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COURSE OVERVIEW

ABOUT THE COURSE

The Infectious Disease Board Review (IDBR) Course is designed specifically for physicians planning to certify or recertify in the Infectious Disease Subspecialty of the American Board of Internal Medicine (ABIM) 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 IDBR course is developed not only to expand your knowledge, but also to help you find areas in which you need to increase your knowledge. Neither the lectures nor the review questions cover all the topics that may be on the ABIM exam. The review questions during the live/virtual, and on-demand courses 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 Maintenance of Certification (MOC) exam allows access to “UpToDate” during the entire exam, registrants who have access to “UpToDate” through their institution could experiment ahead of the exam, accessing IDBR online questions and “UpToDate" simultaneously, perhaps using different browsers. After answering a question from the IDBR Question Sets, 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 “UpToDate” will need to be focused and limited. The certifying exam does not provide “UpToDate” access.

The course lectures, board review sessions, and web-based course materials (including the Primers and Study Guides; Online-Only Lectures etc.) will be available for one year following the course so that the 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 (ABIM) 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 Infectious Disease Board Review Course
Phone: (301) 818-6754
Email: info@idboardreview.com

CME PROVIDER

The George Washington University
Office of Continuing Education in the Health Professions
Phone: (202) 994-4285
Email: cehp@gwu.edu

GUIDE TO COURSE MATERIALS APP

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

With the App you can:

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

To Access the App via Mobile Device:

1. Search for "eventScribe" in the Apple App Store or Google PlayStore.
2. Install and open the eventScribe app.
3. Search for your event app by entering **2026 IDBR**.
4. To start using the app, please log in with the email and password emailed to you prior to your arrival.

Please Note:

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

Make the Most of Your Course Experience with the
2026 IDBR Course Mobile App!

Take Notes | View & Share Schedules | Personal Summary | Social Features

1. Download the Eventscribe App

Scan the QR Code or go to the Apple App Store or Google Play and search for **Eventscribe**.

App Icon

Install and open the app. Find your event icon in the Upcoming Events (bottom row) or search for **2026 IDBR**. Tap the event icon to launch your event's app.

Event Icon

2. Login to the App

To start using the course app, please login with your personal access information.
Your personal access information was sent to you by email via eventscribe.com.

How to Access the Presentation Slides:
You can browse by 'Day', by 'Presentation title', or by 'Speaker'. Click the presentation image to get to the slides. At the bottom right corner, you will see the "Slides" icon - click in order to access the slides.

How to Download All Presentation Slides:
You should download all presentation slides if you plan on going through the slides without internet access.
Click 'Get Slides' at the bottom of the page. Depending on your internet speed, the entire download should take up to 15 minutes.

Browse the event information and create a personal schedule by tapping on the star next to presentation titles.

ACCREDITATION, CME & MOC CLAIM INFORMATION - PHYSICIANS

TYPES OF CREDIT

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

- Reviewing the Lecture Recordings – 43.50 credits
- Completing the Online Materials – 71.50 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.

HOMESTUDY 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 enduring activity for a maximum of 43.50 *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 43.50 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, 2026, in order for the MOC points to count toward any MOC requirements that are due by the end of 2026.

CEHP will continue to submit participant completion data for the course until December 31, 2027. No ABIM MOC credit will be awarded for this activity after December 31, 2027.

OVERVIEW AND INSTRUCTIONS FOR CLAIMING CME CREDIT AND MOC POINTS

COURSE MATERIALS

LECTURE RECORDINGS

- Participants can receive CME credits and MOC points by watching/listening to the lecture recordings and completing the daily course evaluations.
- In addition, the archived recordings are 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.

TO CLAIM CME CREDIT(S):

- Complete the five (5) session/speaker evaluations.
- Complete the final course evaluation called “Overall Evaluation.”
- 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.

TO CLAIM MOC POINT(S):

- Be sure to update your name, ABIM number, and date of birth in your IDBR Course account.
- You will be asked to attest whether you want your participation in the homestudy course to be reported to the ABIM.

ONLINE MATERIALS

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 enduring material for a maximum of 71.50 *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 71.50 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 MOC POINTS

Participants can earn up to 71.50 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, 2026, in order for the MOC points to count toward any MOC requirements that are due by the end of 2026.

CEHP will continue to submit participant completion data for the course until December 31, 2027. No ABIM MOC credit will be awarded for this activity after December 31, 2027.

