includes non-bacterial pathogens, such as fungal organisms

Understanding the Prostatitis NIH Consensus Categories

Condition	Bacteriuria	Localized to Prostate	Abnormal Rectal Exam	Systemic Illness
I Acute Bacterial Prostatitis	+	+	+	+
II Chronic Bacterial Prostatitis	+	+	–	–
III Chronic Pelvic Pain Syndrome	–	–	–	–
IV Asymptomatic Inflammatory Prostatitis	–	–	+/–	–

McGowan, Chapter 110, in Mandell, Douglas, and Bennett's Principles and Practice of Infectious Diseases, 9th edition

Understanding the Prostatitis NIH Consensus Categories

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IV Asymptomatic Inflammatory Prostatitis	–	–	+/–	–

McGowan, Chapter 110, in Mandell, Douglas, and Bennett's Principles and Practice of Infectious Diseases, 9th edition

Case #3

A 69 year-old man presents with pain in the lower abdomen, rectum, and perineum for the past 48 hours. He has chills and nausea in addition to urinary urgency, frequency, and dysuria. Gentle digital rectal examination finds a painful and swollen prostate. He has not been able to pass urine for the past 10 hours.

Management should include:

A. Nitrofurantoin
B. Urology consultation for catheterization
C. Culture of expressed prostatic secretions
D. PSA (prostate specific antigen) levels

Case #3

A 69 year-old man presents with pain in the lower abdomen, rectum, and perineum for the past 48 hours. He also has chills in addition to urinary urgency, frequency, and dysuria. Gentle digital rectal examination finds a painful and swollen prostate. He has not been able to pass urine for the past 10 hours.

Management should include:

A. Nitrofurantoin-doesn't penetrate tissue or help with bacteremia
B. Urology consultation for catheterization—may need suprapubic, or transurethral placed with care
C. Culture of expressed prostatic secretions-do not massage the prostate firmly as this may cause bacteremia
D. PSA (prostate specific antigen) levels—will be elevated, non-specific

Acute bacterial prostatitis: clinical presentation

- Acutely ill patient
- Prostatic tenderness is the distinguishing feature
- Fever, chills, irritative urinary symptoms
- Lower abdominal, rectal, or perineal pain
- Voiding difficulties
- Pathogenesis: from infection in the urinary tract, prostate biopsy, or hematogenous spread
- Risk factors: urinary catheters, urinary stasis, urinary instrumentation

UpToDate Acute Bacterial Prostatitis
Brede and Shoskes, Nat Rev Urol 2011

Infectious prostatitis: Causative agents

Acute **> 60% caused by**

- *Escherichia coli*
- *Proteus*
- Other Enterobacterales
- *Pseudomonas*
- Staph, strep, enterococci
- *Salmonella typhi* (HIV)
- Burkholderia (traveler to SE Asia or N. Australia)
- STI: gonorrhea or chlamydia

Chronic or immunocompromised

- Mycobacteria
- Fungal
  - Cryptococcus
  - Histoplasma
  - Aspergillus
  - Coccidioidomycosis
  - Candida
  - Blastomycosis

Diagnostic workup of prostatitis

- Physical exam
  - Painful prostate
- Urinalysis and urine culture
- Consider blood cultures
- Failure to improve within 48-72 hours
  - Prostate ultrasound, computed tomography (CT) scan, MRI
- Call urology if unable to void

Antibiotic treatment of prostatitis

- Acute prostatitis
  - Start broad—cephalosporins, carbapenems, +/-aminoglycoside
  - Treatment duration 6 weeks
- Oral options: fluoroquinolones, sulfonamides, tetracyclines, macrolides, fosfomycin all penetrate the prostate
- Chronic prostatitis
  - Duration unclear—4, 6, 12 weeks all reported

Lipsky et al, Clinical Infect Dis 2010
Schaeffer and Nicolle, NEJM 2016
Chou et al, Drugs 2022
UpToDate Chronic Bacterial Prostatitis

Case #4

A 72 year-old man presents with pain in the perineum, penile tip, and scrotum, which has been going on for the past three months. He had lower back pain a week ago, but the pain has since subsided. He has had two episodes of UTI with burning on urination in the past six months. On physical examination, his prostate is boggy and tender to palpation. What is the most common cause of a chronic form of this condition?

A. Herpes

B. Chlamydia

C. *E. coli*

D. Candida

Case #4

A 72 year-old man presents with pain in the perineum, penile tip, and scrotum, which has been going on for the past three months. He had lower back pain a week ago, but the pain has since subsided. He has had two episodes of UTI with burning on urination in the past six months. On physical examination, his prostate is boggy and tender to palpation. What is the most common cause of a chronic form of this condition?

A. Herpes

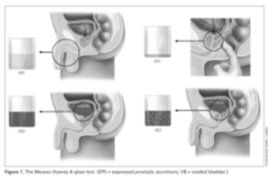
B. Chlamydia

C. ***E. coli*** —most likely cause of chronic prostatitis especially given the history of recurrent urinary tract infection

D. Candida

Chronic bacterial prostatitis

- Patients not acutely ill
- Recurrent UTI with same organism is common
- The four-glass Mears-Stamey test is cited often
- In practice urologists more often do the two-glass test
  - Urine samples pre/post prostatic massage



Sharp et al, Am Fam Physician 2010

Case #5

A 55 year-old man with HIV/AIDS (CD4 32) was referred to urology for obstructive voiding symptoms. Prostate exam revealed asymmetric enlargement. Urinalysis and urine culture unremarkable. Ultrasound showed bilateral nodules consistent with malignancy. Biopsy revealed:

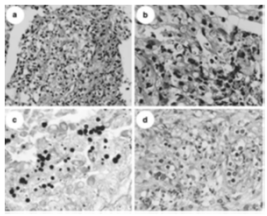
A. Candida

B. E. coli

C. Cryptococcus

D. Aspergillus

E. Nocardia



Wada et al, Prostate Cancer and Prostatic Dis 2008
Adams et al, Urology 1992
Wise and Shteynshlyuger, Curr Urology Rep 2006

Online Only Lectures - Epididymitis, Orchitis, and Prostatitis

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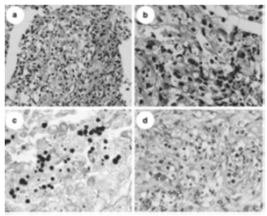


Granulomas with round organisms that are clearly yeast on silver stain and have visible capsules

Case #6

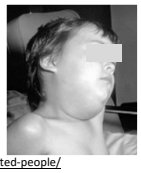
A 35 year-old man who is a member of a religious group that does not support vaccination attended a wedding in Nebraska. Two days later he developed pain in his left ear and jaw tenderness. Eleven days later he had noticeable swelling under both sides of his jaw, fever, and painful swelling of his left testicle. The likely causative agent is:

A. Mumps
B. Measles
C. Escherichia coli
D. Neisseria gonorrhea

Case #6

A 35 year-old man who is a member of a religious group that does not support vaccination attended a wedding in Nebraska. Two days later he developed pain in his left ear and jaw tenderness. Eleven days later he had noticeable swelling under both sides of his jaw, fever, and painful swelling of his left testicle. The likely causative agent is:

A. Mumps-parotid swelling and orchitis
B. Measles
C. Escherichia coli
D. Neisseria gonorrhea



https://www.scientificamerican.com/article/a-mumps-outbreak-among-fully-vaccinated-people/

https://www.cdc.gov/mumps/about/photos.html

Orchitis (isolated involvement of testes)

- Viral infections are common
  - Mumps
  - Coxsackie B
  - Lymphocytic choriomeningitis
- Bacterial
  - Contiguous spread from epididymis
  - Same organisms as epididymitis
    - *E. coli* and other enterics
    - Also same rare organisms (TB, fungal)

https://www.environmentandsociety.org/arcadia/mumps-post-secondary-environment-targeted-advertising-2007-2008-alberta-mumps-vaccination

To Wrap Up:

- Epididymitis
  - Consider sexually transmitted infection versus *E. coli* and other enteric flora
- Prostatitis
  - Consider acute bacterial prostatitis in men with febrile UTI—detected by physical exam
  - Consider chronic bacterial prostatitis in men with recurrent or relapsing UTI
- Fungal, TB, and other indolent organisms (Brucella) can invade and infect the male genitourinary tract
- Isolated orchitis is rare in adults—consider viral etiology

Is everything clear now?

- trautner@bcm.edu
- @bwtrautner

OL4

Management of AIDS-Related Opportunistic Infections III

Dr. Henry Masur

IDBR INFECTIOUS DISEASE BOARD REVIEW AUGUST 20-24 2022

Management of AIDS-Related Opportunistic Infections III

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

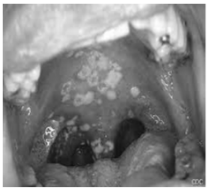
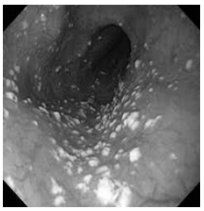
7/24/2022

INFECTIOUS DISEASE BOARD REVIEW AUGUST 20-24 2022

Disclosures of Financial Relationships with Relevant Commercial Interests

- None

Mucosal Candidiasis

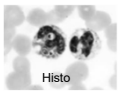




Candida

- **Mucosal candidiasis is characteristic**
  - Oral, Esophageal, Rectal, Vaginal
- **Invasive candida is not AIDS related**
  - Candida in blood should raise suspicion of catheter related blood stream infection, IV substance use disorder etc
- **Fluconazole primary prophylaxis or chronic suppression**
  - NOT recommended
    - Initial or recurrent or relapse episode usually not common esp with ART and are easily treatable

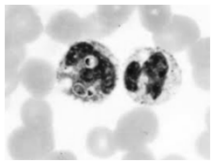
Other Fungal Diseases That Are Covered Elsewhere in IDBR

- **Look for questions on patients with HIV and ….**
  - **Histoplasmosis**
  - **Coccidiomycosis**
  - **Talaromycosis**



Histoplasmosis

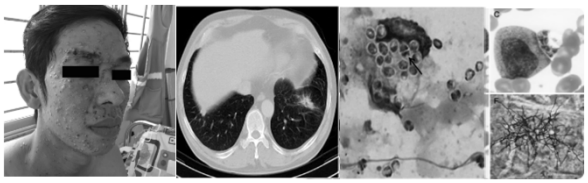
- **Most common OI in some countries**
- **Clinical Presentation**
  - CD4>200 cells/uL
    - Focal disease like immunocompetent
  - CD4<200 cells/uL
    - Disseminated disease
      - Fever, weigh loss, fatigue, hepatosplenomegaly
      - Meningitis
      - Septic Shock
      - *GI manifestations : fever, diarrhea, abdominal pain



- **Diagnosis**
  - Antigen detection: very sensitive in urine and blood for disseminated disease
  - BAL antigen also useful
  - Cultures useful but….takes several weeks to grow..and is a lab hazard

Talaromyces – Formerly Penicilliosis marnefii

- **Rarely if ever seen in US**
- **Common in Asia transmitted by bamboo rat or abiotically**
- **Serum antigen test (research) sensitive and specific**
- **Treat with Ampho or Itraconazole**



Herpesviruses

CMV

Non ARS Question

In an HIV positive patient (CD4 count = 50 cells/uL), a positive CMV PCR test of which of the following specimens would be MOST suggestive that CMV is the cause of end organ disease:

A. Esophageal biopsy to diagnose CMV esophagitis
B. Colonic biopsy to diagnose CMV colitis
C. Bronchoalveolar lavage to diagnose CMV pneumonia
D. Blood to diagnose CMV retinitis
E. CSF to diagnose CMV encephalitis

Non ARS Question

In an HIV positive patient (CD4 count = 50 cells/uL), a positive CMV PCR test of which of the following specimens would be MOST suggestive that CMV is the cause of end organ disease:

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B. Colonic biopsy to diagnose CMV colitis
C. Bronchoalveolar lavage to diagnose CMV pneumonia
D. Blood to diagnose CMV retinitis
E. CSF to diagnose CMV encephalitis

CMV Syndromes
CD4<50 and VL Positive In Almost All Cases

- **Retinitis (30% of Patients Before ART)**
- **Colitis**
  - Can lead to perforation
- **Ventriculitis**
  - Rapid cognitive decline with cranial nerve involvement
- Radiculopathy, Myelitis, Mononeuritis Multiplex, Guillain-Barre
- Esophagitis (uncommon)
- Adrenalitis (rare)
- Pneumonia (rare)

Diagnosis of HIV Related CMV Disease

- **Serology**
  - Disease unlikely if IgG seronegative
  - Rarely done
- **Cytology**
  - Rarely useful
- **Biopsy**
  - Helpful if many inclusions and substantial inflammation
- **PCR**
  - Correlates with CD4 Count
  - "Less than ideal" sensitivity and specificity for clinical disease

Diagnosis of HIV Related CMV Disease

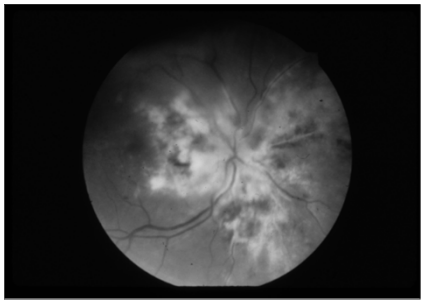
- **Serology**
  - Disease unlikely if IgG seronegative
  - Rarely do
- **Cytology**
  - Rarely us
- **Biopsy**
  - Helpful if many inclusions and substantial inflammation
- **PCR**
  - Correlates with CD4 Count
  - "Less than ideal" sensitivity and specificity for clinical disease

- **Clinical Presentation**
- **Consider Other Causes**
  - **(HSV, VZV, Toxo, Syphilis etc)**

Diagnosis of CMV Retinitis

- **Funduscopic exam**
  - Bilateral in 30% of untreated patients
  - Mustard and Ketchup
  - Necrosis of retina
  - Little vitreal inflammation
- **PCR of blood not useful: 70% sensitive, very non specific**
- **Vitreal taps for diagnosis with PCR rarely necessary**
  - Tap positive in 80% of cases

CMV Retinitis



Therapy for CMV Retinitis

(Ganciclovir intraocular implant no longer available)

- **Immediate sight-threatening lesions**
  - ART
  - IV Ganciclovir or Valganciclovir 900 mg PO (bid x 14–21 days), then qd for at least 3-6 months plus
  - Intravitreal ganciclovir weekly over several weeks until lesion inactivity
    - Injections can be associated with infections or retinal detachment and hemorrhage
- **Small peripheral lesions**
  - ART
  - Oral valganciclovir for at least 3-6 months and immune reconstitution
  - +/- intravitreal ganciclovir

Salvage Therapy for CMV Retinitis
(Hard to Ask on Exam)

- **Systemic Options**
  - **Ganciclovir higher dose**
  - **Foscarnet IV**
  - **Foscarnet IV plus Ganciclovir IV**
  - **Cidofovir IV**
- **Intraocular**
  - **Ganciclovir or Foscarnet**

Treatment of Other CMV Syndromes

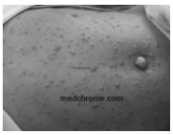
- **IV or Oral Ganciclovir or Foscarnet**
- **Duration hard to test**
  - Colitis or Esophagitis
    - 21-42 days or until clinical resolution
  - Ventriculitis
    - Not certain: some would use ganciclovir plus foscarnet

Varicella in PWH

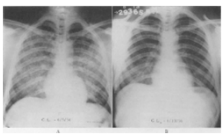
- **Uncommon in US**
- **Important to make the diagnosis by**
  - Exposure
  - Clinical Presentation
  - PCR or DFA of skin lesion

Treatment of Varicella in PWH

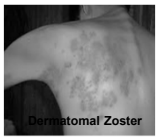
- **Uncomplicated**
  - **Valacyclovir or Famciclovir x 5-7 days**

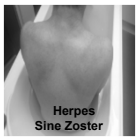


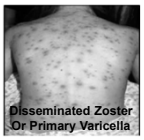
- **Complicated**
  - **IV Acyclovir x 7-10 Days**

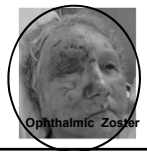


Localized and Disseminated Herpes Zoster









Herpes Zoster

- **Pre ART**
  - 15 fold high incidence of zoster than general population!!
- **Post ART**
  - Still increased risk even on suppressive ART
- **Localized (dermatomal)-common**
  - **Common at all CD4**
    - Frequency inversely proportional to CD4 even if VL<50
    - Recurrence is common with HIV
  - **Unmasking often observed soon after initiation of ART**

Herpes Zoster

- **Disseminated-very rare with HIV**
  - **Almost always CD4<200**

Therapy for Dermatomal Zoster

- **Acyclovir, Famciclovir, Valacyclovir**
  - **Treat within 1 week of rash onset or…. if not fully crusted**
    - (Longer "permissible window" compared to immunologic normal)
      - 48-72 hrs esp if age >50yo
      - Duration 7-10 Days
  - **Steroids NOT recommended to reduce post herpetic neuralgia**

Varicella Post Exposure Prophylaxis

Close Exposure to Varicella or Zoster and Susceptible*

- **Varicella Seronegative HIV Patients**
  - **VariZIG (High titer plasma derived)** **OR**
    - within 96 hrs of exposure ideally but can give up to 10 days
  - **Preemptive Acyclovir** **OR**
    - starting 7-10 days post exposure X 5-7 days
  - **Varicella Vaccination within 5 days of exposure**
    - Only if CD4>200
    - Don't vaccinate within 5 months of varizig or 3 d of ACV

*Susceptible: No known history of Varicella or Shingles and No Vaccine or known to be varicella negative

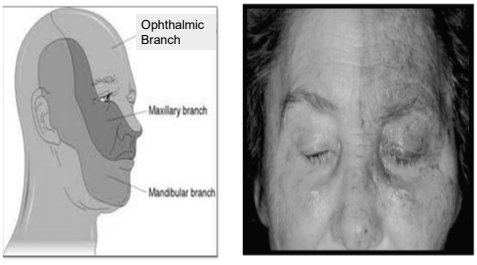
Prevention of Zoster

- **Recombinant VZV glycoprotein E /adjuvant AS01B (RZV-Shingrix)**
  - Age>18 years
  - Recommended regardless of CD4 count by OI Guideline
    - ACIP is neutral

Three Zoster Syndromes You Should Recognize

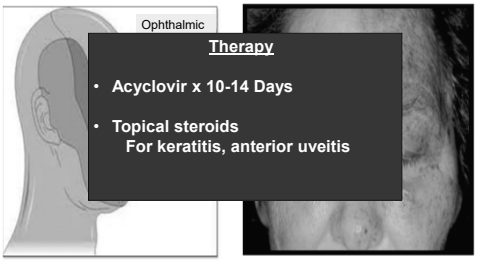
Zoster Ophthalmicus

Ophthalmic Branch CN V



Zoster Ophthalmicus

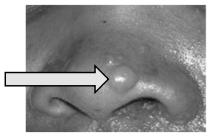
Ophthalmic Branch CN V

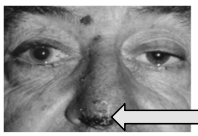


Complications
HIV-Associated Zoster Ophthalmicus

- **Ocular**
  - 50% of Herpes zoster ophthalmicus
- **VII nerve palsy**
- **CNS**

Hutchinson's Sign As Precursor to VZV Eye Disease
(Nasociliary Nerve of Ophthalmic Branch CN V)





Vesicles on the tip of the nose, or vesicles on the side of the nose

Accompanies development of ocular manifestations

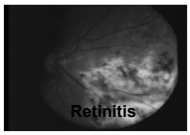
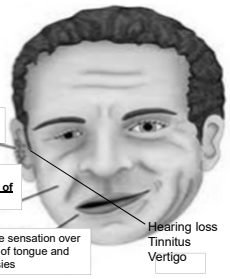


Image C. Stephen Foster, MD, Massachusetts Eye Research and Surgery Institute

Ramsay-Hunt Syndrome-Herpes Zoster Oticus
Geniculate Ganglion of Cranial Nerve VII
External Ear Vesicles and Facial Nerve Paralysis



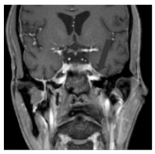
Ear Pain

Vesicular rash on external ear

Lower motor neuron paralysis of facial nerve

Loss of taste sensation over anterior 2/3 of tongue and VIII CN palsies

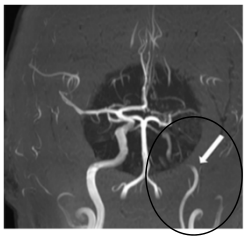
Hearing loss
Tinnitus
Vertigo



Meningeal Compression of Trigeminal Ganglion

Rx: Valacyclovir +/- Prednisone

Herpes Zoster Ophthalmicus
Vascular Inflammation and Occlusion/Stroke



Fugate JE, January 2020, Practical Neurology

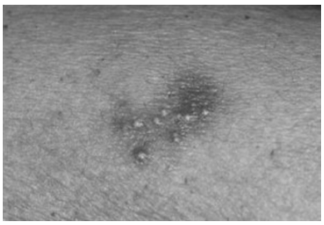
Zoster Ophthalmicus Related Stroke
Carotid Intimal Involvement

- **Days or months post zoster (median 4 months)**
- **Occasionally cutaneous lesions absent (33%)**
- **DX-PCR of CSF or VZV antibody production in CSF**
- **Rx acyclovir plus probably steroids**

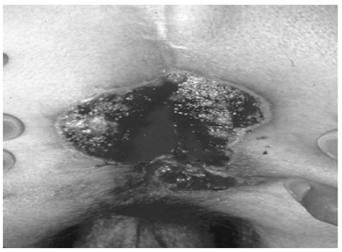
Herpes Simplex

- **Common Manifestations at any CD4**
  - Usual localized cutaneous and genital lesions
- **Dissemination**
  - Extremely uncommon at any CD4 count
- **Occurrences at low CD4**
  - Esophagitis
  - Retinitis
  - Dissemination
  - Chronic, extensive genital ulcers, often ACV resistant
- **Diagnosis**
  - Culture or PCR useful for cutaneous lesion
  - Culture or PCR NOT Useful for mucosal surface-may indicate shedding only

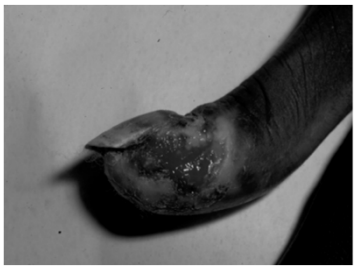
Localized Herpes Simplex



Perirectal HSV
Look for Acyclovir Resistance



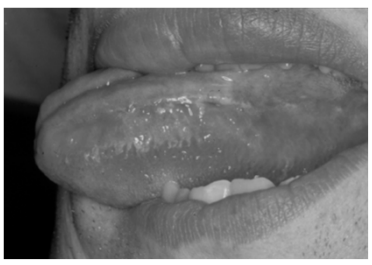
Herpetic Whitlow
Look for Acyclovir Resistance

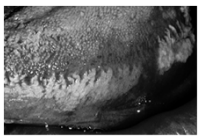


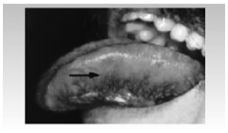
HIV Diseases Associated with EBV

- **Oral Hairy Leukoplakia**
- **CNS Lymphoma (described later)**
- **Effusion cell lymphoma (described later)**

Oral Hairy Leukoplakia
EBV Associated







Question #1

Which of the following protozoa can be treated successfully with TMP-SMX?

A. Cyclospora
B. Cryptosporidia
C. Enterocytozoa
D. Encephalitozoa
E. Naegleria

Answer #1

Which of the following protozoa can be treated successfully with TMP-SMX?

A. Cyclospora
B. Cryptosporidia
C. Enterocytozoa
D. Encephalitozoa
E. Naegleria

What Are the Most Common Causes of Diarrhea in Patients with HIV Infection in US?

- **Salmonella enterica**
- **Shigella**
- **Campylobacter**
- **Clostridioides**
- **Colitis/Proctitis**
  - STDs (LGV, GC, Syphilis)
- **Rare and Probably Non Testable (Hard to Diagnose)**
  - Enterohepatic Helicobacter species, non jejuni-non coli Campylobacter
  - CMV, MAC, Kaposi

ASD, Sanchez, CID, 2007

Antiretroviral Therapy and Enteric Disease

- **ART initiation or continuation should not be delayed**
  - **Absorption**
  - **Drug interactions**

Clinical Manifestations of Enteric Diseases

- **Self Limited Gastroenteritis**
- **Severe and Prolonged Diarrhea**
  - Especially Salmonella and Cryptosporidia, Microsporidia, Isospora
- **Bacteremia with extra-intestinal manifestations**
  - Salmonella

Salmonella and Shigella
HIV-Infected Persons

- **Salmonella**
  - **Bacteremia more common in HIV pos (esp low CD4) than HIV neg**
  - **Bacteremia merits HIV test**
  - **Treat all infected patients to reduce likelihood of bacteremia**
  - **Recurrence common**
  - **If recurrence, long term suppression appropriate esp if VL elevated-**
    - **(How long?)**
- **Shigella**
  - **Highly transmissible**
  - **Rarely bacteremic**
  - **Probably treat all diarrhea to reduce shedding, transmission**
  - **Rarely recurs**

What Are the Most Common Causes of Diarrhea in Patients with HIV Infection in US?

• **Clostridioides difficile**	**54%**
• **Campylobacter**	**14%**
• **Shigella**	**14%**
• **Salmonella**	**7%**

ASD, Sanchez, CID, 2007

Intestinal Coccidia (subclass of Apicomplexa)

Cryptosporidium
- *C. parvum:* cows
- *C. hominis:* humans

Cyclospora cayetanensis

Cystoisospora belli

- **All have worldwide distribution**
- **All transmitted by water or food contaminated with oocysts**
- **Organisms invade enterocytes and are mainly small intestine**
- **All cause watery diarrhea that can be prolonged & severe in immunocompromised**

Cryptosporidia

- **Epidemiology**
  - Small inoculum adequate for transmission
  - Shedding persists after sx resolve
  - Notorious outbreaks in municipal water supplies (Milwaukee)
    - Day care centers, animal contact, water parks, oysters, person to person

Cryptosporidia

- **Clinical Course**
  - **Immunocompetent**
    - Self limited in 10-14 d (nausea, fever, diarrhea)
    - Occasional entry into biliary or pancreatic
  - **Immunosuppressed (not just HIV!)**
    - Potentially chronic

Cryptosporidia

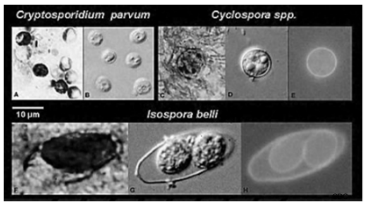
- **Microbiology**
  - Intracellular protozoan
- **Pathology**
  - Normal hosts
    - small bowel
  - Immunosuppressed
    - small and large bowel

Cryptosporidia

- **Diagnosis**
  - **Secretory diarrhea: no blood, mucous**
  - **One stool sample usually adequate**
    - Modified acid fast, immunofluorescent, ELISA, PCR
  - **Small > large bowel Biopsy**
- **Therapy**
  - **Nothing specific documented to be effective**
    - Possible efficacy: Nitazoxanide, Paromomycin, Azithromycin
  - **ART**
- **Prevention**
  - **Avoid suspect animals + contaminated water (pools, ponds) + day care**

Intestinal Coccidia Characteristics

Pathogen	Size	Stain	Treatment
Cryptosporidium	4 µm	m acid-fast	None
Cyclospora	10 µm	m acid-fast	TMP/SMX
Cystoisospora	20 µm	m acid-fast	TMP/SMX



Microsporidia

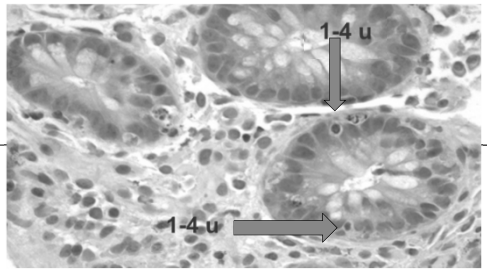
- **Fungus-Not Protozoon**
  - Intracellular
  - Confusing taxonomy
    - Encephalitozoon, Enterocytozoan, Septata….many others
- **Diseases in Immunocompetent Patients**
  - Self limiting diarrhea
  - Keratitis

Microsporidiosis in HIV

- **Enterocytozoa (mostly *E. bieneusi*)**
  - **Diarrhea (CD4 < 50)-90% of cases in US**
    - **sometimes with biliary, pancreatic duct involved**
- **Encephalitozoa (mostly *E. intestinalis*)**
  - **Diarrhea (CD4<50)-10% of cases in US**
    - (*E. intestinalis* was formerly Septata intestinalis)
  - **Disseminated disease with many different species**
    - Encephalitis, myositis, keratoconjuctivitis, cholangitis et al

Microsporidia-Diagnosis

- **Direct Culture**
  - None
- **Microscopy**
  - PCR
  - Stains
    - H + E and many others



Small Bowel Biopsy: Enterocytozoon bieneusi spores
Location: near the luminal surface of enterocyte
(Brown-Hopp, 1000x)

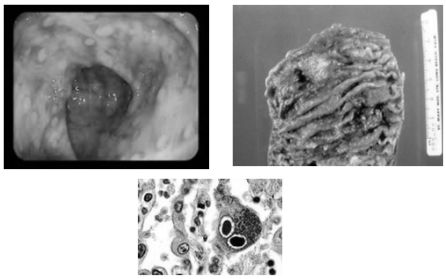
Therapies for Microsporidiosis

Organism	Frequency	Therapy
• Encephalitozoon intestinalis	(10%)	Albendazole
• Entercytozoon bieneusi	(90%)	None (Nitazoxanide) (Fumagillin-Not Available)

Bacterial Enteric Disease and HIV

- **Opportunistic**
  - **Salmonella**
  - **(NOT Shigella)**
  - **non jejuni non coli Campylobacter**
  - **Helicobacter**
- **Also look for proctitis and STDs in certain risk groups**
  - **GC**
  - **Chlamydia**
  - **Syphilis**

CMV Colitis



Clinical Disease Due to CMV Colitis

- **Clinical Presentation**
  - **Anorexia, abdominal pain**
  - **Non specific large bowel diarrhea**
    - Mild, moderate, severe
- **Diagnosis**
  - **Colonoscopy with cytology or biopsy**
  - **PCR non specific**
- **Therapy**
  - **Ganciclovir, Valganciclovir, Foscarnet**
  - **Duration: 21-42 days IV vs oral**

HIV Associated Cholangiopathy

Idiopathic and/or Related to GI Pathogen

- **Biliary obstruction and liver injury in patients with Low CD4**
  - **Presentations**
    - Papillary stenosis
    - Intrahepatic sclerosing cholangitis
    - Bile duct stricture
- **Clinical Manifestations**
  - **Nausea and vomiting**
  - **Severe RUQ pain**
  - **Fever**
  - **Diarrhea and Weight Loss**
  - **Less jaundice than other cholangiopathies**

HIV Associated Cholangiopathy

- **Associations/Causes**
  - **Cryptosporidia**
  - **Microsporidia**
  - **CMV**
- **Diagnosis and Treatment**
  - **ERCP**
  - **Sphincterectomy**
  - **Treatment of associated pathogens**
  - **ART**

Diffuse HIV-Related Encephalopathies

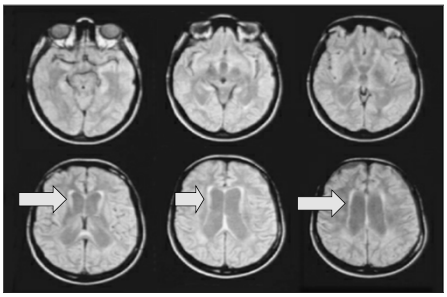
Question #2

A 32-year-old female with HIV infection VL = 100k, and a CD4 count below 10 cells/mm3has failed all available ART regimens.

Her mother brings her to clinic because of confusion for 1-2 weeks. She is afebrile, oriented x 1, and slow to respond. She has nystagmus and CN VI palsy on the right.

The MRI is shown.

MRI Related Encephalitis



Question #2

Which PCR test would support the diagnosis that is most likely in this case?

A. JC
B. EBV
C. CMV
D. HHV6
E. HHV8

Answer #2

Which PCR test would support the diagnosis that is most likely in this case?

A. JC
B. EBV
C. CMV
D. HHV6
E. HHV8

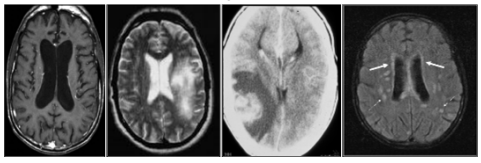
CMV Encephalitis

- **Imaging**
  - **Periventricular Enhancement**
  - **(Micronodular throughout CNS)**
- **Clinical and Laboratory Characteristics**
  - **Low CD4 (<50)**
  - **Rapid onset (days or weeks-unlike HIV)**
  - **Focal CN findings or nystagmus**
  - **CSF pleocytosis sometimes with polys**

Question #3 non ARS

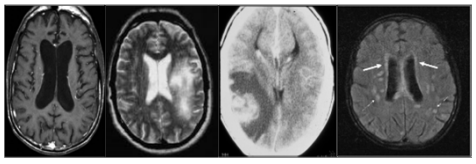
Can you tell what the following lesions are in an HIV infected patient with CD4 <50 cells and dementia of uncertain duration?

A. B. C. D.



Question #3 non ARS

A. HIV Dementia **B. PML** **C. Toxo** **D. CMV**



Question #4

- **A 35-year-old male with long standing HIV, untreated, is brought to the ER for a seizure. His CD4 has been < 20 cells.**
- **The patient admits that he has had a slowly progressive left lower extremity weakness, and his performance at his accounting firm has deteriorated in the past few months.**
- **MRI findings of a right parietal white matter lesion with no atrophy or ventricular dilation.**
- **CSF shows wbc 20 (100% lymphs), protein 60**

Question #4

- **Which of the following CSF PCR tests would be the most useful?**

A. Jakob Creutzfeldt virus
B. HIV
C. EBV
D. BK virus
E. JC virus

Answer #4

- **Which of the following CSF PCR tests would be the most useful?**

A. Jakob Creutzfeldt virus
B. HIV
C. EBV
D. BK virus
E. JC virus

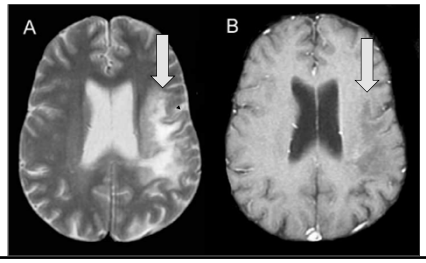
HIV Encephalopathies

Feature	PML	HIVE	CMV
Onset	Subacute	Subacute	**Acute**
CD4	<100	<100	<50
Dementia	+	+	+
Motor deficit	+	+	+/-
Sensory deficit	+	-	-
MRI			
Location	**Asymmetric**	Symm	Symm
Cortical atrophy	-	+	-
Micronodular	-	-	+
Periventricular	-	-	+
CSF PCR	**JC + 70%**	**Not helpful**	**CMV+**

Progressive Multifocal Leukoencephalopathy

A. T2-weighted image = increased signal in the left hemisphere

B. T1-weighted image = decreased attenuation (dark).



Progressive Multifocal Leukoencephalopathy (PML) (JC Virus Encephalitis)

- **Polyomavirus (JC)**
  - **Transmission probably by respiratory route human to human**
    - >80% adults infected by JC by antibody testing
  - **Only known disease is PML**
    - Most cases in patients with well defined immunodeficiency

PML Can Be Associated with Immunosuppressive Diseases Other than HIV

- **Transplants**
- **Cancers**
  - Esp Fludarabine
- **Monoclonal Antibodies**
  - Rituximab
  - Efalizumab-T cell blocker for psoriasis > 3 yrs (withdrawn)
  - Natalizumab
    - (Adhesion molecule inhibitor for Multiple Sclerosis or Crohn's-within 18 months)
- **High Dose Corticosteroids**

Progressive Multifocal Leukoencephalopathy (PML or JC Virus Encephalitis)

- **Disease of White Matter >> Gray Matter**
  - **Slowly progressive**
  - **Non enhancing (80%)**
  - **Multiple focal defects rather than diffuse encephalopathy**
  - **No fever or headache**
  - **Optic nerves and spinal cord usually spared**
  - **Seizures 20%**
    - **(when lesions abut gray matter)**

Progressive Multifocal Leukoencephalopathy

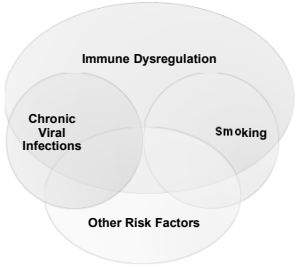
- **CSF:**
  - Cells + protein may be elevated
  - PCR for JC+ in 70-90% of biopsy proven patients
    - Specificity not 100%: interpret with clinical scenario
- **Differential Diagnosis**
  - Multiple Sclerosis
- **Plasma PCR**
  - Correlates with immunosuppression rather than being diagnostic for PML

Progressive Multifocal Leukoencephalopathy

- **Prognosis without ART**
  - **50% die in 2-4 months**
- **Therapy for PML**
  - **ART or reduction in immunosuppression for non HIV**
  - **Check point Inhibitors: nivolumab and pembrolizumab**
  - **Virus specific T cells**
- **Therapy for Inflammatory PML**
  - **IRIS post ART or withdrawal of Natalizumab: Steroids**

HIV and Cancer

HIV and Cancer



Question #5

What virus is associated with HIV-related multicentric Castleman disease?

A. CMV
B. HSV
C. HHV 6
D. HHV 7
E. HHV 8

Answer #5

What virus is associated with HIV-related multicentric Castleman disease?

A. CMV
B. HSV
C. HHV 6
D. HHV 7
E. HHV 8

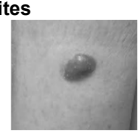
Most Cancers Overrepresented Among Patients with HIV are Related to a Virus

AIDS-Defining	Virus
• Kaposi's Sarcoma	HHV-8
• Non-Hodgkin's Lymphoma	EBV
• Invasive Cervical Carcinoma	HPV
Non-AIDS Defining	
• Multicentric Castleman	HHV-8
• Primary Effusion Cell Lymphoma	HHV-8, EBV
• Anal Cancer	HPV
• Hodgkin's Disease	EBV
• Leiomyosarcoma (pediatric)	EBV
• Squamous Carcinoma (oral)	HPV
• Merkel cell Carcinoma	MCV
• Hepatoma	HBV, HCV

What is Merkel Cell Carcinoma?

Don't Mistake for Benign Lesion

- **Hopefully this is too obscure for the exam**
- **Associated with Merkel cell polyomavirus (MCPyV)**
  - 80% of adults are seropositive
- **Rapidly growing epithelial tumor**
  - Associated with immunosuppression
- **Can metastasize to regional nodes or distant sites**
- **Treatment**
  - Beyond ID boards



Human Herpes Virus 8 (HHV 8)

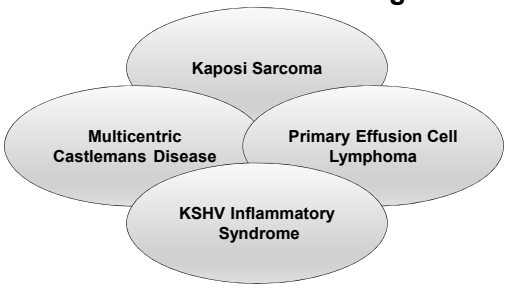
KSHV Associated Diseases (KAD)
Also Reviewed in Herpes Virus Lecture

- **Important**
  - Kaposi sarcoma- (Declining incidence)
  - Castleman disease- (Increasing incidence)
  - Primary Effusion cell lymphoma
  - Kaposi sarcoma inflammatory syndrome
- **Seroprevalence**
  - General population: 2%
  - Men who have sex with men: 13-58%
    - IVDU-no clear association
- **Testing with PCR or Antibody**
  - Not widely done or useful routinely
- **Transmission**
  - Saliva >> sex

Human Herpes Virus 8 (HHV 8)

- **Role of HHV 8 PCR**
  - None clinically
- **Anti HHV 8 Antiviral Therapy**
  - **No role**
    - **Susceptible to Ganciclovir, Foscarnet, Cidofovir**

HHV-8/KSHV Associated Malignancies

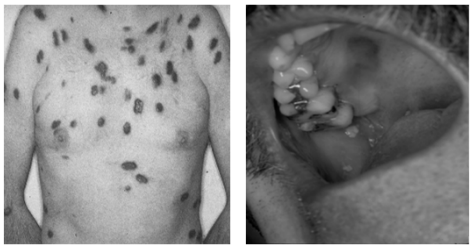


Kaposi Sarcoma

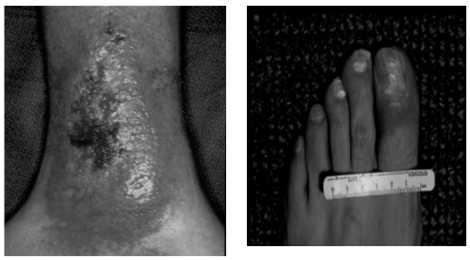
- **Angioproliferative tumor**
- **Four major subtypes**
  - **Classic:**
    - **Indolent** cutaneous **proliferative disease (mainly affecting extremities)**
  - **Endemic**
    - Equatorial and sub-Saharan Africa
  - **Organ transplant associated**
    - After transplant
  - **Epidemic**
    - AIDS-related

Yarchoan and Uldrick. NEJM. 2018. 378:1029-1041

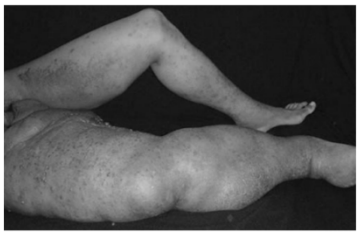
Kaposi Sarcoma



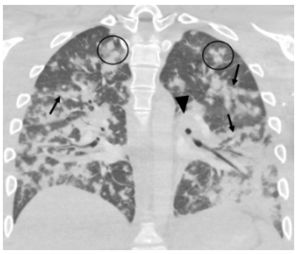
Kaposi Sarcoma



Lymphedema Due to Kaposi Sarcoma



Pulmonary KS



- **Not all have skin lesions**
- **Nodules and alveolar filling**
- **Hemoptysis**
- **Bloody pleural effusion**
- **Endobronchial Lesions**

Clin Infect Dis 2018: 66: 232

Kaposi Sarcoma-Diagnosis

- **Biopsy**
  - Immunohistochemical staining with antibodies recognizing HHV-8-encoded latency-associated nuclear antigen (LANA)
  - Polymerase chain reaction (PCR) to identify HHV-8 sequences within tumor tissue

Kaposi Sarcoma Therapy

- **Antiretroviral Therapy**
  - KS often regresses with ART alone
  - Look for IRIS (unmasking or paradoxical worsening)
- **Antiherpes drugs have minimal efficacy**
- **Chemotherapy**
- **Local excision or radiation**

Kaposi Sarcoma

- **Local Therapies**
  - Intralesional vinblastine
  - Topical cis retinoic acid
  - Radiation therapy
- **Systemic Therapies**
  - Pomalidomide
  - Liposomal doxorubicin (doxil)
  - Paclitaxel

Multicentric Castleman Disease

- **B Cell Disorder**
- **Not Only HIV**
  - Occurs with other immunosuppressive disorders
- **Presentation mimics lymphoma, endemic fungi, TB**
  - Occurs at any CD4 count
  - Fever, weight loss, lymphadenopathy, hepatosplenomegaly
  - Cytopenias, Hypergammaglobulinemia

Castleman Disease : Adenopathy and Splenomegaly

Multicentric Castleman Disease

- **Diagnosis**
  - **Biopsy of lymph node or bone marrow**
  - **HHV-8 levels correlate with disease activity**
    - **Not** diagnostic
- **Therapy**
  - **ART**
  - **Some combination of—(not testable)**
    - Rituximab, Prednisone, Liposomal Doxorubicin, Anti IL6 (sarilumab), AZT + ValGCV

Body Cavity Lymphoma
(Primary Effusion Lymphoma)

- **Uncommon but testable**
  - 4% of AIDS Associated Lymphomas
  - Any CD4 counts
  - HHV-8 plus EBV associated
- **B cell malignancy but no B or T markers**
  - CD45+
- **Presentation**
  - Pleural/pericardial/peritoneal effusion
    - local disease
  - Masses unusual but organ infiltration occurs

Body Cavity Lymphoma
(Primary Effusion Lymphoma)

- **Diagnosis**
  - **Effusion cytology**
    - nuclear HHV8 by immunohistochemistry
- **Therapy and prognosis**
  - **Unclear**

KSHV Inflammatory Cytokine Syndrome

- **Castleman's Disease without positive histology**
- **Can present as sepsis**
  - Fever, hypotension, hypoxia
  - Pulmonary, GI, CNS manifestations
  - Similar to Castleman's but no adenopathy or splenomegaly
- **Diagnosis of exclusion**
- **Pathogenesis**
  - Elevated levels of IL 6 and IL 10
  - Elevated levels of HHV-8
- **Treatment**
  - Unclear: Rituximab, anti-IL-6

EBV Associated Lymphomas

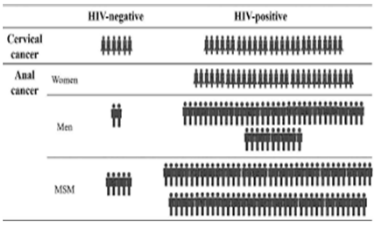
Diffuse Large B Cell Lymphoma in HIV

- **Typically present with**
  - advanced stage and "B symptoms"
- **EBV associated**
- **Outcomes**
  - comparable to non-HIV patients
- **CNS disease frequent**

HHV6 and HHV7 in Patients with HIV
Always the Wrong Answer on Exam for HIV

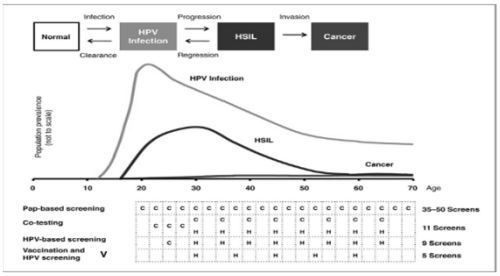
- **HHV6 in Immunocompetent Children**
  - Transmitted by saliva to 70-90% US population
  - Causes Roseola (Sixth Disease), febrile seizures, encephalitis
- **HHV-6 and HIV NOT IMPORTANT**
  - Several cases of fever, pneumonitis, encephalitis
  - Rx: Foscarnet active against both A and B strains
- **HHV7**
  - Clinical: Uncertain importance if HIV + or neg
  - Rx: Foscarnet, cidofovir >> ACV, GCV

HPV Related Squamous Cell Carcinomas
HIV Related



Oral Squamous Cell Carcinomas Also Over-represented Among PWH

Natural History of HPV Related Cervical Cancer



HSIL =High-grade squamous intraepithelial lesion)

HPV Related Tumors

- **Prevention**
  - **Same as non HIV population**
    - Condom for preventing transmission and penile cancer
    - Circumcision
    - Vaccine
      - 9 valent vaccine to all males and females 9-26 yo regardless of HIV status
  - **Cervical screening for HPV with Pap test for women 21-29 yo**
    - Co testing for HPV not recommended
  - **Anal screening "recommended by some experts"**
  - **Oral screening not proven beneficial and not recommended**
  - **Antiretroviral Therapy**
- **Treatment**
  - Probably beyond scope of ID boards

What is Risk of Opportunistic Infection in PWH with Neoplastic Disease

- **Not clearly different than the sum of:**
  - **Risk from HIV (CD4 count and viral load)**
  - **Risk from antineoplastic agent (Rituximab, Campath, steroids etc**
  - **Risk from tumor**
  - **Anti-OI prophylaxis**
  - **Drug Interactions**

What Else Could Be On The Exam?
Some Topics That Could Be Easy to Make Into Questions

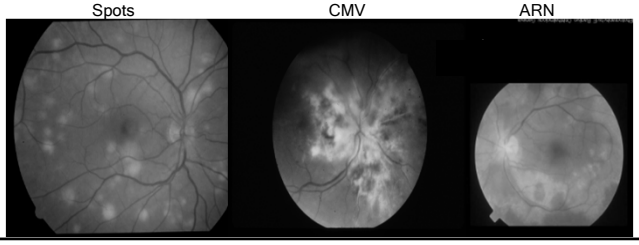
- **Ophthalmology**
  - Retinitis due to pathogens other than CMV
  - Retinal lesions that are not retinitis
- **Hematology**
  - Acute anemia due to Parvovirus
- **Tick bites**

Herpes Zoster Associated Retinitis

- **Acute Retinal Necrosis: Immunocompetent or HIV/CD4>100**
  - Cutaneous zoster may or may not occur
  - VZV >>HSV, CMV
  - Presents peripherally with pain, floaters
  - WBC in vitreous +/- aqueous
  - Unilateral but can become bilateral if untreated
  - Retinal detachments common
  - Acyclovir followed by long course of valacyclovir +/- intravitreal ganciclovir (14 weeks)
- **Peripheral Outer Retinal Necrosis: HIV/ Immunosuppressed (CD4<50)**
  - Multifocal with little inflammation
    - VZV >>HSV, CMV
    - Often involves optic nerve
    - Associated with retinal detachment, blindness
    - Therapy rarely successful
    - Acyclovir IV plus intravitreal ganciclovir or foscarnet or gcv/foscarnet for long period of time

Will You Be Able to Tell These Apart?