OVERVIEW OF ONLINE MATERIALS

CLAIMING CME AND MOC

ONLINE ONLY LECTURES	CME HOURS: 7.25	MOC POINTS: 7.25
• There are fifteen (15) lectures that feature topics that were not covered in the live course.		
QUESTION SETS	**CME HOURS: 56**	**MOC POINTS: 56**
• There are five (5) sets of 100 board prep questions. • There is one (1) set of 35 HIV Therapy 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.		
PRIMERS AND STUDY GUIDES	**CME HOURS: 10**	**MOC POINTS: 10**
• 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, 2026, you should have received an email confirmation from info@idboardreview.com before or on June 15 with information on accessing the online materials.
- If you register after June 15, 2026, you will receive the access information included in the registration confirmation email.

Current Access

Instructions for accessing the Online Materials:

- Course Page: https://cme.idboardreview.org/idbr26hs/content/2026-infectious-disease-board-review-homestudy-course
- Go to the course enrollment page.
- Click **REGISTER** under the course module titles.
- Complete all required profile fields (marked with a red asterisk*).
- Click "Create New Account."
- Once your account has been created, enter access code **26IDBRHS.**
- Click the "Unlock" button.
- Click the "Enroll" button.
- Select one of the course materials to begin studying.

Important Links

Please note that you must be logged in to access.

- Main Course Link: https://cme.idboardreview.org/idbr26hs/content/2026-infectious-disease-board-review-homestudy-course
- To Edit Your User Profile: https://cme.idboardreview.org/user/login?destination=my/edit/profile
- To View/Download Your CME Certificate After Completing the Course: https://cme.idboardreview.org/user/login?destination=my/activities
- To View the List of Course Activities: https://cme.idboardreview.org/user/login?destination=my/activities/pending

FACULTY LISTING

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Henry Masur, MD*

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

FACULTY DISCLOSURES & RESOLUTIONS

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

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

PLANNERS

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

Both planners also resolved financial disclosures.

STAFF

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

The following faculty members (speakers) disclosed commercial relationships:

FACULTY MEMBER	FINANCIAL DISCLOSURE(S)
Barbara D. Alexander, MD, MHS	• Consulting: Scynexis/GSK, HealthTrackRx, DevleBio, Anvil Diagnostics • Research Grant (Institution): Karius • Clinical Trials (Site PI/Study PI): Scynexis, F2G, Basilia • Royalties (Chapter Author): UpToDate, Biomeme
Paul G. Auwaerter, MD	• Consulting: Medical-Legal, Tonix Pharmaceuticals, Tarsus Pharmaceutics • Research: Pfizer (Investigational Lyme Disease vaccine)
Helen Boucher, MD	• Editor: ID Clinics of North America, Sanford Guide
Douglas Black, PharmD	• Contributing Editor: Sanford Guide to Antimicrobial Therapy
Henry F. Chambers, MD	• Equity: Moderna, Merck • Data Monitoring Committee: Merck
Susan E. Dorman, MD	• Salary support from NIH and CDC grant funding - several clinical trials of novel TB regimens and novel TB diagnostics
Michael Klompas, MD	• Grant Funding: Centers for Disease Control and Prevention, Agency for Healthcare Research and Quality, Massachusetts Department of Public Health • Royalties: UpToDate

FACULTY MEMBER	FINANCIAL DISCLOSURE(S)
Camille Kotton, MD	• Consulting: Evrys, Merck, Shire/Takeda, AiCuris, QIAGEN, Roche Diagnostics, Kamada, Biotest • Data Monitoring Committee: Merck • Adjudication Committee Member: Merck, Shire/Takeda • Research Funding: AiCuris, QIAGEN, Kamada • Speaker: Merck, Shire/Takeda, QIAGEN, Roche Diagnostics, Kamada, Biotest
Robin Patel, MD	• Consulting: PhAST, Iterum Therapeutics, DEEPULL DIAGNOSTICS, Claryx, Inc., Nostics, CARB-X • Grant Funding: MicuRx Pharmaceuticals, ImmuCell • Patent: Bordetella pertussis/parapertussis PCR; a device/method for sonication (royalties paid by Samsung to Mayo Clinic; Anti-biofilm substance; PET imaging of bacterial infection with a PET probe filed • Honoraria: UpToDate
Andrew T. Pavia, MD	• Commercial Interests: Antimicrobial Therapy Inc, Haleon
Jennifer Saullo, MD	• Chapter Author: UpToDate
David L. Thomas, MD, MPH	• Data and Safety Monitoring Board: Merck, Rho • Advisory Board: Excision Bio
Richard J. Whitley, MD	• Steering Committee: NIAID COVID-19 Recover, Recover VITAL Study • Scientific Advisory Board: Treovir, LLC, Altesa Biosciences • Board of Directors: Evrys Bio, Virios Therapeutics • Past Chairperson: Merck Letermovir DMC, GSK IDMC for Zoster and NIAID COVID-19 Vaccine DSMB
Kevin L. Winthrop, MD	• Research Grant: Insmed, AN2 • Consulting: Insmed, AN2