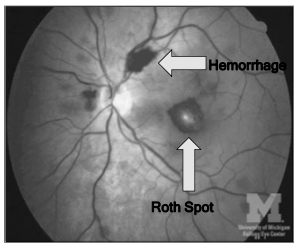
Cotton Wool Spots | CMV | ARN



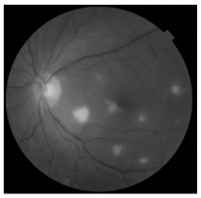
Other Lesions That Might Fool You

- **Retinal disease related to another issue**
  - IV drug use
  - Blood stream infection due to IV catheter

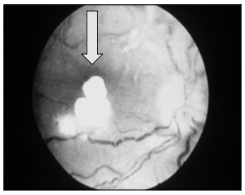
Bacterial Endocarditis
Unrelated to HIV—Related to IVDU or Other Factors



This Might Be Seen In Patient with AIDS But…Related to IVDU or CLABSI Candida Chorioretinitis and Endophalmitis



Chorioretinitis (early)
Diagnose empirically
No Vitreous Haze
Systemic Rx alone



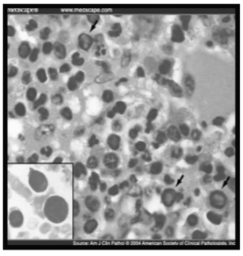
Endophthalmitis (late)
Diagnose with vitreal tap
Central Vitreal Fluff Ball
Vitreal Haze
Rx: Systemic Rx, Intravitreal Ampho, Vitrectomy

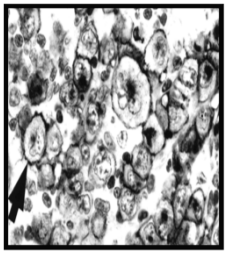
Parvovirus Can Cause Severe Anemia in Patients with HIV Infection

Symptoms	**Weakness over weeks-months**
Hemoglobin	**2.5 - 6.5 g/dl**
Reticulocytes	**Low**
Erythropoietin	**> 500 units (80%)**
Marrow	**Hypocellular**
CD4 Count	**Variable**
B19 Serology	**Variable (40% +)**
B19 PCR	**Positive (Gold Standard)**
	Sensitive but can be positive for months
Therapy: IVIG	**Usually Successful**

Parvovirus in HIV Infected Patient

Inclusion Bodies | **Pronormoblasts**





Ticks and HIV with "Septic Shock"

- **Exam question**
  - HIV patient presents with fever and shock or hemolysis
  - Clues: outdoor exposure, geography, peripheral smear
- **Tick borne diseases that are more severe in HIV**
  - *Ehrlichia*
  - Anaplasma
  - Babesia

The End

OL5

ID Bootcamp: HIV

Dr. Roy Gulick

Online Only Lectures – ID Bootcamp: HIV

Speaker: Roy Gulick, MD

IDBR INFECTIOUS DISEASE BOARD REVIEW AUGUST 20-24 2022

ID Bootcamp: HIV

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

6/8/2022

INFECTIOUS DISEASE BOARD REVIEW AUGUST 20-24 2022

Disclosures of Financial Relationships with Relevant Commercial Interests

- No pharmaceutical or device company relationships.
- Co-Chair, U.S. DHHS Adult and Adolescent ART Treatment Guidelines Panel

ID Boards – Medical Content: 15% HIV

- Epidemiology (<2%)
- Pathogenesis (<2%)
- Lab testing (<2%)
- HIV Treatment Regimens (4.5%)
- Opportunistic Infections (5%)
- Malignancies (<2%)
- Other complications of HIV (2%)
- Related issues (<2%)

Morbidity and Mortality Weekly Report (MMWR): 1981

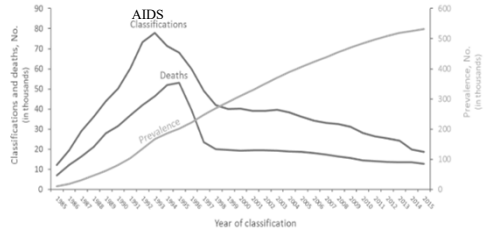
1981 June 5;30:250–2

Pneumocystis Pneumonia – Los Angeles

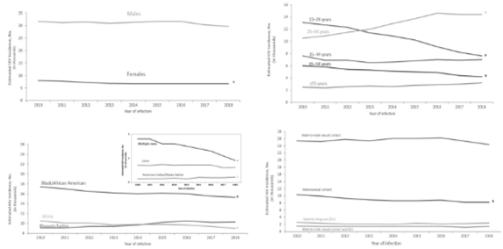
In the period October 1980-May 1981, 5 young men, all active homosexuals, were treated for biopsy-confirmed *Pneumocystis carinii* pneumonia at 3 different hospitals in Los Angeles, California. Two of the patients died. All 5 patients had laboratory-confirmed previous or current cytomegalovirus (CMV) infection and candidal mucosal infection. Case reports of these patients follow.

2022: >79 million people infected globally; ~1/2 have died

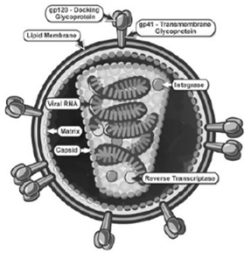
AIDS, Deaths, and Diagnosed HIV Infection Ever Classified
1985–2015 — US and 6 Dependent Areas



HIV Incidence ≥13 Years Old 2010–2018—U.S.



Human Immunodeficiency Virus (HIV)



- formerly HTLV-III; isolated 1983-4
- human retrovirus – outer glycoprotein coat, inner protein coat and genetic material: RNA (2 strands)
- types: HIV-1 and HIV-2
- subtypes (clades): B most common in North America and Europe
- zoonosis from primates (~1900)
- target cell: CD4+ T-lymphocyte

Question 1

Which is the current sequence of initial and confirmatory HIV diagnostic testing?

A. ELISA, followed by Western Blot.
B. ELISA, followed by HIV RNA.
C. ELISA, followed by immunoassay.
D. HIV RNA, followed by Western Blot.
E. HIV RNA, followed by ELISA.
F. HIV RNA, followed by immunoassay.

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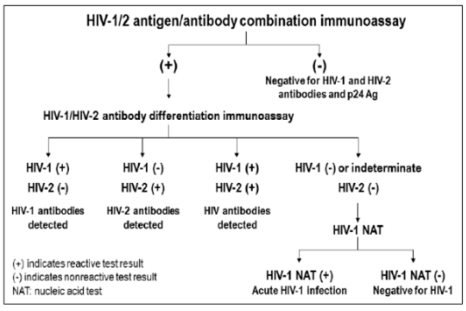
F. HIV RNA, followed by immunoassay.

HIV Testing

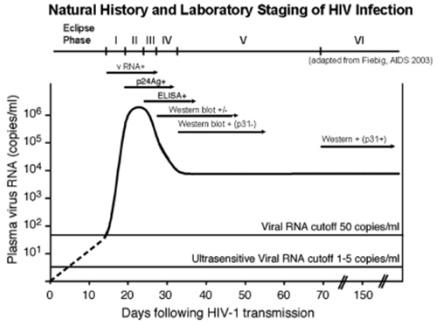
- HIV antibody testing (indirect)
  - Screening test: HIV-1, HIV-2 antibodies by ELISA
  - If repeatedly positive, proceed to confirmatory test
    - Immunoblot or 2nd HIV rapid test
  - 20-minute oral test and 1-minute blood test
- HIV viral testing (direct)
  - p24 antigen
  - viral culture
  - HIV RNA (viral load)
- Newer combination antibody + antigen test
  - window period 3 months → 2 weeks

Recommended Laboratory HIV Testing Algorithm for Serum or Plasma Specimens



CDC 6/14

Natural History and Laboratory Staging of HIV Infection



Cohen JID 2010;202:S270

Question 2

Who should NOT be routinely offered HIV testing?

A. 32 year old pregnant woman in a stable relationship.
B. 23 year old sexually active monogamous gay man.
C. 75 year old former injection drug user.
D. 10 year old pre-pubescent girl.
E. All of them should be routinely offered HIV testing.

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E. All of them should be routinely offered HIV testing.

U.S. Preventive Services Task Force (UPSTF)

Recommendations

- Screen adolescents and adults ages 15 to 65 for HIV infection.
- Screen all pregnant women.
- Younger adolescents and older adults who are at increased risk should also be screened.
- This is a grade A recommendation ("high certainty that the net benefit is substantial").
- Federal Rule: Private Insurance and Medicare must offer A or B services without a co-pay.

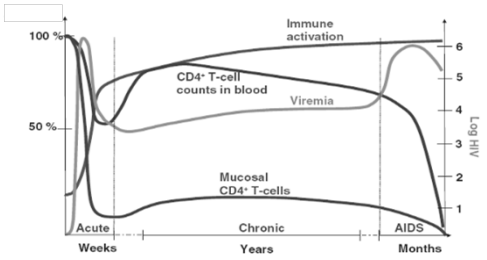
Ann Intern Med 2013;159:1-36

HIV Transmission Risks

Exposure from HIV+ source	Risk per exposure (%)	Risk per exposure (number)
Blood transfusion	93%	9/10
Needle-sharing injection drug use	0.6%	1/167
Percutaneous needle stick	0.2%	1/500
Receptive anal sex	1.4%	1/70
Insertive anal sex	0.1%	1/1000
Receptive penile-vaginal sex	0.08%	1/1250
Insertive penile-vaginal sex	0.04%	1/2500
Oral sex	low	very low
Mother-to-child	23%	1/4

Patel AIDS 2014;28:1509

Time Course of HIV Infection



Grossman Nature Medicine 2006; 12: 289-295

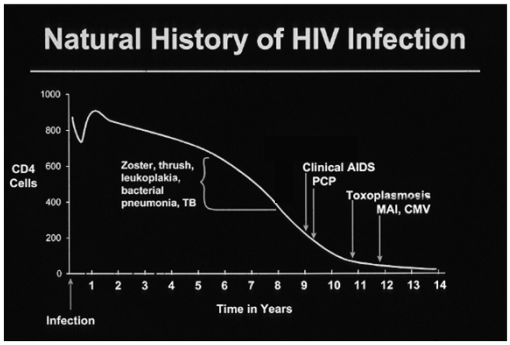
CDC Adult AIDS Case Definition

- 1982: "AIDS" -- list of diseases (definitive diagnosis) and disqualifying conditions
- 1985: HIV antibody testing added to definition
- 1987: presumptive diagnoses with a positive HIV antibody added
- 1993: CD4 <200 (without symptoms) and other diagnoses added

Opportunistic Infections (OI)

- Definition: Infection caused by an organism capable of causing disease only in a host whose resistance is lowered (by other diseases or by drugs)
- AIDS-related:
  - Bacterial: MAC, tuberculosis
  - Fungal: PCP, Cryptococcus, Histoplasma
  - Viral: CMV
  - Parasitic: Toxoplasma
  - Malignancies: Kaposi's sarcoma, NH-lymphoma

Natural History of HIV Infection



Goal of Antiretroviral Therapy

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

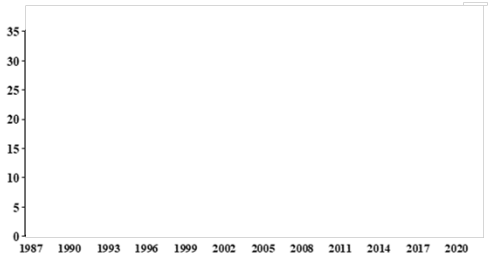
When to start ART?

Guidelines	AIDS/ sx	CD4 <200	CD4 200-350	CD4 350-500	CD4 >500
US DHHS '22 www.clinicalinfo.hiv.gov					
IAS-USA '20 JAMA 2020;324:1651-69					

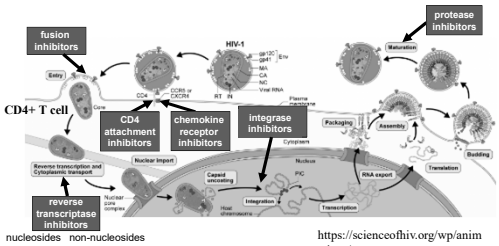
U.S. DHHS HIV Treatment Guidelines (1/22):

- ART is recommended for all persons with HIV to ↓ morbidity and mortality **(AI)** and to prevent transmission of HIV to others **(AI)**.
- Initiate ART immediately (or as soon as possible) after HIV diagnosis.

Antiretroviral Drug Approval: 1987 - 2022



Life Cycle of HIV



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

Approved ART: 2022*

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)

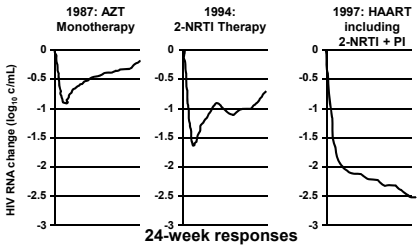
protease inhibitors (PIs)
- saquinavir (SQV)
- ritonavir (RTV)
- indinavir (IDV)
- nelfinavir (NFV)
- lopinavir/r (LPV/r)
- atazanavir (ATV)
- tipranavir (TPV)
- darunavir (DRV)

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

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

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

Antiretroviral Activity: 1987-1997



Fischl, *NEJM,* 1987 Eron, *NEJM,* 1995 Hammer, *NEJM,* 1996 Gulick, *NEJM,* 1997 Cameron, *Lancet,* 1998

Question 3

Which class of ART is recommended for initial HIV treatment for most patients?

A. All nucleoside analog (NRTI) regimen.
B. Non-nucleoside (NNRTI)-based regimen.
C. Protease inhibitor (PI)-based regimen.
D. Integrase inhibitor (INSTI)-based regimen.
E. Entry inhibitor (EI)-based regimen.

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E. Entry inhibitor (EI)-based regimen.

What to start?

Recommended regimens:

1 or 2 nucleoside analogues + integrase inhibitor
bictegravir/tenofovir alafenamide (TAF)/emtricitabine (FTC)
dolutegravir/abacavir/lamivudine
dolutegravir + (FTC or lamivudine [3TC]) + (TAF or tenofovir disoproxil fumarate [TDF])
dolutegravir/3TC

Alternative regimens: non-nucleoside (NNRTI)-, protease inhibitor (PI)-, and elvitegravir (EVG)-based

U.S. DHHS HIV Treatment Guidelines 1/22

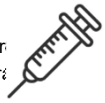
Approved Single-Tablet ART Regimens

TDF/FTC/EFV (2006)
TDF/FTC/RPV (2011)
TDF/FTC/EVG/c (2012)
ABC/3TC/DTG (2014)
TAF/FTC/EVG/c (2015)
TAF/FTC/RPV (2016)

DTG/RPV (2017)*
TAF/FTC/BIC (2018)
TAF/FTC/DRV/c (2018)
TDF/3TC/DOR (2018)
DTG/3TC (2019)

*FDA approved for maintenance therapy

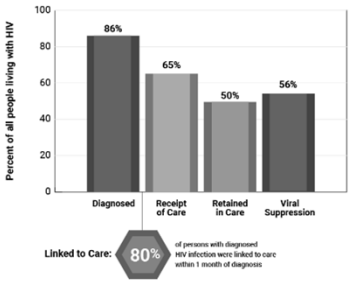
Cabotegravir (CAB)



- Integrase inhibitor similar to similar to dolutegr
- Potent in people with HIV (5, 10, 30, 60 mg ora
  Spreen HIV Clin Trials 2013;14:192
- Nanotechnology formulation; injectable
- Phase 3 studies of IM CAB/rilpivirine (RPV) for treatment switch demonstrated non-inferiority to standard oral treatment regimens
  - Orkin NEJM 2020;382:1124
  - Swindells NEJM 2020;382:1112
- U.S. FDA approved the combination of IM CAB + RPV monthly for switch treatment in January 2021
  - For patients undetectable on ART without a history of virologic failure, drug resistance, or chronic HBV infection

FDA APPROVED

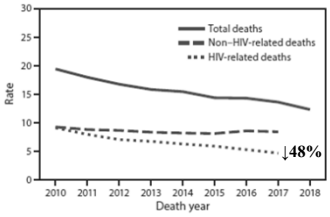
Prevalence-based HIV Care Continuum, U.S. and 6 Dependent Areas, 2018



www.hiv.gov

U.S. HIV Deaths: 2010-2018

FIGURE 1. Age-adjusted rates* of total deaths,† human immunodeficiency virus (HIV)–related deaths,§ and non–HIV-related deaths among persons aged ≥13 years with diagnosed HIV infection — United States, 2010–2018¶

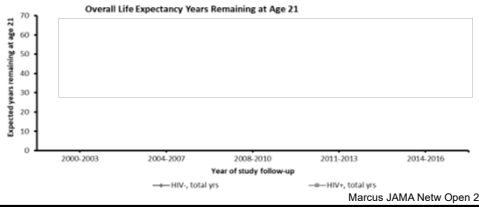


Bosh, MMWR 2020;69:1717-24

Kaiser: Life Expectancy of People with/without HIV

Cohort of adults with HIV in care 2000-2016 (N=39,000)
Matched 1:10 with uninfected (N=387,785)
Study population:
Avg 41 yo, Asian 5%/Black 25%/Latinx 24%/white 45%, MSM 70%, HS 20%, IDU 8%
Results: Narrowing of the survival gap – now 9 years shorter with HIV vs no HIV

- ***No gap if ART initiated before CD4 < 500!***

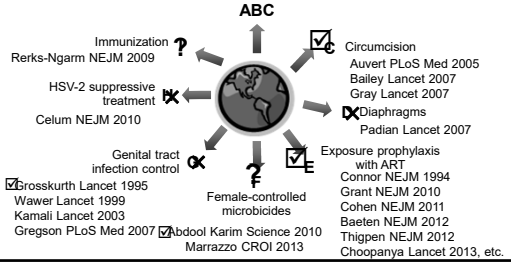


Marcus JAMA Netw Open 2020;3:e207954

HIV Prevention Strategies

Adapted from Ramjee *IAS Meeting* 2006, #TUPL02

Abstain, **B**e faithful, **C**ondoms, **C**ounseling & testing



Question 4

Which PrEP regimen is FDA-approved for at-risk men and women?

A. Daily tenofovir disoproxil fumarate (TDF)/emtricitabine (FTC).
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HIV Prevention Strategy: PrEP

- Pre-exposure prophylaxis
- Strategy of administering HIV medications to uninfected, at-risk individuals
- Optimal drug candidates:
  - potent, safe, tolerable, and convenient
  - – = co-formulated tenofovir/FTC
- Potential concerns:
  - used widely for treatment; drug resistance; toxicities (kidney, bone); cost (>$10,000/year)
- 2012: FDA approves TDF/FTC for PrEP
- 2019: FDA approves TAF/FTC for PrEP
- 2021: FDA approves injectable CAB for PrEP

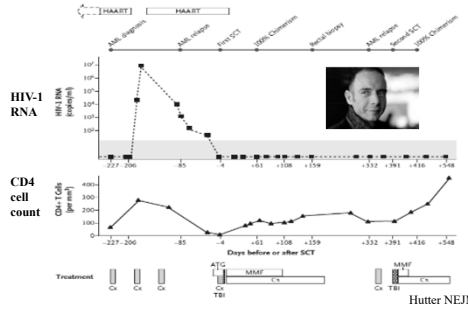
Recent PrEP Studies

Study (reference)	Study population	Design	Results: Reduction in HIV Infection
PROUD McCormack Lancet 2015;387:54-60	544 HIV- MSM in UK	TDF/FTC (daily) immediate vs. delayed	TDF/FTC immediate: **86% reduction**
IPERGAY Molina NEJM 2015;373:2237	400 HIV- MSM in France and Canada	TDF/FTC (on demand) vs. placebo	TDF/FTC: **86% reduction**
HPTN 083 Landovitz NEJM 2022;385:595	4570 HIV- MSM and transgender women globally	TDF/FTC (daily) vs. CAB injections (every other month)	CAB non-inferior and **superior** to TDF/FTC

Federal Plan to End AIDS by 2030

February 2019
https://www.hiv.gov/

HIV Cure (N=*1*) 3!



Hutter NEJM 2009;360:692

Cure #2
Gupta
Nature
2019;568:
244-248.

Cure #3
Bryson
CROI 2022
Abstract
#65

Conclusions

- HIV/AIDS is a worldwide pandemic.
- Routine HIV testing should be offered to ALL patients.
- Antiretroviral therapy (ART) ↓ HIV RNA, ↑ CD4 cell counts, prevents disease progression, and prolongs healthy survival.
- Current ART consists of 3-drug therapy and is increasingly available worldwide.
- Current life expectancy for HIV+ people on therapy approaches that of the general population.
- Prevention continues to be key.
- Cure research is in progress.

Acknowledgments

- Cornell HIV Clinical Trials Unit (CCTU)
- Division of Infectious Diseases
- Weill Cornell Medicine
- NY Presbyterian
- AIDS Clinical Trials Group (ACTG)
- Division of AIDS, NIAID, NIH
- The patient volunteers!

rgulick@med.cornell.edu

OL6

ID Bootcamp: Transplant

Dr. Camille Kotton

Online Only Lectures - ID Bootcamp: Solid Organ and Stem Cell Transplant

Speaker: Camille Kotton, MD

IDBR INFECTIOUS DISEASE BOARD REVIEW AUGUST 20-24 2022

ID Bootcamp: Solid Organ and Stem Cell Transplant

Camille Nelson Kotton MD, FAST, FIDSA
Clinical Director, Transplant & Immunocompromised Host Infectious Diseases Group, Infectious Diseases Division, Massachusetts General Hospital
Associate Professor, Harvard Medical School

6/1/2022

Disclosures of Financial Relationships with Relevant Commercial Interests

Camille Nelson Kotton, Disclosures		
Company	Role	Details
Evrys	Consultant	CMV treatment in transplant
Merck	Consultant, Adjudication committee member, Data monitoring committee, symposium speaker (CME)	Transplant infections CMV antiviral trial, adjudication Pneumococcal vaccine, adjudication
Oxford Immunotec	Consultant, research, Symposium speaker (CME)	Novel diagnostics in transplant patients, TB in Immunocompromised Hosts
Shire/Takeda	Consultant, Adjudication committee member, symposium speaker (CME)	CMV management in transplant patients
Hookipa	Consultant, principal investigator on clinical trial CMV vaccine in kidney transplant recipients	CMV vaccine in kidney transplant recipients
AiCuris	Research	Local PI, use of pritelivir in immunocompromised patients with resistant herpes
Roche Diagnostics	Research	Review of risk factors for herpes viral infections after transplant

Outline: What I Hope You Will Learn

- Type of immunosuppression seen with organ transplant
- Timeline of infection
- Prevention is paramount
  - Gaps in prophylaxis help develop the differential diagnosis
- Syndromes
- Diagnostics
  - Differential diagnosis is broad, imperative to obtain diagnosis
- Treatment – including drug interactions
- Latest strategies for prevention, recognition, diagnosis, and treatment
  - Guidelines
  - Best practices for safety and practice improvement
- **Bootcamp: meant as an introduction to subsequent similar talks**

The More Immunocompromised Host

- Hematopoietic stem cell transplant (HSCT) < 2 years
  - ↑ if graft versus host disease
- Solid organ transplant (SOT) < 1 year
  - ↑ if rejection
- AIDS with low CD4 counts
- Active leukemia or lymphoma, generalized malignancy, aplastic anemia, recent radiation tx
- Congenital immunodeficiency
- Immunosuppressive medications
- Chronic hepatic or renal disease, diabetes
- Autoimmune diseases

https://wwwnc.cdc.gov/travel/yellowbook/2022/travelers-with-additional-considerations/immunocompromised-travelers, Kotton, Kroger, Freedman

The Less Immunocompromised Host

- Stem cell transplant recipients > 2 years post-transplant, not on immunosuppressive drugs, no graft versus host disease
- Chemotherapy for leukemia/lymphoma or cancer more than 3 months earlier with malignancy in remission
  - Those who have received immunotherapy with agents such as checkpoint inhibitors may need longer
- HIV patients with >500 CD4 lymphocytes
- Asplenia
- Nutritional deficiencies
- Steroid inhalers, topical steroids, intra-articular, bursal, or tendon injection of steroids, or on high-dose steroids over a month ago

https://wwwnc.cdc.gov/travel/yellowbook/2022/travelers-with-additional-considerations/immunocompromised-travelers, Kotton, Kroger, Freedman

Host considerations: *"Net state of immunosuppression"*

Dr. Robert Rubin, Massachusetts General Hospital

IMMUNOSUPPRESSION IS ADDITIVE

- Disease state may alter the immune system
  - Autoimmune diseases
  - Advanced organ failure
  - Other organ compromise: kidney, liver
- Comorbidities/conditions
  - Diabetes, obesity, malnutrition/weight loss
  - Hypogammaglobulinemia
  - Viral infections (HIV, CMV, EBV, HCV)
  - Altered microbiome
  - Advanced age
- Exogenous immunosuppression
  - Pre-transplant immunosuppression (i.e. autoimmune hepatitis)
  - Induction agents @ time of transplant
  - Chronic immunosuppression
  - Treatment of rejection

National Organ Transplant Data – USA

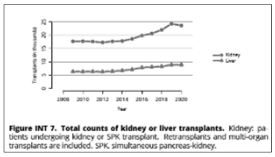


Figure INT 7. Total counts of kidney or liver transplants. Kidney: patients undergoing kidney or SPK transplant. Retransplants and multi-organ transplants are included. SPK, simultaneous pancreas-kidney.

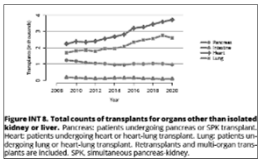


Figure INT 8. Total counts of transplants for organs other than isolated kidney or liver. Pancreas: patients undergoing pancreas or SPK transplant. Heart: patients undergoing heart or heart-lung transplant. Lung: patients undergoing lung or heart-lung transplant. Retransplants and multi-organ transplants are included. SPK, simultaneous pancreas-kidney.

>850,000 transplants done in USA since 1988

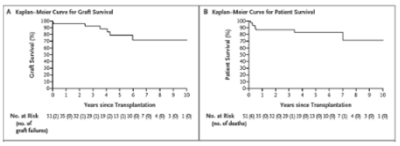
OPTN/SRTR 2020 Annual Data Report:
Introduction, AJT Feb 2022

What's Trendy? (Might be on boards?) Hepatitis C Donors and Organ Transplant

- Many programs are using hepatitis C positive donors into negative or positive recipients and treating after transplant
  - Yes, we are infecting people with hepatitis C
- Can be either HCV viral load and/or antibody positive
- For all organs, ~100% clearance
- Was often research protocol, now moving towards standard of care
- Need to have a good plan for medications (insurance)
- Trend towards shorter treatment protocols

Longer-Term Outcomes of *HIV-Positive–to–HIV-Positive Renal Transplantation*, Selhorst, Muller et al, NEJM 2018

- n=51
- 8 patients (16%) died after transplantation from non–graft-related causes
- No transmission of drug resistant virus
- **5-year overall survival and graft survival similar to the 3-year overall survival and graft survival observed among HIV-positive patients who received an organ from an HIV-negative donor in the United States**



HIV Organ Policy Equity (HOPE) Act: USA

- **Permits donated, HIV-positive organs to be used for transplantation in HIV-positive patients**
  - Previously prohibited by federal law
- **An active program at multiple centers**
  - Research setting only
- **+/- Half of organ donors have false positive testing**
  - Screening test positive, confirmatory test (done later, takes time) negative

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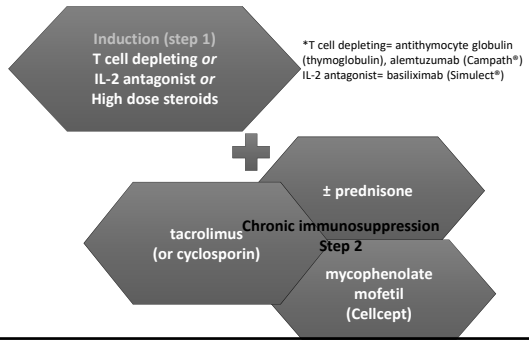
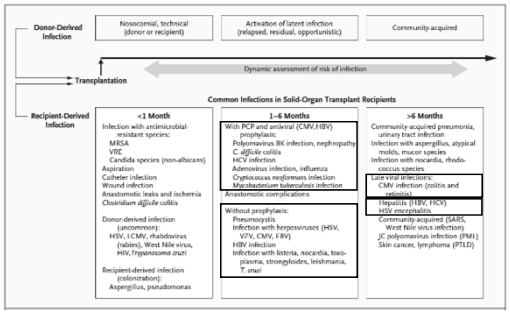
Common Immunosuppression after Organ Transplant



Timeline of Infection after Organ Transplantation

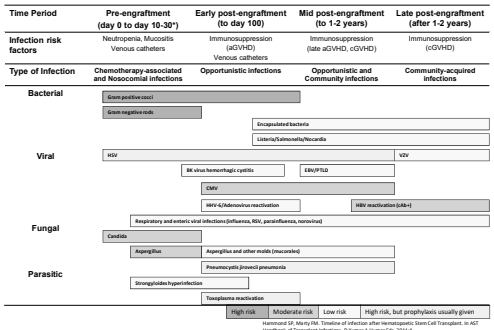


Fishman, Infection in Solid-Organ Transplant Recipients, NEJM 2007

Common Immunosuppression after Stem Cell Transplant

- Chemotherapy
- Anti-graft versus host disease prophylaxis
  - Tacrolimus, cyclosporin
  - Methotrexate
  - Mycophenolate mofetil
  - Antithymocyte globulin (rabbit)
- Anti-graft versus host disease treatment
  - The first-line treatment of acute GVHD is methylprednisolone

Timeline of Infection after HSCT



Hammond SP, Marty FM. Timeline of infection after Hematopoietic Stem Cell Transplant. In: ACT Handbook of Transplant Infections, D Kumar A Humar Eds. 2011;4.

Prevention & Prophylaxis

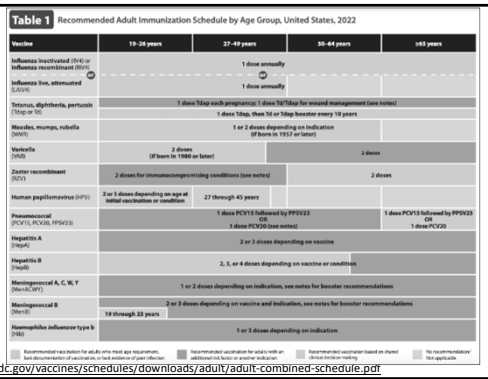
- Pre-immunosuppression evaluation**
  - Vaccines
  - Screening for latent infections
  - Plan for chronic infections
  - Optimize diabetes, stop smoking/marijuana use, etc
  - Education
- Management: peritransplant/initiation of immunomodulatory
- Prophylaxis and/or screening after transplant/immunomodulatory therapy started

Pre-Immunosuppression Evaluation (MGH)

	Everyone	If risk factors
Hepatitis B surface antigen	x	
Hepatitis B core antibody (IgG not IgM)	x	
Hepatitis B surface antibody	x	
Hepatitis C	x	
HIV	x	
Tuberculosis screening	x	
Coccidioides serology		x
Strongyloides serology		x
Trypanosoma cruzi (Chagas disease)		x

Pre-Solid Organ Transplant Evaluation (MGH)

	Everyone	Vaccinate if neg	If risk factors
Hepatitis A	x	x	
Hepatitis B surface antigen	x		
Hepatitis B core antibody (IgG not IgM)	x		
Hepatitis B surface antibody	x	x	
Hepatitis C	x		
HIV	x		
Tuberculosis screening	x		
Varicella	x	x	
Cytomegalovirus	x		
Mumps-measles-rubella	x	x	
Syphilis antibody	x		
Coccidioides antibody			x
Strongyloides serology			x
Trypanosoma cruzi (Chagas disease)			x



https://www.cdc.gov/vaccines/schedules/downloads/adult/adult-combined-schedule.pdf

Influenza vaccine or Live flu vaccine =

Recombinant zoster vaccine =

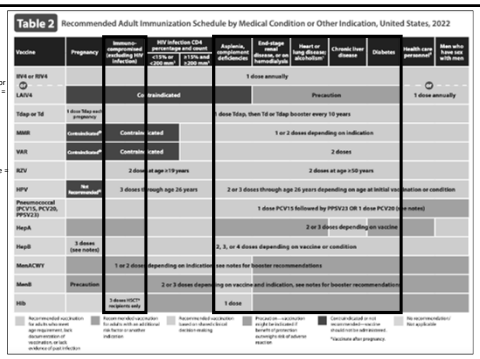


Table 2 Recommended Adult Immunization Schedule by Medical Condition or Other Indication, United States, 2022

Vaccine	Pregnancy	Immuno-compromised (including HIV infection)	HIV infection CD4 percentage and count <15% or <200 mm³	HIV infection CD4 percentage and count ≥15% and ≥200 mm³	Asplenia, complement deficiencies	End-stage renal disease, or on hemodialysis	Heart or lung disease, alcoholism	Chronic liver disease	Diabetes	Health care personnel*	Men who have sex with men
RV4 or RV5					1 dose annually						
LAIV4	Contraindicated						Precaution			1 dose annually	
Tdap or Td	1 dose Tdap each pregnancy				1 dose Tdap, then Td or Tdap booster every 10 years						
MMR	Contraindicated*	Contraindicated			1 or 2 doses depending on indication						
VAR	Contraindicated*	Contraindicated			2 doses						
RZV		2 doses at age ≥19 years			2 doses at age ≥50 years						
HPV	Not recommended*	3 doses through age 26 years			2 or 3 doses through age 26 years depending on age at initial vaccination or condition						
Pneumococcal (PCV15, PCV20, PPSV23)					1 dose PCV15 followed by PPSV23 OR 1 dose PCV20 (see notes)						
HepA					2 or 3 doses depending on vaccine						
HepB	3 doses (see notes)				2, 3, or 4 doses depending on vaccine or condition						
MenACWY		1 or 2 doses depending on indication			see notes for booster recommendations						
MenB	Precaution		2 or 3 doses depending on vaccine and indication, see notes for booster recommendations								
Hib		3 doses HSCT recipients only			1 dose						

Recommended vaccination for adults who meet indication criteria or have documentation of vaccination or lack evidence of past infection | Recommended vaccination for adults with an additional risk factor or another indication | Recommended vaccination based on shared clinical decision-making | Precaution—vaccination ought be indicated if benefit of protection outweighs risk of adverse reaction | Contraindicated or not recommended—vaccine should not be administered. *Vaccines after pregnancy. | No recommendation/ Not applicable

https://www.cdc.gov/vaccines/schedules/downloads/adult/adult-combined-schedule.pdf

CDC: Who Should Get Tested for TB

- TB tests are generally not needed for people with a low risk of infection
- Certain people should be tested for TB bacteria because they are more likely to get TB disease, including:
  - People who have spent time with someone who has TB disease
  - **People with HIV infection or another medical problem that weakens the immune system**
  - People who have symptoms of TB disease (fever, night sweats, cough, and weight loss)
  - People from a country where TB disease is common (most countries in Latin America, the Caribbean, Africa, Asia, Eastern Europe, and Russia)
  - People who live or work somewhere in the US where TB disease is more common (homeless shelters, prison or jails, or some nursing homes)
  - People who use illegal drugs

www.cdc.gov/tb/topic/testing/

Latent TB Screening

- Medical history
- Epidemiologic risk factors
- TB skin test (TST)
- Interferon gamma release assay (IGRA) (blood test) (sometimes preferentially vs TST, IDSA guidelines 2016)
  - T-SPOT.®*TB*
  - QuantiFERON®-TB Gold
- Radiographic findings
  - Old granulomatous disease, apical scarring

T-SPOT.®*TB* and QuantiFERON®-TB Gold

- Enumerates effector T-cell response to stimulation with a combination of peptides simulating ESAT-6 and CFP10 (+ TB7.7 for QFN) antigens
- Detects prior exposure to:
  - *M. tuberculosis* complex organisms (*M. tuberculosis, M. bovis, M. africanum, M. microti, M. canetti)*
  - *M. kansasii, M. szulgai,* and *M. marinum*
- Not + with prior BCG vaccine (bacille Calmette–Guérin)
- Interpret test correctly:
  - If either test or PPD positive, take as positive
  - Borderline results = partway b/w + and negative
  - **Indeterminate results = assay did not work**

Your patient has latent TB. Should and when should you start chemoprophylaxis? When can immunosuppressive medications be started?

A. Start TB chemoprophylaxis ASAP as per guidelines. (Ensure no active TB, pulmonary or extrapulmonary.) Can start immunosuppression any time.
B. Avoid TB chemoprophylaxis. Too many side effects, and too much hassle.
C. Most of my patients had BCG vaccine as children, and test false + as older adults. I don't give TB chemoprophylaxis.

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Excellent Prophylaxis is Paramount… and provides important clues on boards questions

- Antivirals
- Pneumocystis/Toxoplasmosis
- Antifungals

Prophylaxis: Solid Organ Transplant Massachusetts General Hospital

CMV/Herpes Antiviral Prophylaxis

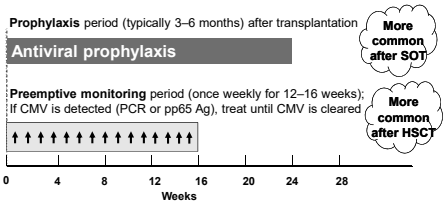
- Valganciclovir if any CMV risk (if either donor and/or recipient are CMV positive)
  - Prevents CMV, herpes, varicella/zoster
- Acyclovir/valacyclovir/famvir **if no CMV risk**
  - Prevents herpes, varicella/zoster
- Duration varies, 3-6 months is common (longer for lung transplant)
- Main side effect is leukopenia and cost with valganciclovir

Donor CMV Antibody	Recipient CMV Antibody	Prophylaxis	Duration
+	+	Valganciclovir	Antithymocyte globulin and D+R- → 6 months
-	+		
+	-		All others 3 months
-	-	ACV/Famvir/ValACV	

Anti-*Pneumocystis*/anti-bacterial

- Trimethoprim-sulfamethoxazole x 6-12 months (longer for heart/lung transplants)
- *or* dapsone or atovaquone if true allergy

CYTOMEGALOVIRUS PREVENTION: Prophylaxis vs. Preemptive Therapy

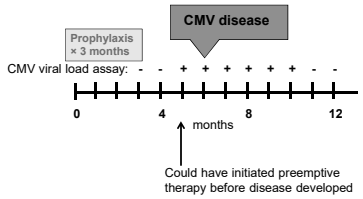


Humar A, Snydman D; AST Infectious Diseases Community of Practice. *Am J Transplant.* 2009;9 (Suppl 4):S78-S86.

Hybrid Strategy for SOT: CMV Surveillance After Prophylaxis

Consider "net state of immunosuppression"

- Weekly monitoring after end of prophylaxis, for ~12 weeks
- High risk (D+/R-) may be highest yield population (for late disease)
  - Other high-risk groups (potent immunosuppression)
- Guidelines experts use approach, not strongly evidence-based



Kotton CN et al, The Third International Consensus Guidelines on The Management of Cytomegalovirus In Solid Organ Transplantation, Transplantation 2018

Antiviral Prophylaxis: Stem Cell Transplant

- Acyclovir/valacyclovir/famvir for everyone
  - Prevents herpes, varicella/zoster
  - Duration varies a lot across programs, 6-12+ months is common
- Letermovir x 100 days if higher CMV risk
  - if recipient is CMV positive – opposite of solid organ (D-R+ is high risk after HSCT)
  - Prevents CMV, NOT herpes, varicella/zoster
  - Decreased mortality
  - If small viral load "blips", carry on and retest a week later – only stop therapy if high blips (>1,000 IU/ml)
- Main side effect is cost with letermovir

Antiviral Prophylaxis/Treatment Agents

Antiviral agent	CMV	HSV	Varicella	BK	Adeno-virus	EBV
Commercially available						
ganciclovir IV/valganciclovir PO	x	x	x			
acyclovir/valacyclovir/famciclovir*	high dose +/-	x	x			
letermovir	x					
maribavir	x					*in vitro*
foscarnet**	x	x	x			
cidofovir**	x	x	x	poor	+/- (IC50)	
Novel/investigational antiviral agents (SOT)						
brincidofovir (not available)	*x*	*x*	*x*	*x*	*x*	*x*

*acyclovir/valacyclovir/famciclovir and letermovir for prophylaxis only
**foscarnet, cidofovir not usually used for prophylaxis

Pneumocystis/Toxoplasmosis

- First line:
  - Bactrim SS daily or DS three times a week
- Second line (only if real Bactrim allergy or intolerance) alternatives:
  - Atovaquone (Mepron) 1500 mg QD
  - Dapsone 100 mg QD
    - √ G6PD
    - watch for methemoglobinemia, low white blood cell count
  - Pentamidine IV q month (does not cover Toxoplasmosis)
- Duration variable, usually until end of PPx

Antifungal Prophylaxis: Solid Organ Transplant

Organ	Common Practice	Comments
Kidney, liver, heart	None for most; some programs give fluconazole/echinocandins peri-liver	Some Nystatin swish and swallow
Pancreas	Fluconazole post-op for variable time, < 1 month	
Lung	Voriconazole, posaconazole, itraconazole for variable times after transplant	Voriconazole and augmented skin cancer, osteitis risks a major concern
Intestinal transplant, Composite tissue	Often longer courses of fluconazole/echinocandins	

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Antifungal Prophylaxis: Hematopoietic Stem Cell Transplant

- Fluconazole often used in first 100 days after HSCT
  - Generally for higher risk receipts
  - Classic population for *C. krusei,* R to fluconazole
- Posaconazole generally reserved for higher risk patients
  - Only FDA approved agent for this indication
- Voriconazole – higher risk of mucormycosis seen

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Sources of Infection after Transplant

- Community-acquired
- Nosocomial
- Prior colonization
  - + Intraoperative *Aspergillus* culture w/ cystic fibrosis & lung transplant → OR 4.36 invasive aspergillosis (Luong *et al*, Transplantation 2014)
- Emerging
- Donor-derived infection
  - Organ graft, blood products

Ten years of donor-derived disease: A report of the disease transmission advisory committee

Am J Transplant. 2021;21:689–702

Daniel R. Kaul[1] | Gabe Vece[2] | Emily Blumberg[3] | Ricardo M. La Hoz[4] | Michael G. Ison[5] | Michael Green[6] | Timothy Pruett[7] | Michael A. Nalesnik[8] | Susan M. Tlusty[2] | Amber R. Wilk[2] | Cameron R. Wolfe[9] | Marian G. Michaels[4]

- The Organ Procurement and Transplantation Network (OPTN) created The Disease Transmission Advisory Committee (DTAC) to review and classify reports of potential disease transmission to inform national policy and improve patient safety.
- January 1, 2008 to December 31, 2017, DTAC received 2185 reports
  - 335 (15%) classified as a proven/ probable donor transmission event
- ~2/3 infection, ~1/3 malignancy
- **Overall risk 17.8/10,000 or 0.178%**
- **All types of infections (!)**
- **Note: initial trigger is transplant center reporting to local organ bank (you!)**

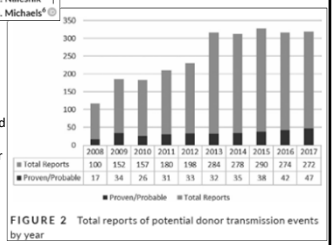
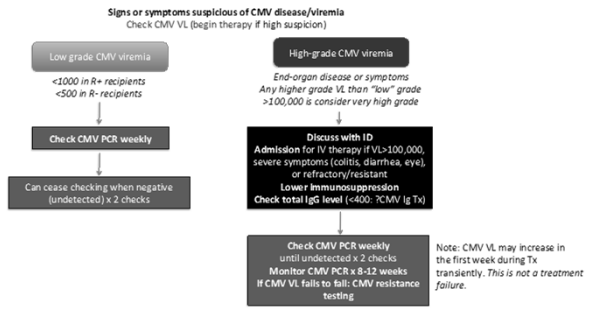


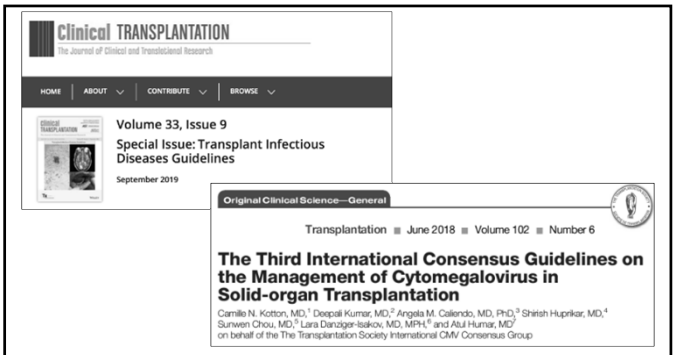
FIGURE 2 Total reports of potential donor transmission events by year

Syndromes

CMV: the most common pathogen after transplant, one of the "*great masqueraders*"

- Asymptomatic viremia**
- CMV syndrome
- End organ disease:
  - Colitis
  - Pneumonitis
  - Retinitis
- Best diagnosed by CMV viral load
- Best treated with valganciclovir or ganciclovir IV
- Treat to resolution of infection and/or viral load – check weekly
- If low absolute lymphocyte count at end, consider secondary prophylaxis or monitoring





https://onlinelibrary.wiley.com/toc/13990012/2019/33/9

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The Dreaded Pulmonary Nodule

For the boards (and clinical medicine), consider the prophylaxis and what's not covered

Let the prophylaxis and epidemiology drive your differential diagnosis

Who gets fungal infections?