AGENDA DAY 1: Saturday, August 22, 2026

#	Start		End	Presentation	Faculty
AM Moderators: Henry Masur, MD and John Bennett, MD					
1	8:00 AM EDT	-	8:30 AM EDT	Introduction	John Bennett, MD and Henry Masur, MD
2	8:30 AM	-	9:30 AM	Core Concepts: Microbiology: What You Need to Know for the Exam	Robin Patel, MD
AM Moderator: Barbara Alexander, MD					
	9:30 AM	-	9:45 AM	Morning Break	
3	9:45 AM	-	10:45 AM	Core Concepts: Antibacterial Drugs I Approach to Resistant Gram-Negative Bacilli	Pranita Tamma, MD
4	10:45 AM	-	11:45 AM	Infections in Hematopoietic Stem Cell Recipients	Jennifer Saullo, MD
	11:45 AM	-	12:15 PM	Lunch Break	
BR1	**12:15 PM**	**-**	**1:00 PM**	**Board Review Day 1**	**Drs. Patel (Moderator), Alexander, Pavia, Saullo and Tamma**
PM Moderator: Robin Patel, MD					
5	1:00 PM	-	1:45 PM	Antifungal Drugs	Barbara Alexander, MD
	1:45 PM	-	2:00 PM	Afternoon Break	
6	2:00 PM	-	3:00 PM	Infections in Solid Organ Transplant Recipients	Barbara Alexander, MD
7	3:00 PM	-	4:00 PM	Respiratory Viral Infections Including Influenza in Immunocompetent and Immunocompromised Persons	Andrew Pavia, MD
	4:00PM	-	4:15 PM	Afternoon Break	
8	4:15 PM	-	5:00 PM	Infections in Cancer Patients	Jennifer Saullo, MD
9	5:00 PM	-	5:15PM	SARS-CoV-2 and COVID-19	Andrew Pavia, MD
	5:15 PM	-	6:00 PM	Welcome Reception	

AGENDA DAY 2: Sunday, August 23, 2026

AM Moderator: Henry Masur, MD

#	Start		End	Presentation	Faculty
10	8:00 AM	-	9:00 AM	Clinical Immunology and Host Defense	Steve Holland, MD
11	9:00 AM	-	10:00 AM	Protozoa That Could Be Tested	Edward Mitre, MD
	10:00 AM	-	10:15 AM	Morning Break	
12	10:15 AM	-	11:00 AM	Brain Abscess, Cavernous Sinus Thrombosis, and Subdural and Epidural Empyema	Allan Tunkel, MD
13	11:00 AM		11:45 AM	Worms You Should Know	Edward Mitre, MD
	11:45 AM	-	12:00 PM	Lunch Break	

PM Moderator: Paul Auwaerter, MD

BR2	12:00 PM	-	12:45 PM	Board Review Day 2	Drs. Auwaerter (Moderator), Bell, Bennett, Mitre, Platts-Mills, and Tunkel
14	12:45 PM	-	1:30 PM	Encephalitis including West Nile and Rabies	Allan Tunkel, MD
15	1:30 PM	-	2:15 PM	Syndromes in the ICU that ID Physicians Should Know	Taison Bell, MD
16	2:15 PM	-	3:00 PM	Ticks, Mites, Lice, and the Diseases They Transmit	Paul Auwaerter, MD
17	3:00 PM	-	3:30 PM	GI Infections Part I	James Platts-Mills, MD
	3:30 PM	-	3:45 PM	Afternoon Break	
18	3:45 PM	-	4:15 PM	GI Infections Part 2	James Platts-Mills, MD
19	4:15 PM	-	4:45 PM	Lyme Disease	Paul Auwaerter, MD
	4:45 PM	-	5:00 PM	Afternoon Break	
20	5:00 PM	-	5:45 PM	Fungal Diseases in Immunocompetent and Immunosuppressed Hosts	John Bennett, MD
21	5:45 PM	-	6:15 PM	Pneumonia	Paul Auwaerter, MD