- Post-solid organ transplant: Incidence of invasive fungal infections in the first year has been reported to be 3%[1]
  - Candidiasis (sterile space), esp liver transplant*[surgery]
  - Cryptococcal disease
    - Among most common causes of meningitis
  - Invasive aspergillosis in 1-15%[2]
    - Accounts for significant % of deaths in first year
    - Mortality dropping in recent times, however
  - Mucormycosis less common, higher mortality
- Stem cell transplant: similar, longer risk if graft-vs-host disease
- Non-transplant immunocompromised hosts: less frequent/"net state of immunosuppression"

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1 Shoham S, Marr K. Invasive fungal infections in solid organ transplant recipients. Future Microbio 2012; 7(5): 639-655
2 Singh N, Husain S, Aspergillosis in Solid Organ Transplantation, AJT, 2013

Diagnostics

- Culture
  - Fungal stain and culture
  - Notify lab not to mince specimen if suspicion of mucormycosis
  - Fungal isolators (blood) very rarely +
    - *Candida* will grow in routine cultures
    - *Histoplasma* better; lysis centrifugation isolators is best
- Pathology: Morphology
  - Septate (*Aspergillus*) vs non-septate (*Mucor/Zygomycetes*) hyphae
  - Grocott-Gomori's (or Gömöri) methenamine silver stain
  - Periodic acid-Schiff (PAS)

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Diagnostics: Fungal Markers

Diagnostic Assay	Specimen	Comments
Cryptococcal antigen	Blood, CSF	High sensitivity/specificity
1,3 beta – D - glucan	Blood	Primarily for yeast; Low sensitivity/moderate specificity *Excellent for Pneumocystis*
Galactomannan	Blood, BAL, other body fluids	Primarily for Aspergillus; Low sensitivity/high specificity on blood, higher sensitivity on body fluids
Aspergillus PCR	Blood, BAL, other body fluids	

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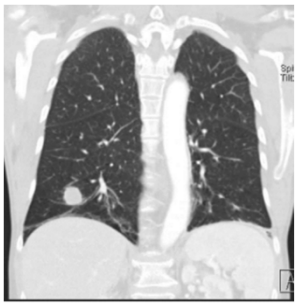
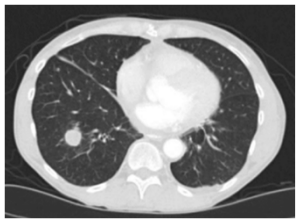
Clinical Vignette

- 54 yo woman with history of primary systemic AL amyloidosis, complicated by cardiac amyloidosis, treated cytoxan/bortezomib/dexamethasone initially, followed by lenalidomide/dexamethasone
- Orthotopic cardiac transplant Feb 2016
- Autologous stem cell transplant, Day 0=7/11/16.
- CMV DNA VL on Day 0 was 29,800 IU/ml.
- Neutropenic sepsis with a blood culture on Day 5 with *Strep salivarius*.
- Ongoing fevers, new 2 cm pulmonary nodule by CT on Day 18

44





45

After ordering bronchoscopy, next best step?

- Start voriconazole
- Start posaconazole or isavuconazole
- Start amphotericin B product
- Start echinocandin (caspofungin/micafungin/anidulafungin)
- Combination therapy

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- Start amphotericin B product
- Start echinocandin (caspofungin/micafungin/anidulafungin)
- Combination therapy

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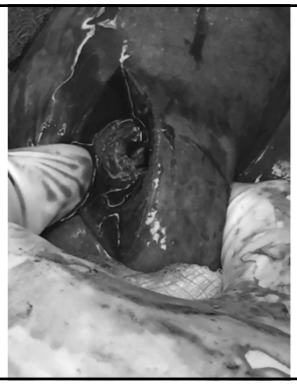
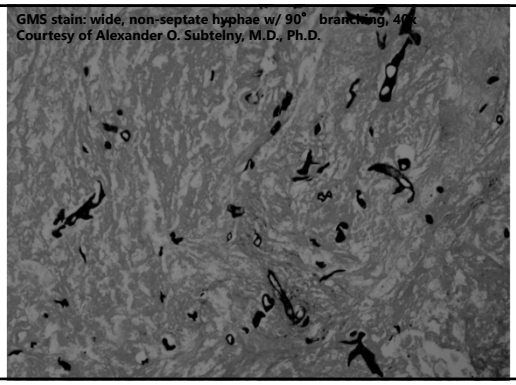
- "She has had a dry cough but denies any sputum production, chest pain, SOB or headache. She has felt very well, and was quite determined to be discharged in the next few days."
- Voriconazole started
- She was underwent bronchoscopy, radial EBUS, washings, brushings and transbronchial biopsy → **nonseptate hyphae seen**
- **Diagnosis: likely Zygomycetes**
- She was switched from voriconazole to dual antifungal therapy with loading of isavuconazole and Ambisome.
- Repeat CT scan performed 2 days later showed significant increase in size of the nodule with new satellite lesions. She proceeded to RLL resection that evening by the cardiothoracic surgeons.

48



49



50

Very Rare RHIZOPUS SPECIES

SUSCEPTIBILITY Performed at UNIVERSITY OF TEXAS HEALTH SCIENCE CENTER, Dept of Pathology, San Antonio, TX

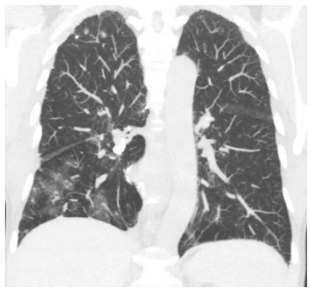
MIC DILUTION METHOD

No CLSI interpretive guidelines available

Amphotericin B	MIC=1
Isavuconazole	MIC=1
Miconazole	MIC=2
Posaconazole	MIC=0.5

In view of this, Ambisome was stopped on POD #9 and isavuconazole converted to 372mg daily for months/indefinite, plan is for radiographic resolution, immune reconstitution (heart transplant immunosuppression is for life).

51

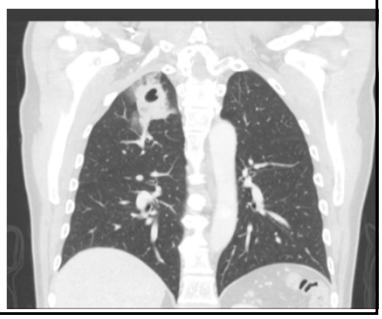


A year after transplant, she presented with disseminated zoster, new patchy infiltrates. Responded well to IV acyclovir.

52

What's This?

- Man in 50s diagnosed with multiple myeloma in 2011 → autologous stem cell transplant in March 2019.
- Due to disease progression in June 2020, he was treated with daratumumab and pomalidomide. He received radiation therapy to the thoracic and cervical spine.
- He consented to participate in a clinical trial protocol and underwent CAR infusion in January 2021. On fluconazole and acyclovir prophylaxis.
- Routine screening PET 4 months later "new thick walled multiloculated cavitary lesion in the right upper lobe with surrounding groundglass and clustered nodularity is concerning for infection, including bacterial as well as atypical and fungal infections in an immunocompromised patient". No symptoms at all



Epidemiology (ID fellow note)

- Living situation - lives with wife, 3 kids
- Outdoor exposures - rare, walks outside with dog in rode, has stopped dirt biking/hiking with thrombocytopenia
- Occupational exposures - Denies, works as a contractor for DoD, currently working at home
- Hobbies - mostly spending time at home right now
- Travel - Frequent travel pre-pandemic for work, has been to Australia, multiple countries in Asia and Europe, never to Africa or South America
- TB – no history of TB or known TB exposures; homeless or incarcerated? Denies
- Animals - Dog
- Food - raw or unpasteurized foods? Denies
- Dental work - None recent, does have a wisdom tooth pressing on a facial nerve
- Smoking - Denies
- Alcohol - Denies
- Recreational drugs - Denies
- Sex and prior STIs- Denies

What would you do next?

A. Start voriconazole, loading dose then maintenance based on weight
B. Start "vancopime" (cefepime plus vancomycin)
C. Start azithromycin
D. A-C (all of the above)
E. Bronchoscopy

Pseudomonas!

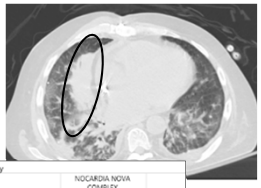
All other studies negative:

- BAL mycobacterial, fungal stains/cultures
- Cryptococcal antigen (blood)
- 1,3 beta D glucan (blood)
- Galactomannan (BAL and blood)
- Pathology: Bronchial epithelium with rare scattered neutrophils. Alveolated lung with fibroinflammatory changes and chronic inflammation. There is no evidence of malignancy. No microorganisms are seen on Brown-Hopps, GMS, Steiner, PAS-D, FITE, and AFB stains. Immunohistochemical stains for CMV, HSV, VZV, and adenovirus are negative. Trichrome and elastic stains were examined. The histologic findings are compatible with acute infection.

04/19/2021 1657	04/29/2021 1323	Wound culture/smear [818905205] (Abnormal) Other from Biopsy RUL LUNG TBBX	
Susceptibility			
		Pseudomonas aeruginosa MIC METHOD	
Amikacin		<=2	Susceptible
Cefepime		2	Susceptible
Ceftazidime		2	Susceptible
Ciprofloxacin		<=0.25	Susceptible
Levofloxacin		1	Susceptible
Meropenem		<=0.25	Susceptible
Piperacillin-tazobactam		<=4	Susceptible
Tobramycin		<=1	Susceptible

Pneumonia

- 45yo s/p heart transplant 3 months earlier on posaconazole, atovaquone prophylaxis (not on TMP-SMX due to renal failure)
- New pneumonia, right middle lobe
- What is the cause?



Susceptibility		NOCARDIA NOVA COMPLEX MIC METHOD	
Comment	SEE NOTES	Note[1]	
Amikacin		Susceptible	
Amoxicillin + Clavulanate		Resistant	
Ceftriaxone		Susceptible	
Ciprofloxacin		Resistant	
Clarithromycin		Susceptible	
Doxycycline		Intermediate	
Imipenem		Susceptible	
Linezolid		Susceptible	
Minocycline		Susceptible	
Moxifloxacin		Resistant	
Tobramycin		Resistant	
Trimethoprim/sulfamethoxazole		Susceptible	

[1] SUSCEPTIBILITY TESTING Performed at the University of Texas Health Center at Tyler, Tyler TX

Let's Switch to Parasites

Clinical Vignette

64yo man from Dominican Republic with end-stage liver disease, chronic abdominal pain, listed for liver transplant

- Eosinophilia (up to 70%) x 6 months
- Recurrent enteric Gram negative rod bacteremias
- Fluffy pulmonary infiltrates
- What does he have?

59

Test Results

Strongyloides Antibody by ELISA: 100.00

INTERPRETATION: POSITIVE

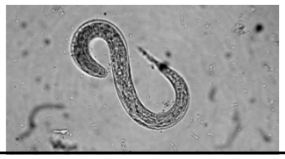
All reactions of <=1.7 units/ml should be considered NEGATIVE.
All reactions >1.7 units/ml should be considered POSITIVE, indicative of infection with *Strongyloides stercoralis* at some indeterminate time.
Sensitivity of the test is 93% and specificity is 98%.

Centers for Disease Control testing

60

Strongyloides

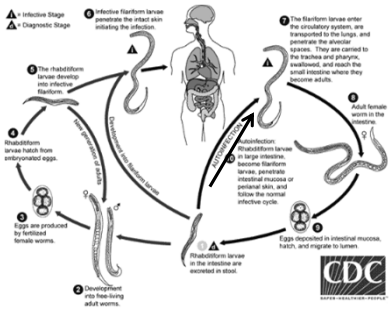
- Nematode "roundworm"
- 100-200 million people worldwide are infected
- Autoinfection*
- >50% mortality immunocompromised patients with disseminated disease



The countries highlighted in **yellow** have sporadic endemicity, on the range of 1-3%. Those that are **orange** are endemic, while those that are **red** are generally hyperendemic, with the highest frequency of *Strongyloides* infection.

http://web.stanford.edu/group/parasites/ParaSites2006/Strongylodiasis/epidemiology.html

Strongyloides stercoralis lifecycle



http://www.cdc.gov/dpdx/strongyloidiasis/

Drug Interactions: Transplant & Antimicrobials

- Azoles
  - Voriconazole, posaconazole > fluconazole
  - Isavuconazole – much less interaction
  - Increase tacrolimus (or cyclosporine, rapamycin)
- Rifamycins
  - Rifabutin < rifampin (=rifampicin)
  - Decrease tacrolimus (or cyclosporine, rapamycin)
  - Increase prednisone
- QT prolongation
  - Combination effect
  - May be present with liver disease
- Recommended: Use of on-line drug interaction calculator

Cardinal Rules 2022: Immunosuppression and Infection

1. Immunosuppression and infections not always straightforward
2. Be prepared to be surprised – think broadly
3. Prepare patient for immunosuppression – role for ID specialists
4. Prophylaxis & vaccines alter the risk equation
   Primary and secondary prevention
5. Consider the source of infection: donor, recipient, blood products, geographic, more antibiotic resistance

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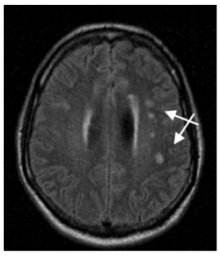
Questions? ckotton@mgh.Harvard.edu

MASSACHUSETTS GENERAL HOSPITAL
TRANSPLANT CENTER

Meningoencephalitis after OLT

- 45yo man moved back home to Boston, cirrhosis/end stage liver disease
- 6 weeks after liver transplant, fevers, headache, seizure
- CSF glucose <20, protein 180, WBC 250 lymph predominant
- Started mycobacterial, fungal coverage



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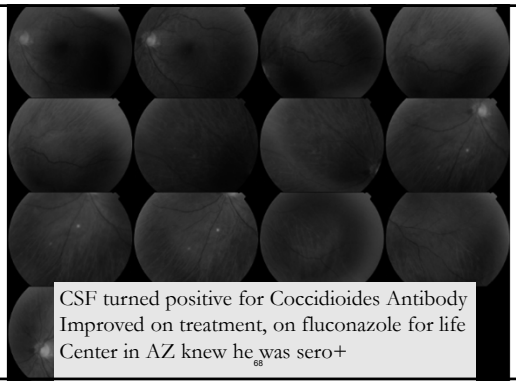

CSF turned positive for Coccidioides Antibody
Improved on treatment, on fluconazole for life
Center in AZ knew he was sero+

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Lip Lesion in a Solid Organ Transplant Recipient

Nicole Theodoropoulos and Michael Angarone

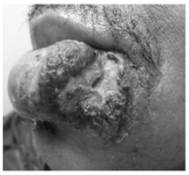


Figure 1. Photograph of lower lip ulcerated lesion at initial presentation.

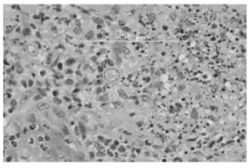


Figure 2. Histopathology of section through lip lesion tissue (hematoxylin-eosin, high-power magnification).

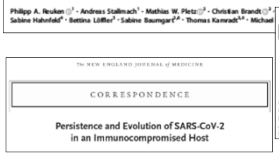
Clinical Infectious Diseases 2012;54(9):1332

COVID-19 and Immunocompromised Hosts

CORRESPONDENCE

Infectious medicine virology

Severe clinical relapse in an immunocompromised host with persistent SARS-CoV-2 infection



CORRESPONDENCE

Persistence and Evolution of SARS-CoV-2 in an Immunocompromised Host

Best treatments?
Role of immunomodulatory therapies?
Best management of immunosuppression?
Optimizing vaccination strategies?

Clinical Infectious Diseases

MAJOR ARTICLE

IDSA hivma

Coronavirus Disease 2019 in Solid Organ Transplant: A Multicenter Cohort Study

Donor-Derived Infections

Of 284 fully evaluated reports, 32 (11.3%) (of >14,000 donors) resulted in a proven/probable transmission of infection, malignancy or other condition to 42 recipients

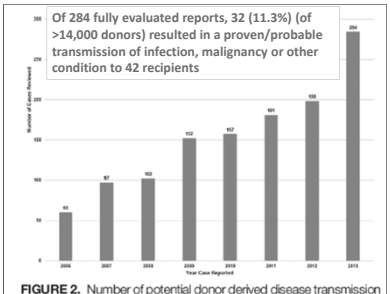


FIGURE 2. Number of potential donor derived disease transmission events reviewed by the DTAC 2006 to 2013.

Green et al, Transplantation 2015

TABLE 2.
Summary of bacteria-associated PDDTE reports to the OPTN Ad Hoc disease transmission advisory committee in 2013

Organism	No. donors reported	No. proven/ probable donors	No. recipients with proven/probable transmission	No. related deaths
Other bacteria	29	4	4	0
Mycobacterium	19	0	0	0
E. coli	3	1	1	0
Enterobacter cl	3	1	1	0
Enterococcus	4	1	1	0
MRSA	10	2	3	1
Streptococcus	5	0	0	0
Staphylococcus	22	1	1	0
Klebsiella	4	1	1	0
Total	99	11	12	1

TABLE 4.
Summary of fungus, parasite, and nonmalignancy/ noninfection–associated PDDTE reports to the OPTN Ad Hoc disease transmission advisory committee in 2013

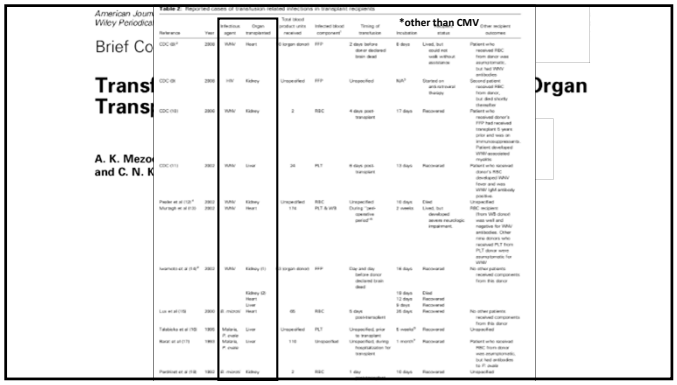
Organism	No. donors reported	No. proven/ probable donors	No. recipients with proven/ probable transmission	No. related deaths
Strongyloides/T. cruzi	5	1	1	1
Coccidioides	4	0	0	0
Aspergillus	3	2	2	1
Candida	10	1	1	0
Cryptococcus	6	0	0	0
Histoplasmosis	5	0	0	0
Other fungus	9	1	1	0
Nonmalignancy/ noninfection	16	3	4	1
Total	58	8	9	3

TABLE 3.
Summary of virus-associated PDDTE reports to the OPTN Ad Hoc disease transmission advisory committee in 2013

Organism	No. donors reported	No. proven/ probable donors	No. recipients with proven/probable transmission	No. related deaths
HBV	12	2	2	0
HCV	11	0	0	0
Adenovirus	4	1	1	0
Community respiratory virus	6	1	2	0
CMV	6	2	4	0
HSV	2	0	0	0
West Nile Virus	10	1	3	0
Other viral	11	1	1	1
Total	62	8	13	1

HCV, hepatitis C virus; HBV, hepatitis B virus.

Green et al, Transplantation 2015



Testing for HBV Infection

- Testing for HBV infection (consisting of testing for HBV surface antigen, HBV surface antibody, and HBV core IgG antibody) is recommended for the following persons:
  - persons born in countries of high and intermediate HBV endemicity (HBsAg prevalence ≥2%);
  - U.S.-born persons not vaccinated as infants whose parents were born in countries with high HBV endemicity (≥8%);
  - persons needing immunosuppressive therapy, including chemotherapy, immunosuppression related to organ transplantation, and immunosuppression for rheumatologic or gastroenterologic disorders; donors of blood, plasma, organs, tissues, or semen.

Prevention of Hepatitis B Virus Infection in the United States: Recommendations of the Advisory Committee on Immunization Practices, MMWR Jan 2018

HBV Levels of Risk –UpToDate

- **Very high risk** — Patients are at very high risk of reactivation (>20 percent risk of reactivation) if they are **HBsAg positive** and are going to receive anti-CD20 therapy (ie, rituximab, ofatumumab, obinutuzumab) or undergo hematopoietic cell transplantation.
- **High risk** — Patients are considered at high risk for reactivation (11 to 20 percent risk of reactivation) if they are **HBsAg positive** and are going to receive high-dose glucocorticoids (eg, ≥20 mg/day for at least four weeks) or the anti-CD52 agent, alemtuzumab.

Antiviral therapy ⬆

- **Moderate risk** — **HBsAg-positive** individuals are at moderate risk of reactivation (1 to 10 percent) if they are going to receive any of the following: cytotoxic chemotherapy **without** glucocorticoids; anti-TNF therapy; or anti-rejection therapy for solid organ transplants.
- Patients who are HBsAg negative and **anti-HBc positive** are at moderate risk for reactivation if they are going to receive anti-CD20 therapy or undergo hematopoietic cell transplantation.

- **Low risk** — **HBsAg-positive** individuals are at low risk (<1 percent) for reactivation if they receive methotrexate or azathioprine. HBsAg-negative and **anti-HBc-positive** individuals are at low risk if they receive high-dose glucocorticoids (eg, ≥20 mg/day) or the anti-CD52 agent alemtuzumab.
- **Very low risk** — HBV reactivation occurs rarely in HBsAg-negative and **anti-HBc-positive** patients receiving the following: cytotoxic chemotherapy without glucocorticoids, anti-TNF therapy, methotrexate, or azathioprine.

Feb 2021

HBV Prevention Based on Levels of Risk -UpToDate

- "**Moderate to very high risk** – We recommend that antiviral therapy be administered concurrently or prior to initiating immunosuppressive therapy to patients who are at moderate to very high risk of HBV reactivation. In such patients, we prefer preventive therapy, rather than waiting for evidence of reactivation, since studies in this population have demonstrated that antiviral therapy started after the onset of reactivation may not prevent a flare."
  - Entecavir, tenofovir (not lamivudine)
- "**Low risk or very low risk** — Among those at low risk or very low risk of reactivation, we perform frequent monitoring so that HBV reactivation can be detected early in its course and appropriate therapy can be initiated."

Feb 2021

Clinical Vignette

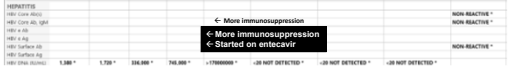
- 70yo man from Syria needs moderate immunosuppression… what do you think?

	10/31/2011 1245	10/6/2011 1130	9/21/2010 1133
HEPATITIS			
HBV Core Ab(s)		Positive *	
HBV Core Ab, IgM	Negative *		Negative *
HBV e Ab	Positive *		
HBV e Ag	Negative *		
HBV Surface Ab		<5.0 *	<5.0 *
HBV Surface Ag		Negative	Negative
HBV DNA (IU/mL)	see comment *		
HCV Ab		Non Reactive	Non Reactive

Clinical Vignette

70yo man originally from Syria needs moderate immunosuppression… what do you think?

	10/31/2011 1245	10/6/2011 1130	9/21/2010 1133
HEPATITIS			
HBV Core Ab(s)		Positive *	
HBV Core Ab, IgM	Negative *		Negative *
HBV e Ab	Positive *		
HBV e Ag	Negative *		
HBV Surface Ab		<5.0 *	<5.0 *
HBV Surface Ag		Negative	Negative
HBV DNA (IU/mL)	see comment *		
HCV Ab		Non Reactive	Non Reactive

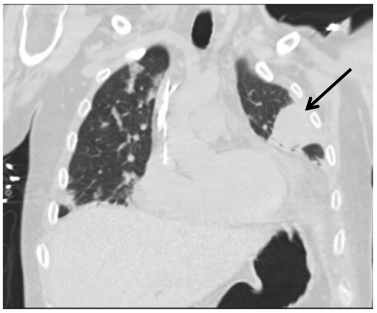


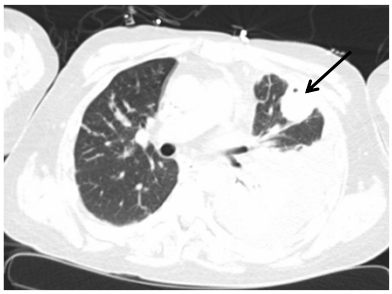
Approach to EBV monitoring

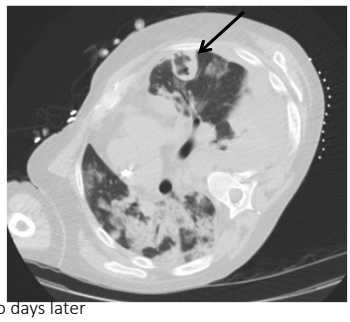
- Only routinely indicated in EBV seronegative recipients of a positive donor
- EBV monitoring post-transplant is done to assess risk for PTLD.
- Screening with EBV PCR periodically (every 1-3 months) for 1 year post-transplant
- If viral load is positive, monitor every month, and if >5,000 or if persistent, reduce IS and consult transplant ID.

Clinical Vignette

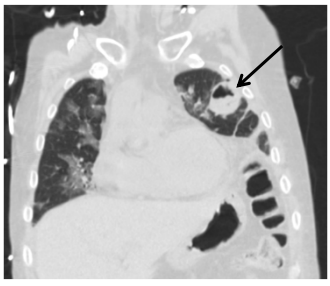
- 36yo male, Type I diabetes, 3 months after kidney/pancreas transplant (on prednisone 5 mg/day, mycophenolate mofetil (Cellcept) 1000mg twice a day, tacrolimus 4 mg twice a day)
- Transferred with three days of worsening left sided abdominal and flank pain
- Chest CT findings concerning for necrotizing pneumonia/cavitating lesion.
- On valganciclovir and TMP/SMX prophylaxis
- Exam: jaundiced, cachectic, dull breath sounds at left base, crackles both lungs







Two days later



Diagnostics

- Fungal markers all negative (blood)
  - 1,3 beta D glucan
  - Galactomannan antigen
  - Cryptococcal antigen
- Thoracentisis → exudate, chest tube placed
- Bronchoscopy, biopsy

What is the diagnosis?

A. Aspergillus
B. Mucormycosis
C. Necrotizing Gram negative
D. Mycobacterial (M. kansasii, etc)
E. Nocardia

Culture Data

LEFT EFFUSION/PLEURAL FLUID (and BAL)

Gram Stain –abundant polys, moderate red blood cells, few mononuclear cells, **no organisms seen**

Fluid Culture - **NOCARDIA NOVA COMPLEX, subspecies *veterana***

MIC DILUTION METHOD

Amikacin	Susceptible
Amoxicillin/Clavulanate	Susceptible **
Ceftriaxone	Intermediate
Ciprofloxacin	Resistant
Clarithromycin	**Susceptible**
Doxycycline	Resistant
Imipenem	**Susceptible**
Linezolid	Susceptible
Minocycline	Intermediate
Moxifloxacin	Resistant
Tobramycin	Resistant
Trimethoprim/Sulfa	**Susceptible**

Treatment

- Brain CT negative for metastatic infection
- Imipenem + azithromycin until radiographic improvement**
- Markedly improved in first few days (?chest tube placement)
- Doing well at 6 months, double treatment stopped
- Will need long term secondary prophylaxis with TMP/SMX

OL7

Other Antibacterial Drugs (Macrolides, TMP, SMX, etc)

Dr. David Gilbert

IDBR INFECTIOUS DISEASE BOARD REVIEW AUGUST 20-24 2022

Other Antibacterial Drugs (Macrolides, TMP, SMX, etc)

David N. Gilbert, MD
Professor of Medicine
Oregon Health and Science University
Chief of Infectious Diseases
Providence Portland Medical Center

6/15/2022

INFECTIOUS DISEASE BOARD REVIEW AUGUST 20-24 2022

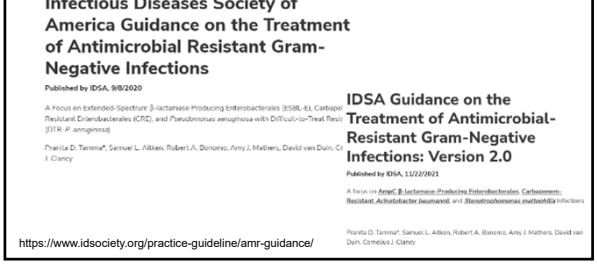
Disclosures of Financial Relationships with Relevant Commercial Interests

- Consultant for Biomerieux
- Research Grant from Biofire

PLAN

- Review testable facets of activity of Polymyxins, Tetracyclines, TMP/SMX, Nitrofurantoin, and Fosfomycin vs gram-negative bacilli
- Dr. Boucher will touch on same drugs as their activity relates to clinical use vs Gram-Positive bacterial infections
- Embedded audience response questions (ARQs) for your interest without any polling

IDSA AMR Guidance – Sep 20, Nov 21


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

Published by IDSA, 9/8/2020

IDSA Guidance on the Treatment of Antimicrobial-Resistant Gram-Negative Infections: Version 2.0

Published by IDSA, 11/22/2021

https://www.idsociety.org/practice-guideline/amr-guidance/

IDSA Guidance on the Treatment of Antimicrobial-Resistant Gram-Negative Infections: Version 1.0 & 2.0

Focus on infections caused by

- Version 1.0
  - Extended-spectrum β-lactamase-producing Enterobacterales (ESBL-E)
  - Carbapenem-resistant Enterobacterales (CRE)
  - ***Pseudomonas aeruginosa*** with difficult-to-treat resistance (DTR-***P. aeruginosa***)
- Version 2.0
  - AmpC β-lactamase-producing Enterobacterales (AmpC-E)
  - Carbapenem-resistant ***Acinetobacter baumannii*** (CRAB,
  - ***Stenotrophomonas maltophilia***

Nov, 2021, https://www.idsociety.org/practice-guideline/amr-guidance-2.0/

Polymyxin Family

- Polymyxin B
- Polymyxin E (Colistin)
- Clinical indication:
  - Alternative salvage therapy for susceptible MDR aerobic GNB

Polymyxins: Mechanisms of action and Resistance

- Mechanism:
  - Binds to LPS (lipid A) & Phospholipids of cell walls of susceptible GNB
  - Displaces divalent cations; resulting membrane disruption, and bactericidal activity
- Acquired Cross Resistance is increasing, esp. among Carbapenemase producing GNBs
  - "R" Due to LPS target change and efflux pumps
  - Plasmid spread of mcr-1 gene
- Guideline reference: Pharmacotherapy 2019;39: 10

Activity vs Aerobic GNB

- Susceptible: *Enterobacterales, ESBLs, KPCs, non-fermenters (Acinetobacter, Stenotrophas, Ps. aeruginosa)*
- Intrinsic Resistance: M—*Morganella sp.*
  - *A---Anaerobes*
  - *P---Proteus sp.*
  - *P---Providencia sp.*
  - *S---Serratia sp.*
- All gram + bacteria are "Resistant"

Polymyxin Pharmacology

- Polymyxin B
  - Uncomplicated dosing
  - Non-renal clearance
  - Drug of choice except for UTI (low/absent urine concentrations)
- Colistin (pro-drug): Colistimethate
  - Complicated dosing
  - Renal excretion
    - Use for UTIs(high urine concentrations)
    - Adjust dose for renal insufficiency
- Often used as part of combination therapy(combination with meropenem failed)

Polymyxins: Reversible Adverse Effects

- Nephrotoxicity (20-60%). Lower risk with polymyxin B
- Neurotoxicity (7-68%). Wide range of problems:
  - Dizziness
  - Paresthesias (circumoral)
  - Vertigo
  - Confusion
  - Ataxia
  - Neuromuscular blockade

The Bottom Line

- Potential salvage therapy for infections due to susceptible aerobic GNB "R" to all beta-lactams, FQs, and AGs
  - Prefer Polymyxin B, over Colistin, except for UTIs
- Mixed results with combination therapy
- Mixed results when used as adjuvant therapy: e.g.
  - Airway nebulization of colistin in patients with pneumonia
  - Intrathecal polymyxin B in patients with meningitis
- Reversible renal and neurotoxicity

Tetracyclines: The Family

- Doxycycline (Many indications)
- Minocycline(Many indications)
- Tigecycline (Don't use)
- Omadacycline(SSTIs, CABP)
- Eravacycline (cIAIs)

Tetracyclines: Mechanisms

- Mechanism of Action:
  - Bacteriostatic: Inhibits protein synthesis
  - Don't combine with bacteriocidal drug
- Major mechanisms of Resistance:
  - Efflux pumps
  - Target protective proteins

Tetracycline Spectrum of Activity

- Aerobic Gram-positive bacteria
- Aerobic Gram-negative bacteria
- Atypical bacteria
- Spirochetes
- New tetracyclines (Eravacycline-a fluorocycline- & Omadacycline- an aminomethylcycline) expand the spectrum of antibacterial activity

In vitro Activity of Eravacycline and Omadacycline vs. Mostly Enteric GNB

- Aerobic Gram-negative bacilli to include:
  - *Enterobacterales*
    - To include ESBL and CPE producers
    - Not active vs *Morganella, Proteus, and Providencia sp.*
- Non-Fermenters
  - Active vs *Acinetobacter baumannii and Stenotrophomonas*
  - *No activity vs Ps. aeruginosa*
- Activity vs ANAEROBIC GNB: e.g. *Bacteroides sp*

New Tetracyclines: In Vitro Activity versus MDR GNB

Bacteria	Minocycline	Omadacycline* (FDA: SSTI;CABP)	Eravacycline* (FDA:IAIs; UTI-NO!)
ESBL producers	0	+	+
KPCs	0	+	+
Metallo-Carbapen.	0	+	+
Acinetobacter	Variable	+	+
Stenotropho.	+	+	+
Pseudomonas	-	-	-
Bacteroides	-	+	+

*Resistant to expulsion by efflux pumps

Tetracycline Pharmacology

- Oral absorption impaired by multivalent cations
- Distribution largest with minocycline (greatest lipid solubility)
- Distribution and Tigecycline:
  - High intracellular levels; very low extracellular concentrations
  - FDA review found increased mortality(CAP, IAI, SSTI)
  - "Only use when no other option"

Women and Children

- Avoid tetracyclines during pregnancy for fear of :
  - Hepatoxicity
  - In utero damage to dentition and bones due to calcium chelation
  - Breast feeding OK as calcium in the milk chelates the tetracycline
- Children and tetracyclines:
  - Try to avoid in children </= 8 y.o. to avoid dental staining and bone damage
  - If needed for critical illness, Amer. Acad. Peds considers DOXYCYCLINE safe for up to 21 days of therapy

Tetracycline Adverse Effects

- ***Clostridioides difficile*** **colitis**
- **Photosensitivity**
- **Hepatotoxicity: minocycline; pregnancy**
- **Treatment of Spirochetal* infections can precipitate Jarisch-Herxheimer reaction**
- **Vertigo: Minocycline most often**

Pertinent spirochets:** ***Treponema pallidum **(80%), Tick-borne & Louse-borne Relapsing fever (54%),**

ARQ 1

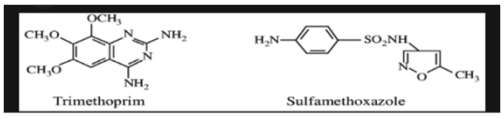
- **A 25 y.o pregnant female (2nd trimester) is admitted with fever, hypotension, nausea, vomiting, and diarrhea.**
- **She just returned from a week camping with family and pet dog in a heavily forested area of northern California. While camping she dutifully picked ticks off the dog !**
- **After blood cultures , empiric therapy was started with piperacillin-tazobactam and vancomycin.**
- **After one week , she is clinically still "septic".**
- **Now, the lab reports the presence of *Francisella tularensis* in her admitting blood cultures.**
- **There is a family history of drug-induced deafness**

- **Which one of the following treatments do you recommend ?**

A. Gentamicin
B. Doxycycline
C.Ceftriaxone
D. Chloramphenicol

Typhoidal Tularemia

- **Doxycycline is now deemed non-teratogenic and is the best option of those offered.**
  - **Systematic reviews demonstrate no correlation between the use of doxycycline during pregnancy and teratogenic effects or dental staining.**
  - **This conclusion applies only to doxycycline and not the other tetracylines.**
- **None of the beta-lactam antibiotics are active vs *F. tularensis***
- ***Even though active, Need to avoid the p*otential toxicities of the aminoglycosides and chloramphenicol**



TMP-SMX: Mechanism

- **TMP and SMX act in sequence to inhibit bacterial synthesis of tetrahydrofolic acid (THF)**
- **THF needed for thymidine synthesis**
- **Thymidine synthesis needed for DNA synthesis**

TMP-SMX Spectrum of Activity vs. Gram Negative Bacilli

Clinical Syndrome	Susceptible Pathogens	Resistant Pathogens
UTIs	*Enterobacterales*	*ESBL producers*
RTIs	*COPD Big 3*; Pneumocystis*	*Mycoplasma*
Diarrhea	*Shigella, Salmonella, ETEC*	*Campylobacter*
Misc.	*Listeria, Nocardia*	
Non-fermenters	*Stenotrophomonas, Burkholderia*	*Pseudomonas aeruginosa, Acineto.*
Anaerobic bacteria	*None*	*Bacteroides fragilis*

**Big 3= S.pneumoniae, Haemophilous influenza, Moraxella catarrhalis*

Multiple Mechanisms of Resistance; Varies with organism

- Mutation of target enzymes
- Decrease in cell wall permeability
- Efflux pumps
- Excess thymidine in the environment

TMP-SMX for *S.pyogenes* Infections

- Failures in treatment of Streptococcal pharyngitis in clinical trials: both IV and PO (JID 1973(supplement) 1973;S693.
- Theorized mechanism: ability of streptococci to utilize exogenous thymidine for DNA synthesis and thereby bypass the inhibitory activities of the sulfamethoxazole and trimethoprim

TMP/SMX: Pharmacology

- Widely distributed to include CSF and Prostate
- Renal excretion by both tubular secretion and glomerular filtration
- Lots of Drug-Drug interactions: e.g.
  - Oral anticoagulants (warfarin)
  - Rifampin
  - Phenytoin
  - ACE inhibitors and ARBs

TMP/SMX: Adverse Effects

- Hemolysis if G6PD deficient
- Promotes folate deficiency;
  - Dangerous in early pregnancy----neural tube defects
  - Low folate associated with pancytopenia
- Derm.: Stevens Johnson syndrome; toxic epidermal necrolysis (TEN), erythema multiforme, photosensitivity
  - More common in elderly and HIV patients
- Aseptic meningitis

TMP-SMX & Proximal Convoluted Tubules

- TMP and creatinine compete for tubular secretion of creatinine by proximal convoluted tubules
  - Creatinine used as surrogate marker of GFR
  - Hence, the calculated Creatinine Clearance falls with TMP therapy due to competition for secretion but no effect on directly measured GFR

More TMP and Distal Renal Tubules

- TMP blocks reabsorption of Na+ in distal convoluted tubules, less exchange for K+ , and serum K+ increases.
- Elevated K+ exaggerated by concomitant ACE Inhibitors or ARB due to reduced serum aldosterone

IV TMP-SMX: Association with Lactic Acidosis

- Possible association of lactic acidosis.
- Hypothesis: caused by propylene glycol in IV formulation Of TMP-SMX

TMP-SMX: Pregnancy and Breastfeeding

- Pregnancy:
  - Avoid in first trimester: risk of neural tube defects
  - Avoid in last trimester: SMX displaces bilirubin bound to albumin; increases unconjugated bilirubin levels with risk of neonatal kernicterus
- Breastfeeding:
  - TMP-SMX is in breast milk; avoid use in G6PD deficient infants
  - "Mothers taking TMP-SMX can breast feed healthy, full-term infants who are at least one month old". AAPs

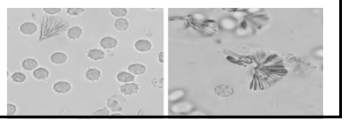
Many Adverse Drug-drug interactions

- Examples:
  - Warfarin
  - Cyclosporin
  - Rifampin
  - ACE inhibitors
  - ARB drugs
  - Many others
- Where available: Therapeutic Drug Monitoring (serum levels)

ARQ 2: Recurrent *E.coli* Cystitis

- 55 y.o. female complains of dysuria and suprapubic tenderness
  - She has a known neurogenic bladder secondary to multiple sclerosis
  - In addition, she is taking an ACE inhibitor and low dose furosemide for hypertension
- Baseline renal function is normal
- Started on TMP-SMX via telemedicine
  - Two days later she presents with fatigue and nausea

Vital signs normal.
U/A: WBCs, RBCs, and Crystals
WBC: 11,000
Serum creatinine: 1.6 mg/dl
Serum Potassium: 5.8 meq/ml
Renal ultrasound: No hydronephrosis



What explains the elevated K+ and Creatinine concentrations ?

- A. Drug induced decrease in the Glomerular Filtration Rate (GFR)
- B. Crystalluria with obstructive uropathy
- C. Impaired distal tubular absorption of sodium
- D. TMP Decreased tubular secretion of creatinine plus impaired distal tubular sodium absorption

ARQ 2 answer

- The correct answer is D:
  - A. Serum creatinine and TMP compete for the proximal tubular secretion of creatinine.
  - B. In addition, the ACE inhibitor impairs the aldosterone-mediated distal tubular absorption of sodium in exchange for the tubular secretion of potassium.
  - C. The result is elevation of the serum levels of both creatinine and potassium.
  - D. The elevated creatinine does not reflect a decrease in the GFR
- Sulfamethoxazole crystals are in the urine but they are soluble enough to not cause obstruction of flow.

ARQ 3

- Which one of the following drugs does not achieve therapeutic concentrations in urine ?
  - A. Colistin (Polymyxin E)
  - B. Nitrofurantoin (Macrobid)
  - C. Moxifloxacin
  - D. Fosfomycin

ARQ 3 Answer

- C is the correct answer.
  - The renal excretion of moxifloxacin is low and hence, moxifloxacin is not recommended for the treatment of UTIs.
- Colistin (Polymyxin E) is a prodrug. Both the prodrug (colistimethate)and active constituent, colistin, reach therapeutic urine concentrations.
  - In distinction, polymyxin B is excreted by the GI tract and does not achieve therapeutic urine concentrations.
- Nitrofurantoin has high urine concentrations but low concentrations in the renal parenchyma.
- Fosfomycin reaches therapeutic concentraions in urine with FDA approved oral regimen. Higher parenteral doses, not available in the US, are needed to achieve adequate renal tissue concentrations.

Nitrofurantoin (Macrobid): Spectrum of Activity

	Susceptible	*Resistant*
Gram-Positive	*Staph. saprophyticus*	*Other Coag neg staph*
	E.faecalis; E.faecium	
		S. aureus (MRSA/MSSA)
	Strep. agalactiae, GpB	
Gram-Negative	*E.coli*	*Proteus species*
	Klebsiella sp	*Serratia species*
		Pseudomonas species

Nitrofurantoin: Mechanisms

- Bactericidal via multiple antibacterial inhibitory mechanisms:
  - Inhibits protein synthesis
  - Blocks aerobic metabolism of susceptible bacteria
  - Inhibits both RNA and DNA synthesis
  - Blocks cell wall synthesis
- FDA licensed in 1953; Resistance remains minimal, perhaps due to multiple antibacterial mechanisms

Warnings

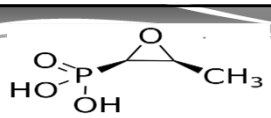
- Avoid in late stage pregnancy and neonates due to risk of hemolytic anemia
- With months of therapy, insidious pulmonary fibrosis
- Risk of hepatic toxicity (often cholestatic)
- Associated with:
  - Peripheral neuropathy
  - Hemolytic anemia in those with G6PD deficiency
- DRESS syndrome: drug rash, eosinophilia, & systemic symptoms

Can you name 4 antibacterials that cause hepatoxiciy ?

- N: for Nitrofurantoin (cholestatic)
- A: for Amoxicillin-clavulanate (cholestatic)
- F: for Fluoroquinolones
- T: for Tetracyclines (in pregnancy)
- A: needed an "A" for NAFTA

Nitrofurantoin dose

- For uncomplicated cystitis:
  - One 100 mg capsule PO with meals BID x 7 days
  - Due to low serum and tissue concentrations, Package Insert recommends pre- and post-treatment urine cultures (rarely done) if worried about associated pyelonephritis
- Nitrofurantoin is Not recommended if CrCl is < 30 ml /min



Fosfomycin

- Originally Phosphonomycin
- Alternative oral therapy for uncomplicated cystitis
- Not yet approved for parenteral therapy in the US
- Distribution includes prostate tissue

Spectrum of activity of oral fosfomycin vs GNBs

- Activity vs Enterobacterales:
  - *E. coli*, to include ESBL + strains
  - *Klebsiella sp.* To include ESBL + strains
  - *Citrobacter sp.*
  - *Proteus sp.*
  - Carbapenemase producers: NO ACTIVITY
- Activity vs Non-fermenters:
  - NO ACTIVITY

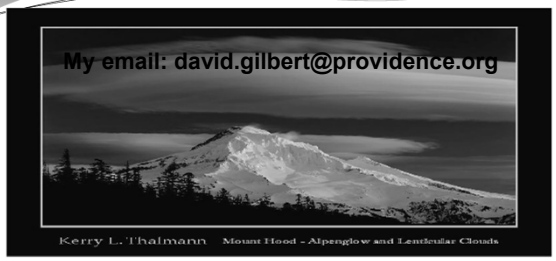
Fosfomycin tromethamine (Monurol)

- Uncomplicated cystitis in females
  - Dose: 3.0 gms po X one dose with or without food
- Complicated UTI, but no pyelonephritis
  - Dose: 3 gm po q3d x 3 doses
  - Lower dose in patients with renal insufficiency
- No serious AEs; Diarrhea in 10% of patients
- Bactericidal mechanism:
  - Inhibition of cell wall synthesis
  - Decreased adherence of bacteria to uroepithelial cells

Susceptibility of non-fermentative Gram-Negative Bacilli Producing ESBLs, Carbapenemases, & "R" to all FQs and AGs

Drug	*Ps.aeruginosa*	*Burkholderia*	*Stenotropho-monas*	*Acinetobacter baumannii com.*
Cefiderocol	+	+	+	+
Eravacycline	---	---	+	+
Polymyxins	+	---	+	+
TMP-SMX	---	+	+	---
Other				See footnote*
Adjunctive Phage Rx	+	?	?	+

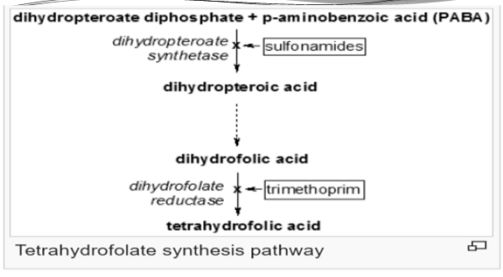
*Polymyxin plus minocycline &/or amp-sulbactam (AAC2021; 65:2021.02.17; Aztreonam + Ceftaz-avi (Infection 2020;48:835); Sulbactam+Durlobactam(I): Current Opinion in Infect. Diseases. 2020;33: 214;



Tetracycline Activity Spectrum

Bacteria	Doxycycline	Minocycline	Omadacycline	Eravacycline
Aerobic GPCs	+	+	+	+
MRSA	+	+	+	+
Aerobic GNB	+	+	+	+
Rickettsial	+	+	+	+
Spirochetal*	+	+	+	+
Plasmodia	+	?	?	?
Ps.aeruginosa	0	0	0	0
Acineto/Steno.	0	Variable	+	+

*Borrelia, Treponema, Leptospira



TMP-SMX: Beyond CA-MRSA

Clinical uses
- UTI
- AECB
- *Pneumocystis jiroveci*
- Traveler's diarrhea
- Shigella
- *Coxiella burnetii*
- *Mycobacteria marinum*
- *Tropheryma whipplei*

More Clinical uses
- Nocardia
- Cholera
- Listeria
- Stenotrophomonas
- Cyclospora
- Isospora
- Toxoplasmosis

Trimethoprim-Sulfamethoxazole

- Mechanism of action:
  - Sequential blockade of two enzymes needed to synthesize folate
- Broad spectrum---Activity vs. GNB:
  - Enterobacterales
  - Non-Fermentative GNBs: *Burkholderia and Stenotrophomonas.*
    - *No activity vs Ps.aeruginosa*
    - Also , no activity vs:*Mycoplasma, Francisella tularensis, and Bacteroides fragilis*

Nitrofurantoin for uncomplicated *E.coli* UTI*

- Pulmonary toxicity with chronic therapy: desquamative interstitial pneumonia with fibrosis
- Intrahepatic cholestasis and hepatitis
- DRESS syndrome: drug rash, eosinophilia, & systemic symptoms

*Cystitis only

OL8

Statistics

Dr. Khalil Ghanem

IDBR INFECTIOUS DISEASE BOARD REVIEW AUGUST 20-24 2022

Statistics

Khalil G. Ghanem, MD, PhD
Professor of Medicine
Division of Infectious Diseases
Johns Hopkins University School of Medicine

6/15/2022

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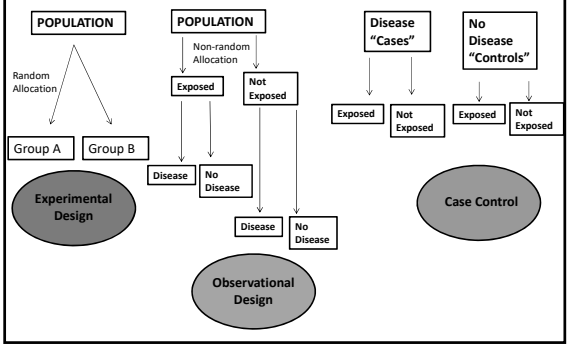
Disclosures of Financial Relationships with Relevant Commercial Interests

- None

Overview

- Study designs
- Incidence & Prevalence
- Relative risk, relative odd, & attributable risk
- Confidence intervals
- Number needed to treat
- Sensitivity, specificity, positive predictive value, negative predictive value
- Bias and confounding

Study Designs



Example: Study Designs

- Choose the most appropriate study design for the following scenarios:
  - You are trying to determine what caused 35 people to experience fever and severe hemorrhagic complications upon returning from a Caribbean cruise
  - You are trying to get a novel influenza vaccine approved by the FDA
  - You are trying to determine whether hormonal contraception increases your risk of HIV

Incidence vs. Prevalence

- **Incidence**= *new* infection occurring during a specified period of time in a population at risk for developing the infection
  - A measure of events (a disease that develops in someone who did not have it), thus, a measure of *risk*
- **Prevalence:** number of affected persons present in the population at a given time(i.e. *existing* infections) divided by the total number of people in the population
- **Prevalence=Incidence X duration of disease**

Example: Incidence vs. Prevalence

- **In a population that includes HIV-infected persons who exhibit high medication adherence, what would the impact of HAART be on HIV incidence and prevalence over a 10 year period?**

  -Incidence= new HIV infections. HAART should decrease the risk of transmission of HIV and thereby **decrease** the incidence

  -Prevalence= all existing HIV infections. HAART allows people with HIV to live longer so it may **increase** the prevalence of HIV

Estimating Risk

- **Relative Risk (RR)**= Incidence in exposed/ Incidence in nonexposed
  - If the RR=1, there is no association
  - If the RR >1, the risk in exposed > nonexposed
  - If the RR<1, the risk in exposed < nonexposed
- **Hazards Ratio(HR)**: A form of RR; HR is instantaneous while RR is cumulative.
- **Odds**= Probability that disease developed/Probability that it did not develop
- **Odds Ratio:**
  - **Cohort study:** ratio of odds of disease occurring in exposed to the odds of disease occurring in non-exposed
  - **Case Control**: ratio of the odds that the cases were exposed to the odds that the controls were exposed
  - If the OR=1, there is no association between exposure and disease
  - If the OR>1, the exposure is positively related to the disease
  - If the OR<1, the exposure is negatively related to the disease

Example: Estimating Risk

- **In a population of 1000 people, 400 were having unprotected sex. Infection-Y occurred in 100 of the 400 who were having unprotected sex and in 5 of the 600 who were not.**
- **What is the RR of Y in those having unprotected sex?**
- **What are the relative odds (odds ratio) of Y in those having unprotected sex?**

- RR: 100/400/5/600= 31.3
- OR: 100/300/5/595=41.3

- The odds ratio is a good estimate of the relative risk when the disease being studied is RARE

Estimating Risk 2

- The **attributable risk** is the proportion of disease incidence that can be attributed to a specific exposure

  AR= Incidence in exposed- Incidence in non-exposed
- This is one of the most important measures when deciding *how* to spend money and resources in public health

Example: Estimating Risk 2

A new deadly fungal infection is described with a mortality rate of 30%. You are given 1 million dollars to spend on prevention in your state.