AGENDA DAY 3: Monday, August 24, 2026

#	Start		End	Presentation	Faculty
AM Moderator: David Aronoff, MD					
22	8:00 AM	-	8:30 AM	Sexually Transmitted Infections: Genital Ulcers Diseases (GUD)	Khalil Ghanem, MD
23	8:30 AM	-	9:15 AM	Zoonoses	David Aronoff, MD
	9:15 AM	-	9:30 AM	Morning Break	
24	9:30 AM	-	10:15 AM	Nocardiosis, Actinomycosis, Rhodococcus and Melioidosis	David Aronoff, MD
25	10:15 AM	-	11:15 AM	Sexually Transmitted Infections: Other Diseases and Syndromes	Khalil Ghanem, MD
26	11:15 AM	-	12:15 PM	Core Concepts: Antibacterial Drugs II Gram Positive Organisms	Helen Boucher, MD
	12:15 PM	-	12:30 PM	Lunch Break	
BR3	**12:30 PM**	**-**	**1:15 PM**	**Board Review Day 3**	**Drs. Aronoff (Moderator), Boucher, Dhanireddy, Dorman, Ghanem, Klompas**
PM Moderator: David Aronoff, MD					
27	1:15 PM	-	2:00 PM	Skin And Soft Tissue Infections	Helen Boucher, MD
28	2:00 PM	-	2:45 PM	Helicobacter and Clostridioides	David Aronoff, MD
	2:45 PM	-	3:00 PM	Afternoon Break	
29	3:00 PM	-	3:45 PM	Immunizations: Domestic, Travel, and Occupational	Shireesha Dhanireddy, MD
	3:45 PM	-	4:00 PM	Afternoon Break	
30	4:00 PM	-	5:00 PM	Hospital Epidemiology	Michael Klompas, MD
31	5:00 PM	-	5:45 PM	Tuberculosis in Immunocompetent and Immunosuppressed Hosts	Susan Dorman, MD

AGENDA DAY 4: Tuesday, August 25, 2026

AM Moderator: Roy Gulick, MD					
#	Start		End	Presentation	Faculty
32	8:00 AM	-	8:45 AM	Clinical Manifestations of Human Retroviral Diseases and Slow Viruses	Frank Maldarelli, MD
33	8:45 AM	-	9:30 AM	HIV-Associated Opportunistic Infections I	Henry Masur, MD
34	9:30 AM	-	9:45 AM	HIV Diagnosis	Frank Maldarelli, MD
	9:45 AM	-	10:00 AM	Morning Break	
35	10:00 AM	-	10:45 AM	Antiretroviral Therapy	Roy Gulick, MD
36	10:45 AM	-	11:00 AM	HIV Drug Resistance	Michael Saag, MD
37	11:00 AM	-	11:45 PM	Antiretroviral Therapy for Special Populations	Roy Gulick, MD
	11:45 PM	-	12:15 PM	Lunch Break	
PM Moderator: Roy Gulick, MD					
BR4	**12:15 PM**	**-**	**1:00 PM**	**Board Review Day 4**	**Drs. Gulick (Moderator), Bloch, Gandhi, Kotton, Maldarelli, Saag, and Whitley**
38	1:00 PM	-	1:30 PM	EBV, HHV 6, HHV 8	Camille Kotton, MD
39	1:30 PM	-	2:15 PM	HIV-Associated Opportunistic Infections II	Rajesh Gandhi, MD
40	2:15 PM	-	3:00 PM	Syndromes Masquerading as Infections	Karen Bloch, MD
	3:00PM	-	3:15 PM	Afternoon Break	
41	3:15 PM	-	4:00 PM	Non-AIDS-Defining Complications of HIV/AIDS	Michael Saag, MD
42	4:00 PM	-	4:30 PM	Pharyngitis Syndromes Including Group A Strep Pharyngitis	Karen Bloch, MD
	4:30PM	-	4:45PM	Afternoon Break	
43	4:45 PM	-	5:15PM	Herpes Simplex and Varicella Zoster	Richard Whitley, MD
44	5:15 PM	-	6:00 PM	Photo Opportunity I: Photos and Questions to Test Your Board Preparation	Rajesh Gandhi, MD