-Persons with ExposureA have a RR of 16 for getting infected.

-Persons with ExposureB have a RR of 2 for getting infected.

➢ **How are you going to spend your money?**

Example: Estimating Risk 2

- ExposureA is spelunking and ExposureB is gardening
- NOW how are you going to spend your money?
- Even though the relative risk of spelunking is far more than gardening, most of the cases in your state are likely the result of gardening (a lot more people garden).
- The attributable risk of gardening, therefore, is much greater than that of spelunking

Exposure	Incidence	Relative Risk	Attributable Risk
Spelunking	32 per million	16	30 per million
No Spelunking	2 per million		
Gardening	640 per million	2	320 per million
No Gardening	320 per million		

Confidence Intervals

- Confidence intervals (CI) are used to indicate the reliability of an estimate
  - CI is *directly* related to the standard deviation and *indirectly* related to the sample size (i.e. the larger the sample size, the smaller the CI)
- In simple terms, a 95% CI means: If you were to repeat this experiment many times, in 95% of the time, your results will fall within this range.
  - The wider the CI surrounding the point estimate, the more uncertainty there is about the reliability of that point estimate

Example: Confidence Intervals

- Match each scenario to the more likely prevalence point estimate and CI:
  - **Scenario 1**: We test 100 people in the population for HIV.
  - **Scenario 2**: We test 3500 people in the population for HIV

A. The prevalence of HIV is 1.3% (95%CI: 1.1 %-1.5%)
B. The prevalence of HIV is 3.3% (95%CI: 0.3%-7.2%)

Number Needed to Treat (NNT)

- NNT= 1/(Rate in untreated)- (Rate in treated)

Example: NNT

RCT for a new Ebola vaccine: the mortality rate in the experimental group is 20% while the mortality rate in the control group is 85%. How many people do we need to vaccinate to prevent one death from Ebola?

NNT= 1/(0.85-0.20)=1.5

Approximately 2 people need to be vaccinated to prevent a single death from Ebola. This would be a GREAT public health intervention in endemic areas.

Sensitivity, Specificity, Positive Predictive Value (PPV), Negative Predictive Value (NPV)

	Disease	No Disease
Positive	True Positive	False positive
Negative	False negative	True negative

Sensitivity= TP/ TP + FN
Specificity= TN/ TN +FP
PPV= TP/ TP + FP
NPV= TN/TN +FN

Sensitivity and specificity are INDEPENDENT of prevalence whereas PPV and NPV are DEPENDENT on prevalence

- **Sensitivity**= the ability of a test to correctly identify those who have a disease
- **Specificity**=the ability of a test to correctly identify those who do not have a disease
- **PPV**= the proportion who test positive and actually have the disease
- **NPV**=the proportion who test negative and actually don't have the disease

Example: Sensitivity Specificity, PPV, NPV

The glycoprotein-G- based antibody tests for the detection of HSV-2 antibodies have a sensitivity of 99% and specificity of 98.5%. We plan to test two populations: (A) 1000 commercial sex workers (B) 1000 nuns confined to a convent.

In which population will the tests have a higher: Sensitivity? Specificity? PPV? NPV?

- Sensitivity and specificity are INDEPENDENT of prevalence of disease. As such, the sensitivity and specificity of these tests will be the same in both populations
- Population A likely has a higher prevalence of HSV-2 compared to population B. As such, the PPV of the test will be higher in population A and the NPV will be higher in population B

Definitions

- **Precision**: How close do the results cluster to ***each other***?
- **Accuracy**: How close do the results cluster to ***the truth***?
- **Bias**: systematic error leading to a decrease in accuracy
  - Bias is reduced by careful study design
- **Confounding**: a distortion in the degree of association between an exposure and an outcome due to a mixing of effects between the exposure and an incidental factor, which is known as the confounder
  - You must adjust for confounding; otherwise, it will lead to misinterpretation of results
- **Effect Modification** (i.e. interaction): a variable that differentially (positively and negatively) modifies the observed effect of a risk factor on disease status. Different groups have different risk estimates when effect modification is present
  - Effect modification is a true phenomenon that should be reported. You do NOT need to adjust for it.

Example: Definitions

- We find no cases of InfectionY in infants but many cases in children and adults. The RR of infection in those >1 year old is 45 as compared to those who are < 1 year old. We later find out that InfectionY is only transmitted when walking barefoot on the beach.
- Age is an example of _____

OL9

Infections in Solid Organ Transplant Recipients

Dr. Barbara Alexander

Online Only Lectures – Infections in Solid Organ Transplant Recipients

Speaker: Barbara Alexander, MD

INFECTIOUS DISEASE BOARD REVIEW AUGUST 20-24 2022

Infections in Solid Organ Transplant Recipients

Barbara D. Alexander, MD, MHS
Director, Transplant Infectious Diseases Service
Head, Clinical Mycology Laboratory
Director, Transplant Infectious Diseases Fellowship Program
Professor of Medicine and Pathology
Duke University

7/13/2022

INFECTIOUS DISEASE BOARD REVIEW AUGUST 20-24 2022

Disclosures of Financial Relationships with Relevant Commercial Interests

- **Consultant: Scynexis, Astellas, HealthTrackRx**
- **Research Grant to My Institution: Leadiant**
- **Clinical Trials (Site PI/Study PI): Astellas, Cidara, Scynexis, Shire, F2G**
- **Royalties (Chapter Author): UpToDate**

Infections in Solid Organ Transplant (SOT) Recipients

- SOT is a life-saving intervention
  - 895,308 SOTs performed in U.S. since 1988
  - 41,355 SOTs performed in 2021
- SOT recipients
  - have compromised immunity / increased infection risk
  - are targets for common, emerging & opportunistic pathogens encountered pre- and post-transplant
  - often have atypical infection presentation owing to their compromised immunity / decreased inflammatory response
  - are on complex medical regimens; drug interactions common

Data from Organ Procurement and Transplantation Network database as of July 13, 2021

WHAT YOU SHOULD KNOW FOR THE BOARD EXAM:

- Infection risk varies based on
  - Organ transplanted
  - Time post transplant
  - Degree of immunosuppression
  - Prophylaxis regimen
  - Unique exposures
- Key drug interactions and drug-induced syndromes
  - Calcineurin inhibitors and azoles, macrolides, rifampin (covered in Dr. Gilbert's antibiotic lecture)
  - Sirolimus associated pneumonitis
  - Calcineurin inhibitors and TTP and PRES

WHAT YOU SHOULD KNOW FOR THE BOARD EXAM:

- The following major clinical syndromes:
  - CMV syndrome & disease
  - EBV & Post Transplant Lymphoproliferative Disorder (PTLD)
  - BK virus nephropathy
  - Aspergillosis, Mucormycosis & Cryptococcosis
  - Tuberculosis
  - Toxoplasmosis
  - Donor-derived infections

PLAY THE ODDS

The data in the stem let's you "play the odds" as to the most likely diagnosis

- **Patient completing valganciclovir prophylaxis 6 weeks prior presenting with fatigue, low grade fever and leukopenia**
  - **CMV**
- **Donor died from skiing accident in fresh water lake in Florida and recipient presents 3 weeks post transplant with encephalitis**
  - **Naegleria**
- **Renal transplant recipient on valganciclovir prophylaxis presents with asymptomatic renal dysfunction**
  - **BK Virus**
- **Lung transplant recipient planted vegetable garden 2 weeks prior while on posaconazole prophylaxis and presents with productive cough and cavitary lung lesion**
  - **Nocardia**

FREQUENCY, TYPE & INFECTION SOURCE IN THE 1ST POST TRANSPLANT YEAR

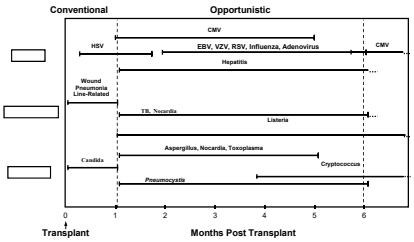
Transplant Type	Infection Episodes per Patient	Bacteremia	CMV Disease * (%)	Fungal Infections (%)	Most Common Source
Lung	3.19	8-25	39	8.6	Pulmonary
Liver	1.86	10-23	29	4.7	Abdomen & Biliary tract
Heart	1.36	8-11	25	3.4	Pulmonary
Kidney	0.98	5-10	8	1.3	Urinary tract

*CMV, Cytomegalovirus; CMV disease rates in the absence of routine antiviral prophylaxis

Table Modified from: Principles and Practices of Infectious Diseases, 9th Edition. Chapter 313. Infections in Solid-Organ Transplant Recipients by Nina Singh and Ajit Lalvani. Editors: Bennett JE, Dolin R, and Blaser MJ. Elsevier Saunders, Philadelphia, PA, 2015.

CLASSIC TIMING OF INFECTIONS FOLLOWING SOLID ORGAN TRANSPLANTATION

Timing altered by:
- Enhanced immunosuppression
- Prophylaxis regimen
- Unique exposures



"EARLY" BACTERIAL INFECTIONS FOLLOWING SOT

Type & site of early bacterial infection varies based on organ transplanted, surgical approach/technique & transplant center

- Risk of peritoneal soilage/infection greater in liver transplantation with Roux-en-Y biliary drainage
- Recipient colonization with resistant organisms (e.g. MRSA, VRE, CRE) pre-transplant, confers risk of post-transplant infection
- Cluster with unusual pathogen - environmental problem? (e.g. *Legionella, M. abscessus* from hospital water distribution systems)

"LATE" BACTERIAL INFECTIONS FOLLOWING SOT

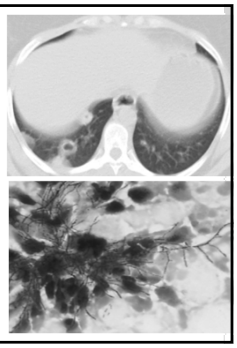
80% OF LATE BACTERIAL INFECTIONS ARE COMMUNITY ACQUIRED

- *Streptococcus pneumoniae*
  - Incidence significantly > in SOT (146/100,000) vs general population (12/100,000)
  - Vaccination recommended
- *Listeria monocytogenes*
  - Bacteremia (Gram + Rods) / Diarrhea / Meningitis
  - Ampicillin treatment of choice
  - High relapse rate, treat for at least 3-6 wks

Kumar D et al., *Am J of Transplant* 2007;7:1209

LATE BACTERIAL INFECTIONS, CONT.

- *Nocardia* species
  - 1%-6% of all SOT recipients
  - Presents most often as pulmonary nodules, CNS (15-20%), skin (15%), or bone (2-5%) lesions
  - Diagnosis: Culture and/or histopathology
    - Branching, filamentous Gram + Rods
    - Partially acid-fast by modified Kinyoun stain
    - *Nocardia* is *Neurotropic*; brain imaging critical
  - Treatment:
    - High dose TMP-SMX drug of choice
    - Otherwise, based on susceptibility data & site of infection
  - TMP-SMX dose used for PCP prophylaxis not protective



CMV DISEASE AFTER SOT
INDIRECT AND DIRECT EFFECTS

INDIRECT Effects:
- Acute and Chronic Rejection
- Opportunistic Super-Infections (Gram negative bacteria & Molds)

DIRECT Effects:
- CMV Syndrome – most common presentation
  - CMV in blood + fever + malaise, leukopenia, atypical lymphocytosis, thrombocytopenia, or elevated liver enzymes
- Tissue Invasive Disease
  - Evidence of CMV on biopsy + compatible signs/symptoms

RISK OF CMV DISEASE AFTER SOT

CMV Serologic Status	Risk Category	Incidence of Disease (%)
D+/R-	High	50+
D+/R+ or D-/R+	Intermediate	10-15
D-/R-*	Low	0
ALA Therapy (R+)		
Induction	Intermediate	25-30
Rejection	High	65

D, Donor; R, Recipient; ALA, Antilymphocyte Antibody

*Should receive leukocyte depleted blood products

CMV DISEASE AFTER SOT
PROPHYLACTIC APPROACHES

UNIVERSAL

All SOT recipients receive therapy during highest risk periods

- Expensive
- May induce resistance
- Some pts exposed unnecessarily

PREEMPTIVE

Treatment based on asymptomatic viral replication in blood

- Optimal viral threshold for initiating therapy not well defined
- Requires serial monitoring with detection assay

NOTE: Letermovir not approved for use in SOT population, only HSCT

CMV PROPHYLAXIS AFTER SOT

Bottomline:

- D+/R- or ALA for rejection → Universal
  - First 3-6 months post-transplant
  - At least 1 month post-ALA for rejection
- R+ → Universal or Preemptive
  - First 3-6 months post-transplant

CMV DISEASE AFTER SOT

- Typically occurs 1-3 months post-transplant
  - Or after prophylaxis is stopped ("late onset")
- Disease of GI Tract and Eye may not have concurrent viremia
  - Diagnosis often requires biopsy/aspiration
- Viral load may continue to rise during first 2 weeks of Rx
  - Don't repeat PCR until Day 14 of treatment
- Treat for 2-3 weeks…
  - DO NOT STOP TIL VIREMIA CLEARs (high risk for relapse)

CMV DISEASE AFTER SOT
GANCICLOVIR RESISTANCE

- **Suspect resistance if prolonged (> 6 weeks) (val)ganciclovir exposure AND:**
  - No reduction in viral load after 14 days of treatment
  - No clinical improvement after 14 days of treatment
- **Management of suspected ganciclovir resistance:**
  - Reduce immunosuppression
  - Switch to maribavir or foscarnet (± CMV hyperimmune globulin)

Lurain et al.JID 2002; Limaye et al Lancet 2000; Limaye et al JID 2002; Kotton et al Transplantation 2013.

CMV DISEASE AFTER SOT
ANTIVIRAL RESISTANCE

Key mutations have been associated with resistance

- UL97 CMV Phosphotransferase gene mutations (most common)
  - Imply ganciclovir resistance


Different levels of resistance to ganciclovir in mutations and deletions in the UL97 gene*.

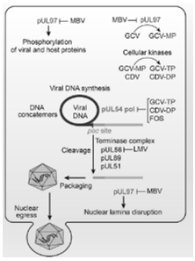
Mutations or Deletions	Ganciclovir ratio†	Interpretation
M460V/I/T, V466G, 595 del, 595–603 del, C518Y, **H520Q, A594V/G, L595S/W, K359T, C603W,** C607Y	5–15	High-grade resistance
L405P, **C592G,** A594E/P/T, E596G, C601R	2–5	Low-grade resistance
V466M, A591V,L595T, N597D, L600I, C603S, C607Y	<2	Insignificant grade resistance

* Bold face indicates the seven most common ("canonical") UL97 mutations conferring ganciclovir resistance.
† IC_{50} of mutant of wild type.

- UL54 CMV DNA Polymerase gene mutations
  - May confer resistance to ganciclovir, foscarnet, & cidofovir

Lurain et al JID 2002; Limaye et al Lancet 2000; Limaye et al JID 2002; Kotton et al Transplantation 2013; Torre-Cisneros at al Transplantation Reviews 2016.

CMV RESISTANCE: NEW DRUG



Maribavir (MBV)

- Multi-modal CMV activity
  - Inhibits CMV DNA replication
  - Interferes with nuclear egress of viral capsid by inhibiting UL97 kinase
- UL97 kinase activates ganciclovir (GCV), thus MBV inhibits GCV activity
  - MBV & GCV should not be used together → ⚠
- MBV is active against many GCV resistant strains
  - Superior to SOC (Valgan/Gan, Foscarnet, or Cidofovir) in HSCT & SOT pts with refractory/resistant CMV infection
    - Cleared CMV viremia & resolved symptoms at 8 weeks
  - FDA approved Nov 2021 for "CMV (with or without genetic mutations that cause resistance) that does not respond to available antiviral treatment…"
  - No activity against other herpes viruses (HSV/VZV) → ⚠

Piret J, Boivin G. Antiviral Research 2019;163:91-105.
Avery RK, et al. Clin Infect Dis. 2021 Dec: Online ahead of print.

CASE 1

- 54 yo male 60 days post-cardiac transplant was treated for rejection with steroids when fever and a non-tender anterior cervical mass appeared.
- Biopsy showed nodal replacement by lymphocytes, many of which stained positively for Epstein-Barr virus as well as for the B cell marker, CD20.
- His plasma EBV viral load was 10,000 copies /ml.

QUESTION #1

The most appropriate treatment for this condition is:

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

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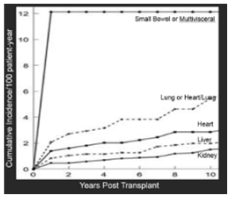
EPSTEIN BARR VIRUS: POST TRANSPLANT LYMPHOPROLIFERATIVE DISORDER (PTLD)

EBV transformed B-lymphocytes give rise to PTLD
- A few cases may arise from T-lymphocytes

Risk factors:
- 1° EBV infection
  - Donor seropositive, Recipient seronegative
- Antilymphocytic antibody therapy (T-cell depletion)
- Organ transplanted
  - Intestine > Lung > Heart > Liver > Kidney

EPSTEIN BARR VIRUS POST TRANSPLANT LYMPHOPROLIFERATIVE DISORDER (PTLD)

- ~3% Cumulative 10 year incidence in SOT population
- Incidence varies based on organ transplanted
  - Small Bowel / Multivisceral – up to 32%
  - Lung / Heart / Liver - 3-12%
  - Kidney - 1-2%
- Biphasic pattern of disease after SOT:
  - First peak (20% cases) occurs 1st post-tx year
  - Second peak occurs 7-10 years post-tx



Olagne, J, et al. Am J Transplant. 2011 Jun;11(6):1260-9.

EPSTEIN BARR VIRUS *POST TRANSPLANT* LYMPHOPROLIFERATIVE DISORDER (PTLD)

Clinical manifestation - wide range
- Febrile mononucleosis-like illness with lymphadenopathy
- Solid tumors
  - Often involve transplanted graft
  - 50% are extranodal masses
  - 25% involve CNS

Definitive diagnosis requires tissue biopsy
- Classification based on histology and clonality
- Molecular (PCR) tests available
  - WHO Standard for Assay Calibration available
  - Whole Blood vs Plasma controversial
  - Misses EBV-negative and some localized cases
  - Used as an aid for Diagnosis and Pre-emptive monitoring with stepwise reduction in immunosuppression to reduce PTLD rates

Petit B et al. Transplantation. 2002;73(2):265.
Peters AC, et al. Transplantation. 2018; 102(9):1553.

EPSTEIN BARR VIRUS *POST TRANSPLANT LYMPHOPROLIFERATIVE DISORDER (PTLD)*

Treatment:
- Antivirals not effective on latently infected lymphocytes
- Reduce Immunosuppression (Response ~ 45%)
- Rituximab: Anti-CD20 monoclonal antibody (Response ~ 55%)
- Cytotoxic Combination (CHOP, ACVBP) Chemotherapy
  - Reserved for non-responsive disease
  - High treatment associated mortality (13%-50%)
- Adoptive Immunotherapy (EBV cytotoxic T-cells)
  - Under study

Allen et al. Am J Transplantation 2013;13:107-120

CASE 2

- 52 yo female S/P cadaveric renal transplant receiving tacrolimus, prednisone and mycophenylate.
- Week 30 post transplant serum creatinine rose from 1.5 to 2.3 mg/dl.
- Tacrolimus levels were in therapeutic range.
- Urinalysis revealed one plus protein and no cells or casts.

QUESTION #2

Which would be most helpful in understanding if BK virus was causing her renal failure?

A. Presence of decoy cells in urine cytology
B. Urine BK viral load
C. Urine culture for BK virus
D. Plasma BK viral load
E. Demonstration of BK inclusions in renal tubular epithelium on renal biopsy

QUESTION #2

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POLYOMAVIRUS *BK VIRUS NEPHROPATHY*

- Ubiquitous, DNA virus
  - 1° infxn – URI during early childhood
  - 80% worldwide population sero+
  - Renal & uroepithelial cells, site of latency
- Cause of nephropathy post renal transplant
  - Up to 15% of renal recipients effected
  - Time to onset 28-40 weeks (majority within 1st yr post tx)
  - Manifests as unexplained renal dysfunction (as does rejection)

Hayashi RY et al. UNOS Database; Abstract 76, 2006 World Transplant Congress; Ramos et al. *J Am Soc Nephrol* 2002;13:2145; Hirsch et al. Transplantation 2005;79:1277-1286

BK VIRUS NEPHROPATHY
DIAGNOSIS

- Replication in urine precedes replication in blood precedes nephropathy
- Renal Bx - "Gold Standard" for diagnosis
- Blood PCR
  - Sensitive (100%) but less specific (88%)
  - Cannot rule out rejection
  - Useful as indicator for biopsy
- Urine Cytology, Electronmicroscopy, & PCR
  - Detection in urine: Low PPV but High NPV

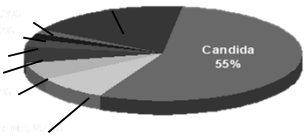
Hirsch et al, Transplantation 2005;79:1277-1286; Nickeleit et al, NEJM 2000;342 (18):1309-1315; Ramos et al. *J Am Soc Nephrol* 2002;13:2145

BK VIRUS NEPHROPATHY
TREATMENT

- Reduce immunosuppression
- Case series with variable success using:
  - Low-dose cidofovir
  - Leflunomide
- New drugs & randomized controlled trials needed
- Preemptive monitoring key to prevention

Hirsch et al. Transplantation 2005;79:1277-1286; Farasati et al. Transplantation 2004;79:116; Vats et al. Transplantation 2003;75:105; Kabambi et al. Am J Transplant 2003;3:186; Williams et al N Engl J Med 2005;352:1157-58.