AGENDA DAY 5: Wednesday, August 26, 2026

#	Start		End	Presentation	Faculty
AM Moderator: John Bennett, MD					
45	8:00 AM	-	9:00 AM	Endocarditis of Native and Prosthetic Devices, and Infections of Pacers and Ventricular Assist Devices	Henry Chambers, MD
46	9:00 AM	-	9:45 AM	Acute Hepatitis	David Thomas, MD
	9:45 AM	-	10:00 AM	Morning Break	
47	10:00 AM	-	10:45 AM	Staphylococcus aureus	Henry Chambers, MD
48	10:45 AM	-	11:30 AM	Chronic Hepatitis	David Thomas, MD
	11:30 AM	-	11:45 AM	Lunch Break	
PM Moderator: Henry Masur, MD					
49	11:45 AM	-	12:30 PM	Nontuberculous Mycobacteria in Normal and Abnormal Hosts	Kevin Winthrop, MD
50	12:30 PM	-	1:15 PM	Principles of Antimicrobial Therapy for Exam: What You Need to Know About Toxicities, PK/PD, Drug-Drug Interactions	Douglas Black, Pharm D
	1:15 PM	-	1:30 PM	Afternoon Break	
51	1:30 PM	-	2:15 PM	Infections of Upper and Lower Urinary Tract	Barbara Trautner, MD
52	2:15PM	-	3:00 PM	Kitchen Sink: Syndromes Not Covered Elsewhere	Stacey Rose, MD

Online Only Lectures			
#	Duration	Title	Faculty
OL – 1	15 min	How to Prepare for the Certification and Recertification, Including the LKA	Helen Boucher, MD
OL – 2	45 min	Antimicrobial Toxicities II	Douglas Black, PharmD
OL – 3	45 min	HIV-Associated Opportunistic Infections III	Rajesh Gandhi, MD
OL – 4	25 min	Statistics	Khalil Ghanem, MD
OL – 5	40 min	Review of Basics: HIV	Roy Gulick, MD
OL – 6	50 min	Review of Basics: Transplant Infectious Disease	Camille Kotton, MD
OL – 7	45 min	Even More Worms	Edward Mitre, MD
OL – 8	45 min	Bone and Joint Infections	Sandra Nelson, MD
OL – 9	30- min	Penicillin Allergy	Sandra Nelson, MD
OL – 10	40 min	Immunomodulatory Agents: What Can Be Tested	Jennifer Saullo, MD
OL – 11	45 min	Treating Antimicrobial Resistant Infections III: Pseudomonas aeruginosa, Acinetobacter baumannii, and Stenotrophomonas maltophilia	Pranita Tamma, MD
OL – 12	45 min	Epididymitis, Orchitis, and Prostatitis	Barbara Trautner, MD
OL – 13	45 min	Bacterial and Viral Meningitis	Allan Tunkel, MD
OL – 14	40 min	Sinusitis and Otitis	John Bennett, MD
OL – 15	25 min	Kitchen Sink: Syndromes Not Covered Elsewhere – Bonus Cases	Stacey Rose, MD

AGENDA DAY 1: Saturday, August 22, 2026

#	Start		End	Presentation	Faculty
AM Moderators: Henry Masur, MD and John Bennett, MD					
1	8:00 AM EDT	-	8:30 AM EDT	Introduction	John Bennett, MD and Henry Masur, MD
2	8:30 AM	-	9:30 AM	Core Concepts: Microbiology: What You Need to Know for the Exam	Robin Patel, MD
AM Moderator: Barbara Alexander, MD					
	9:30 AM	-	9:45 AM	Morning Break	
3	9:45 AM	-	10:45 AM	Core Concepts: Antibacterial Drugs I Approach to Resistant Gram-Negative Bacilli	Pranita Tamma, MD
4	10:45 AM	-	11:45 AM	Infections in Hematopoietic Stem Cell Recipients	Jennifer Saullo, MD
	11:45 AM	-	12:15 PM	Lunch Break	
BR1	**12:15 PM**	**-**	**1:00 PM**	**Board Review Day 1**	**Drs. Patel (Moderator), Alexander, Pavia, Saullo and Tamma**
PM Moderator: Robin Patel, MD					
5	1:00 PM	-	1:45 PM	Antifungal Drugs	Barbara Alexander, MD
	1:45 PM	-	2:00 PM	Afternoon Break	
6	2:00 PM	-	3:00 PM	Infections in Solid Organ Transplant Recipients	Barbara Alexander, MD
7	3:00 PM	-	4:00 PM	Respiratory Viral Infections Including Influenza in Immunocompetent and Immunocompromised Persons	Andrew Pavia, MD
	4:00PM	-	4:15 PM	Afternoon Break	
8	4:15 PM	-	5:00 PM	Infections in Cancer Patients	Jennifer Saullo, MD
9	5:00 PM	-	5:15PM	SARS-CoV-2 and COVID-19	Andrew Pavia, MD
	5:15 PM	-	6:00 PM	Welcome Reception	

Saturday, August 22, 2026

01

Introduction

Drs. Bennett and Masur

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Introduction to IDBR 2026

John E. Bennett, MD
Henry Masur, MD

8/19/2026

Disclosures of Financial Relationships with Relevant Commercial Interests

- None

IDBR Directors and Co-Directors

John Bennett

Henry Masur

Barbara Alexander
Duke

David Aronoff
Indiana University

Paul Auwaerter
Johns Hopkins

Trip Gulick
Weill Cornell

Robin Patel
Mayo

Andy Pavia
University of Utah

Richard Whitley
University of Alabama

Board Review Question Editor

Karen Bloch, MD, MPH
Professor of Medicine
Associate Division Director for Clinical Affairs
Division of Infectious Diseases
Vanderbilt University Medical Center

1 Introduction

Speaker: John Bennett, MD and Henry Masur, MD

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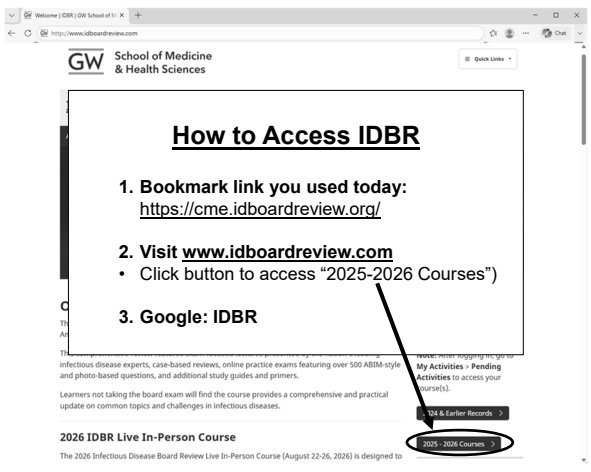
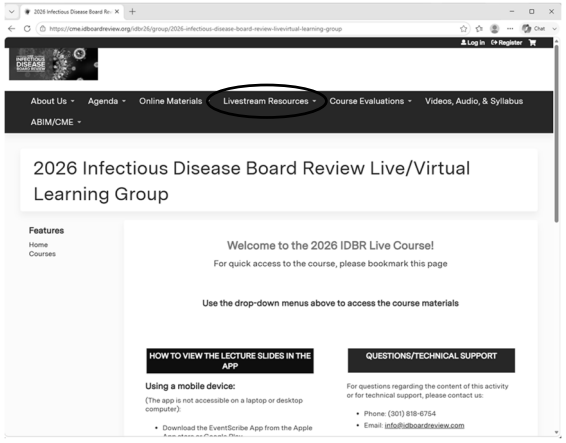
This Is Board Review

- **This is Board Review**
  - …not meant to be "What's New"
  - This may not mimic your practice but
    - Hopefully will mimic exam
    - Faculty provides their *"best guess"* about type of questions for certification, recertification, and LKA exams
- ABIM Rules
  - We abide by confidentiality rules of ABIM
  - We will NOT tell you what has been on past exams…even if we know!!!

IDBR Program
(Online Resources Available Until 12/2027)

- **Live/Virtual course for 5 days**
  - Live board review questions
  - Rationales and daily scores published online by username at end of each day
- **Online board review type questions**
  - 500 Online questions with rationales
- **Online Primers (8)**
  - Clinical Microbiology, Microbial Resistance, Rickettsia, and more
- **Online recordings of Live 2026 lectures**
  - **Posted ASAP- within 2 weeks after course**
    - Also available as MP3 audio file
- **Online-only lectures (15)**
  - Talks we wished we had time for during these 5 virtual days