INVASIVE FUNGAL INFECTIONS IN SOLID ORGAN TRANSPLANT RECIPIENTS



Type of fungal infection varied depending on organ transplanted

TRANSNET data
Slide courtesy of P. Pappas, MD.
Pappas P et al. CID. 2010;50:1101-1111.

INVASIVE FUNGAL INFECTIONS ACCORDING TO ORGAN TRANSPLANTED N=16,808

	Kidney	Heart	Pancreas	Liver	Lung	Small Bowel
12 Month IFI Incidence (%)	1.3	3.4	4.0	4.7	8.6	11.6
IFI Type (%)					70% Molds	
Candidiasis	49	49	76	68	23	85
Aspergillosis	14	23	5	11	44	0
Other molds	7	10	3	6	26	0
Cryptococcosis	15	10	5	6	2	5
Endemic	10	3	6	5	1	0
Pneumocystosis	1	3	1	0	2	0
Other	4	2	4	4	2	10

Pappas P, Alexander B, Andes D, et al. CID 2010;50:1101-1111

INVASIVE FUNGAL INFECTIONS
RISK FACTORS AFTER SOT

Each solid organ group will have unique risks for IFIs

Strongly influenced by medical & surgical factors including technical complexity

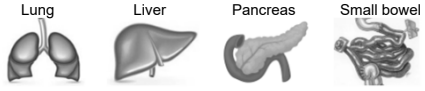
Liver
- Re-transplantation
- Pre-tx fulminant hepatic or renal failure
- Heavy *Candida* colonization peri-tx
- Large volume intra-operative transfusions
- Bleeding complications requiring re-operation
- Choledochojejunostomy

CANDIDA

Lung
- Vulnerable anastomotic site
- Continuous environmental exposure
- *Aspergillus* colonization of airways
- CMV pneumonitis
- Acute rejection
- Obliterative bronchiolitis

ASPERGILLUS

ANTIFUNGAL PROPHYLAXIS FOR SOLID ORGAN TRANSPLANT RECIPIENTS



Lung	Liver	Pancreas	Small bowel
• All recipients • *Candida* & Molds	• High-risk recipients • *Candida*	• High-risk recipients • *Candida*	• All recipients • *Candida*
Per ISHLT Guidelines	Per AST Guidelines		

Husain S, et al. *J Heart Lung Transpl.* 2016;35:261-82. Silveira FR, Kusne, AST ID COP. *Am J Transpl.* 2013;13:220-27. Singh NM, Husain S, AST ID COP. *Am J Transpl.* 2013;13:228-41.

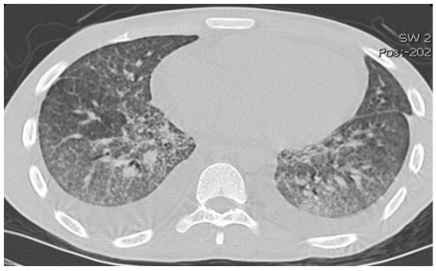
TUBERCULOSIS

- 34-74 fold higher risk of active disease in SOT recipients than general population
- Incidence 1% - 6% (up to 15% in endemic areas)
- Median onset 9 months post-tx (0.5-144 months)
- 33% of infections are disseminated at diagnosis
- Treatment
  - Rifampin-based regimens associated with graft loss/rejection in 25%
- Mortality ~30%
- Treat latent TB prior to transplant when possible

CASE 3

- 35 yo female s/p heart transplant in France 90 days prior presented with fever, dyspnea and a diffuse pneumonia on chest CT.
- She was receiving prednisone, tacrolimus & mycophenolate.
- Both recipient & donor were CMV negative; she was not on CMV prophylaxis.
- She was on inhaled pentamidine for PCP prophylaxis.

CHEST CT



CASE 3

Trimethoprim-sulfamethoxazole was started empirically and she began improving.

Bronchoalveolar lavage (BAL) was negative for:

- pneumocystis by direct fluorescent antibody stain & PCR,
- fungi by calcifour white / potassium hydroxide stain,
- mycobacteria by AFB smear,
- bacteria by Gram stain, and
- respiratory viruses by multiplex PCR

Routine bacterial BAL and blood cultures were negative.

QUESTION #3

Assuming trimethoprim-sulfamethoxazole was causing her improvement, which additional test on the BAL might have explained her improvement?

A. PCR for CMV
B. PCR for toxoplasmosis
C. PCR for tuberculosis
D. Galactomannan
E. Cold enrichment culture for Listeria

QUESTION #3

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E. Cold enrichment culture for Listeria

TOXOPLASMOSIS

- After SOT, acute toxoplasmosis can develop from reactivation, acquisition via blood transfusion or ingestion of contaminated food or water, or from the donated organ
- Donor seropositive/Recipient seronegative at high risk
- HEART > LIVER > KIDNEY TRANSPLANT
- Presents with myocarditis, pneumonitis & meningitis
- DIAGNOSIS:
  - PCR
  - Giemsa smear of BAL
  - Brain aspirate for tachyzoites
  - Immunoperoxidase stain of endocardial biopsy or other tissue
- TREATMENT: sulfadiazine-pyrimethamine-leucovorin

CASE 4

Liver transplant recipient on bactrim & valganciclovir prophylaxis

presented 21 days post transplant with confusion, tremors, lethargy, anorexia

- Rapid progressive neurologic decline → agitation & delirium →intubation
- Brain MRI: non-revealing
- Blood & urine cultures: negative
- CSF: lymphocytic pleocytosis (25 WBCs/mm^3) & elevated protein
  - Gram stain, bacterial, fungal cultures negative for organisms
- Empiric intravenous ganciclovir, vancomycin, ceftriaxone & ampicillin
- Day 6 Repeat MRI: diffuse encephalitis
- Expired 13 days after neurologic symptom onset
- Donor was previously healthy presenting with subarachnoid hemorrhage
  - Toxicology screen: + cocaine & marijuana
  - Brain CT: expanding subarachnoid hemorrhage
  - Recently on camping trip

QUESTION #4

This presentation is most consistent with:

A. CMV encephalitis
B. HHV6 encephalitis
C. VZV encephalitis
D. Rabies encephalitis
E. Cryptococcal meningitis

QUESTION #4

This presentation is most consistent with:

A. CMV encephalitis
B. HHV6 encephalitis
C. VZV encephalitis
D. Rabies encephalitis
E. Cryptococcal meningitis

"EXPECTED" DONOR-DERIVED INFECTIONS

- **Expected = known before tx or for which there are recognized standard prevention guidelines**
  - Cytomegalovirus (CMV)
  - Epstein–Barr virus (EBV)
  - Toxoplasmosis

*United Network for Organ Sharing / Organ Procurement and Transplant Network
Ison M et al. Am J Transplant. 2009;9:1929-1935.

"UNEXPECTED" DONOR-DERIVED INFECTIONS VIRUSES, VIRUSES, & PARASITES, OH MY…

- Lymphocytic choriomeningitis virus (LCMV)
  - Hamsters and rodents
  - 4 outbreaks (3 USA, 1 Australia); 9 deaths

- Rabies virus
  - Unreported bat bite in donor
  - 3 outbreaks (2 USA, 1 Germany); 8 deaths

- Chagas' Disease (Trypanosoma cruzi)
  - Reduviid bug (Latin America)
  - Screening tests lack sensitivity
  - Multiple transmissions reported

- HIV, Hep C, Hep B, West Nile Virus (WNV)
  - Remember the "Window" prior to development of antibodies
  - Nucleic Acid Tests decrease "window" to ~5-10 days (HIV), 6-9 days (HCV)

Fisher SA et al. N Engl J Med. 2006;354:2235-2249. MMWR Morb Mortal Wkly Rep. 2008;57:799-801. Kusne S et al.Transpl. 2005;11:1295-1297. Maier T et al. CID 2010;50:1112-1119.Mattner F et al.Infection. 2007;35(4):219-24. Grossi PA, et al. Am J Transpl. 2009;9:S19-S26.

TYPICAL PRESENTATIONS OF UNEXPECTED DONOR DERIVED INFECTIONS

- Most present in the first 3 months post transplant
- Look for epidemiologic clues for potential donor exposure in the stem (e.g. possible bat bites, new pet hamsters, tap water nasal irrigations, recent travel to a region endemic for certain pathogens)

PATHOGEN	PRESENTATION
LYMPHOCYTIC CHORIOMENINGITIS VIRUS	ENCEPHALITIS
RABIES	ENCEPHALITIS
TOXOPLASMOSIS	DIFFUSE PNEUMONIA MYOCARDITIS RETINITIS ENCEPHALITIS
WEST NILE VIRUS	MENINGITIS ENCEPHALITIS POLIOMYELITIS-LIKE FLACCID PARALYSIS
CHAGAS' DISEASE	FEVER MYOCARDITIS
ACANTHAMOEBA	SKIN LESION ENCEPHALITIS
BALAMUTHIA MANDRILLARIS	ENCEPHALITIS
VISCERAL LEISHMANIASIS	PANCYTOPENIA HEPATOSPLENOMEGALY
MALARIA	FEVER

VACCINATION RECOMMENDATIONS FOR SOT

Update vaccinations pre SOT:

- COVID
- Hepatitis A, Hepatitis B, Flu, TDaP, Pneumococcal
- Live Varicella, MMR vaccines (≥4 wks pre-tx)
- HIB, Meningococcal if planned splenectomy (e.g. Multivisceral Tx)

Recommended post SOT:

(Delay 1 month post-tx; 3–6 months to maximize response)

- COVID
- Pneumococcal
- Tetanus-diphtheria toxoid
- Inactivated Influenza

Live vaccines are NOT recommended after SOT including:

- Measles Mumps Rubella
- Varicella
- Inhaled influenza
- Oral polio
- Yellow fever
- BCG
- Small pox
- Salmonella typhi (oral)

SOLID ORGAN TRANSPLANT
PATIENT TRAVEL

- **REGIONAL EXPOSURES**
  - **COCCIDIOIDOMYCOSIS: Southwest U.S.**
  - **HISTOPLASMOSIS: Central/Mid-Atlantic U.S.**
  - **VISCERAL LEISHMANIASIS: Spain, Mediterranean Basin**
  - **MALARIA: Tropics**
  - **BABESIA MICROTI: Northeast & Upper Midwest U.S.**
- **AND ALL THE "NORMAL" RISKS TO TRAVELERS**
  - **DIARRHEA**
  - **STIs**
  - **MDR-TB**
  - **BLOOD SUPPLY (need for TRANSFUSIONS), etc….**
- **AVOID LIVE VACCINES: Yellow Fever, Oral typhoid, etc.**
- **DRUG INTERACTIONS →Transplant meds + travel related prophylactic agents**

KEY DRUG TOXICITIES / SYNDROMES

- Calcineurin inhibitors and TTP and PRES (RPLS)
- Sirolimus-induced pneumonitis
  - Progressive interstitial pneumonitis (22% in one study)
  - Risk factors: late switch to sirolimus & impaired renal function
  - Symptoms: dyspnea, dry cough, fever, and fatigue
    - Radiographic & bronchoalveolar lavage consistent with bronchiolitis obliterans organizing pneumonia & lymphocytic alveolitis
  - Recovery with sirolimus withdrawal

Euvrard S et al. N Engl J Med. 2012;367(4):329. Champion L et al. Ann Intern Med 2006;144:505. Weiner SM et al. Nephrol Dial Transplant. 2007;22(12):3631.

OTHER PEARLS FOR BOARDS…

If you're thinking PCP but its not → think TOXO

Patient presenting atypically during first month post transplant → think donor transmitted infection
- Rabies, WNV, Coccidioides, Chagas, LCMV (look for epidemiologic clues in stem)

Remember drug interactions and syndromes
- Addition of mold active azole leading to acute kidney injury from elevated CNI
- TTP and PRES induced by calcineurin inhibitors
- Sirolimus-induced pneumonitis

Remember *Strongyloides* hyperinfection syndrome

TB- Don't miss a case!

BKV, CMV and EBV/PTLD – know how to diagnose and manage

Thank You!

barbara.alexander@duke.edu

OL10

Even More Worms

Dr. Edward Mitre

Online Only Lectures – Even More Worms

Speaker: Edward Mitre, MD

IDBR INFECTIOUS DISEASE BOARD REVIEW AUGUST 20-24 2022

Even More Worms

Edward Mitre, MD
Bethesda, MD

7/25/2022

IDBR INFECTIOUS DISEASE BOARD REVIEW AUGUST 20-24 2022

Disclosures of Financial Relationships with Relevant Commercial Interests

- **None**

Major Helminth Pathogens

TREMATODES

Blood flukes
- *Schistosoma mansoni*
- *Schistosoma japonicum*
- *Schistosoma haematobium*

Liver flukes
- *Fasciola hepatica*
- *Clonorchis sinensis*
- *Opisthorchis viverrini*

Lung flukes
- *Paragonimus westermani*

Intestinal flukes
- *Fasciolopsis buski*
- *Metagonimus yokagawai*

CESTODES

Intestinal tapeworms
- *Taenia solium*
- *Taenia saginata*
- *Diphyllobothrium latum*
- *Hymenolepis nana*

Larval cysts
- *Taenia solium*
- *Echinococcus granulosus*
- *Echinococcus multilocularis*

NEMATODES

Intestinal
- *Ascaris lumbricoides*
- *Ancylostoma duodenale*
- *Necator americanus*
- *Trichuris trichiura*
- *Strongyloides stercoralis*
- *Paracapillaria philippinensis*
- *Enterobius vermicularis*

Tissue Invasive
- *Wuchereria bancrofti*
- *Brugia malayi*
- *Onchocerca volvulus*
- *Loa loa*
- *Trichinella spiralis*
- *Angiostrongylus cantonensis*
- *Anisakis simplex*
- *Toxocara canis/cati*
- *Baylisascaris procyonis*
- *Gnathostoma spinigerum*

Intestinal Flukes

Fasciolopsis buski
("Giant Intestinal Fluke" 2cm w x 8 cm)
- acquisition: eating encysted larval stage on aquatic vegetation
- symptoms: usually asymptomatic
  - can cause diarrhea, fever, abdominal pains, ulceration, and hemorrhage

Dx: eggs in stool

Metagonimus yokagawi
(2.5mm x 0.75mm)
- acquisition: eating larvae in undercooked fish
- symptoms: diarrhea and abdominal pain

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Hymenolepis nana

"Dwarf tapeworm" (4-6 cm long)

Found worldwide → the most common cestode infection of humans

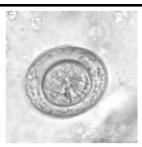
Predator (larval stage): rodents, humans
Prey (tapeworm stage): beetles!

Acquisition: by ingestion of eggs in contaminated food or water
OR by ingestion of infected grain beetle!

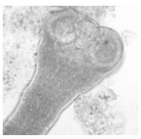
Symptoms: Often asymptomatic
With large parasite burdens, can cause
-loose stools, diarrhea
-crampy abdominal pain
-weakness

Diagnosis: finding eggs or proglottid segments in stool
(note: sometimes confused for pinworms)

Treatment: praziquantel 25 mg/kg x 1, repeat dose in 10 days
(higher than for most tapeworm infections)

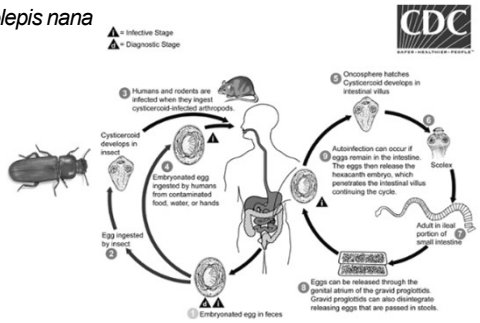


H. nana egg in wet mount
(note the hooklets)
CDC DpDx



H. nana scolex in stool sample
(note the hooklets and suckers)
CDC DpDx

Hymenolepis nana

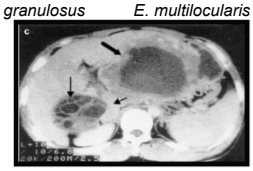


Echinococcus multilocularis

fox/rodent lifecycle

causes an infiltrative, tumor-like growth in liver
- → poorly demarcated
- → has a semi-solid nature (does <u>not</u> form large cysts)

E. granulosus *E. multilocularis*



Lancet 2003;362:1295-304

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- *Baylisascaris procyonis*
- *Gnathostoma spinigerum*

Paracapillaria philippinensis

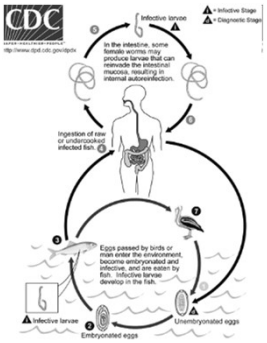
<u>Epidemiology:</u> primarily SE Asia

<u>Risk factor:</u> **eating raw freshwater fish**

<u>Sxs:</u>
often initially asymptomatic

Over time develop:
- borborygmus
- abdominal pain
- watery diarrhea

→ If not treated over weeks to months get large electrolyte losses and dehydration which can lead to death



Paracapillaria philippinensis

<u>Pathogenesis:</u>

Eat infected raw fish

→ larvae released into intestine

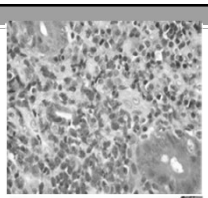
→grow to adults which burrow in mucosa

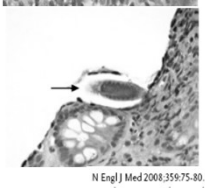
→ female worms lay eggs (oviparous)

→ some female worms are larviparous

→ some larvae burrow into the intestinal lining and develop into adults

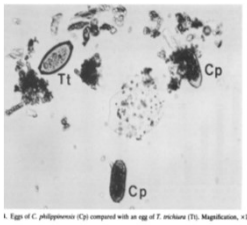
→ over weeks to months the worm burden increases (from a few worms to tens of thousands) and symptoms progress



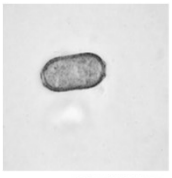


N Engl J Med 2008;359:75-80.

Paracapillaria philippinensis



Cross J, Clin Micr Reviews, 1992



N Engl J Med 2008;359:75-80.

Dx: stool o/p (eggs similar to Trichuris)

Rx: 10 d course albendazole + supportive Rx (IVF, replete electrolytes, etc.)

Enterobius vermicularis (pinworm)

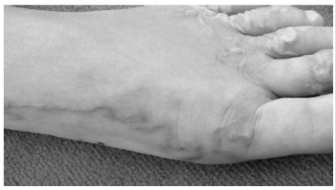
- Found everywhere
- Fecal/oral
- Humans are the only hosts
- peri-anal itching (rare: appendicitis)

Dx: stool o&p exams not very helpful
→ "pinworm paddle test" early am before showering or defecating
→ eggs have one flat side

Rx: pyrantel pamoate, albendazole, or mebendazole single dose
→ treat all members of household
→ retreat everyone in two weeks
→ careful trimming of fingernails, handwashing, washing of bedclothes to rid house of eggs

Question

A 13 year old girl developed a pruritic rash on her foot after moving to rural northeast Florida. Which of the following helminths is the most likely cause of the rash?



Am Fam Physician 2010, 81(2): 203-4.

A. *Enterobius vermicularis*
B. *Ascaris lumbricoides*
C. *Trichuris trichiura*
D. *Toxocara canis*
E. *Anyclostoma caninum*

Cutaneous Larva Migrans

Creeping eruption caused by dog or cat hookworms

Ancylostoma caninum
Ancylostoma braziliense
Uncinaria stenocephala

- Worms migrate laterally
- Unable to penetrate basal membrane of human skin
- Can occur 2-8 weeks after exposure

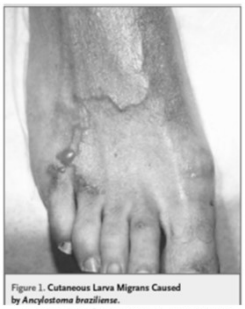


Figure 1. Cutaneous Larva Migrans Caused by *Ancylostoma braziliense*.
N ENGL J MED 351;8 WWW.NEJM.ORG AUGUST 19, 2004

Nodding syndrome

Neurological disease
- *Progressive cognitive dysfunction*
- *Nodding seizures – especially when children start to eat*
- *Growth stunting*

→ associated with Onchocerciasis

Tanzania 1960s
South Sudan 1990s
Northern Uganda 2007

A child in Uganda with nodding syndrome.
NPR 2/15/2017

May be due to cross-reactive antibodies, triggered by Onchocerca infection, that recognize leiomodin-1 in the hippocampus

Johnson et al, Science Translational Medicine 2017 v9 issue 377

Onchocerciasis in the U.S.?

The Emergence of Zoonotic *Onchocerca lupi* Infection in the United States – A Case-Series

Clinical Infectious Diseases® 2016;62(6):778–83

- *Onchocerca lupi → an infection of wolves*
- *as with O. volvulus, is transmitted by blackflies*
- *6 human cases reported to date*
- *3 with deep nodules near cervical spinal cord*
- *Southwestern U.S.(Arizona, New Mexico, Texas)*

Question

A 6 yo boy from Indiana who has a pet dog and likes to play in a sandbox presents with fever, hepatosplenomegaly, wheezing, and eosinophilia. He has never travelled outside the continental U.S.

The most likely causative agent acquired in the sandbox is:

A. *Anisakis simplex*
B. *Onchocerca volvulus*
C. *Enterobius vermicularis*
D. *Toxocara canis*
E. *Anyclostoma braziliense*

Toxocariasis (and Baylisascariasis)

Due to dog (*Toxocara canis*), cat (*Toxocara cati*), and raccoon (*Baylisascaris procyonis*) ascarids.

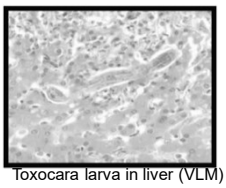
Humans acquire infection by ingestion of animal feces.
In humans → larvae hatch in intestine and migrate to liver, spleen, lungs, brain, and/or eye.

Symptoms

Visceral Larva Migrans (VLM)
usually 2-5 year olds
fever, eosinophilia, hepatomegaly
also wheezing, pneumonia, splenomegaly

Ocular Larva Migrans (OLM)
often in 10-15 year olds
retinal lesions that appear as solid tumors

Baylisascaris often more severe and more likely to cause CNS disease (eosinophilic meningitis)



Toxocara larva in liver (VLM)
CDC DPDx

Toxocariasis

Dx: Clinical picture + Toxocara antibody testing
(serum and intraocular fluid by ELISA testing)

NOTE: Toxocara IgG is only supportive b/c many individuals have + Ab due to prior exposure

Rx: usually self-limited disease.
acute VLM or OLM can be Rx with albendazole and steroids

Gnathostoma spinigerum and hispidum

Undercooked freshwater fish (ceviche!), frogs, birds, reptiles
Asia (esp Thailand), Central/South America, parts of Africa

→ Disease due to migrating immature worms.
→ Often with peripheral eosinophilia

SKIN: migratory, painful subcutaneous swellings (recur every few weeks, can last for years)
creeping eruption/cutaneous larva migrans

TISSUE: visceral larva migrans
eosinophilic meningoencephalitis
radiculomyelitis
ocular disease (anterior and posterior uveitis)

Dx: empiric or by biopsy, no antibody test available in the U.S.

Rx: can be difficult, may require 3 weeks of albendazole

Good Luck!

Ed Mitre
edwardmitre@gmail.com