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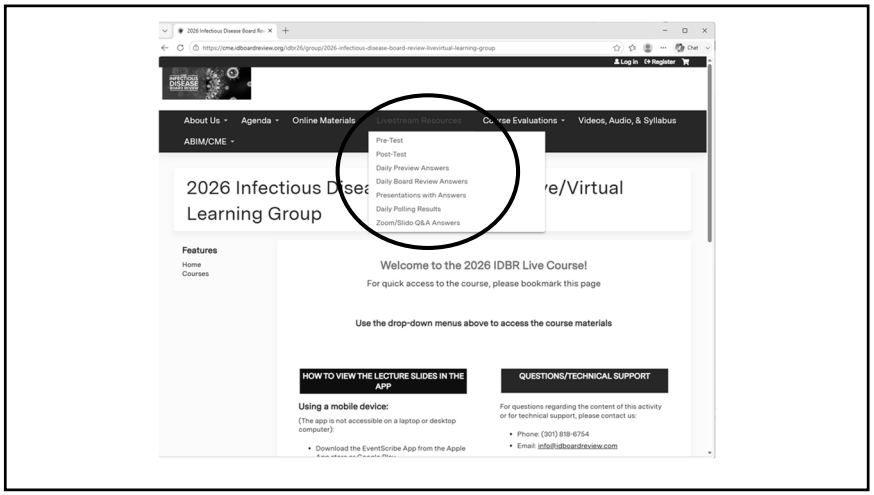
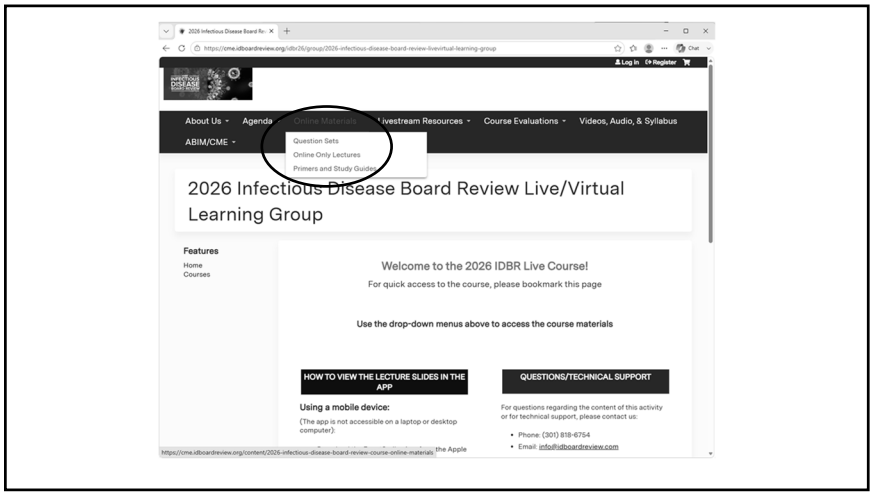
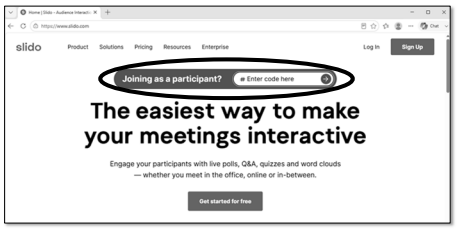




How to Vote if You Are Attending the Live Course – IN PERSON

- Recommended to use **cell phone** to vote
  - Can also use web browser on MAC/PC desktop, Laptop, or Tablet
- Go to **Slido.com** or use QR code and enter **Participant Code #4015 289**
- Enter your name and email address
- **Do not log into Zoom/Slido integration**

Join at
slido.com
 # 4015 289



How to Vote if You Are Attending the Live Course - VIRTUAL

If logging into Zoom on a MAC/PC desktop or laptop:

- Log into Zoom, which will include the live lecture and audience response system (Slido)
- Click **Open** on the prompt to take part in Slido
- Enter your name and email address
- You will see the ARS questions pop up on the right-hand side of the screen when the speaker is presenting a question
- Having trouble logging into Slido polling in Zoom?
  - Open Slido.com in a web browser on MAC/PC desktop, Laptop, or mobile device

Join at
slido.com
 # 4015 289

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How to Vote if You Are Attending the Live Course - VIRTUAL

If logging into Zoom on a mobile device:

- You will need to open a web browser to log into Slido

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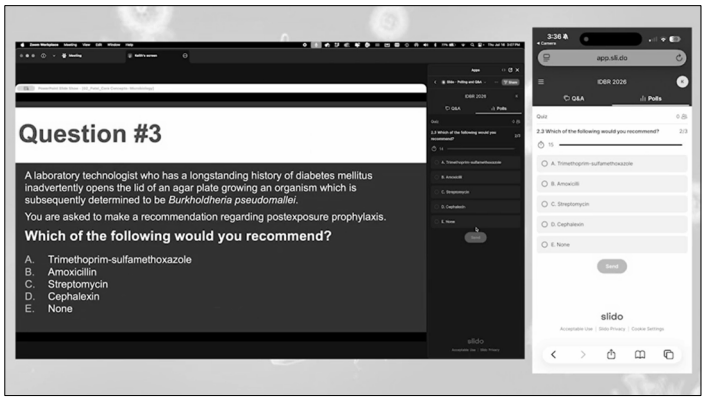
slido.com
 # 4015289

Zoom & Slido Polling

Slido Polling Integrated in Zoom Webinar



Look Up Results Each Day by Slido Login

- Log into Slido with a username likely to be unique
- Use the exact same username every day, i.e., the same spelling and capitalization
- Can be a pseudonym
- Results will be posted using truncated usernames to ensure anonymity

Join at
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 # 4015289

1 Introduction

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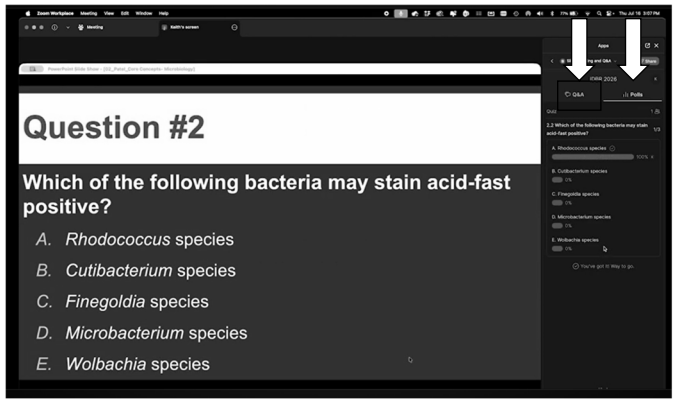
If You Are Taking the HOMESTUDY Course

- You will see the audience response question, but you will not be able to vote electronically

How to Interact with Faculty

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

Q & A in Slido



IDBR App

- Download the IDBR App from Apple store or Google Play store
  - Download EventScribe
  - Search for course by entering "**2026 IDBR**"
  - Log in with the email and password that was emailed to you
  - Problems: email info@idboardreview.com or call (301) 818-6754
- You can use this app during the course, and through December 2027, on your cell phone or tablet to look at the syllabus

IDBR INFECTIOUS DISEASE BOARD REVIEW

1 Introduction

Speaker: John Bennett, MD and Henry Masur, MD

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Problems Accessing The Course

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

CME and MOC

Total Possible: 116.25 CME and 116.25 MOC

- **CME**
  - **You must fill out lecture evaluations (via IDBR website)**
  - **You must request CME (via IDBR website)**
  - **You must complete the pre-test and post-test**
  - Total possible hours – 116.25
    - **Lectures – 43**
    - **Enduring Material – 73.25 (Question Sets; Primers and Study Guides; Online Only Lectures)**
- **MOC: one hour CME = 1 MOC credit**
  - You must first obtain CME per above
  - You must give IDBR your ABIM number
  - You must apply via ABIM website so we can link to ABIM
  - You must get 70% on post-test (11/15 correct)
    - **(three tries of same test permitted with rationales available after each try)**

Which Will You Be?

How to Get the Most Out of Course

- This is a long course
- Decide how you learn best over 10+ hours x 5 days
  - If you don't/can't watch the lectures consecutively…they are all archived
  - Reviewing the Preview Questions before the session will improve your experience
- Use the Audience Response System (ARS)/Slido to Answer Questions
  - To stay awake, be engaged, and be competitive!
  - Answer the questions and see how you compare to your peers

1 Introduction

Speaker: John Bennett, MD and Henry Masur, MD

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Behind the Scenes Staff

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Managing Director

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Recording

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Zoom / Slido

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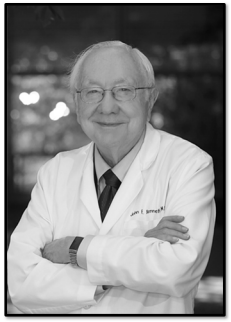
Advice from Jack Bennett, MD



Two Extraneous Things

1. **Convert short term memory into long term memory**
   - **Repetition**: review syllabus or EventScribe (circle right answers, underline important points)

2. **OK to use ChatGPT/Gemini (etc.) for the LKA questions**
   - Keep questions simple to avoid long, indirect answers
   - Drug interactions, microbial spectrum, side effects
     - Voice: transcription errors on medical terms. Spell out.
     - Suspect a wrong answer? Ask a different way.
   - Don't expect privacy

Question #1

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

Why are you taking this course?

A. Initial ABIM ID Certification
B. Recertification ten-year exam
C. Preparing for Longitudinal Knowledge Assessment Modules
D. Update in ID--- unrelated to ABIM Board Certification Exam

1 Introduction

Speaker: John Bennett, MD and Henry Masur, MD

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Question #2

Where do you work?

A. East, United States
B. Midwest, United States
C. South, United States
D. West, United States
E. Canada
F. Europe
G. Asia
H. Other

Question #3

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

A. Question sets only
B. Primers only
C. Online-only lectures
D. Several of the above
E. None of the above

Question #4

Which of the following will not grow on sheep blood, chocolate and/or MacConkey agar?

A. *Granulicatella adiacens*
B. *Bordetella pertussis*
C. *Brucella melitensis*
D. *Vibrio cholerae*
E. *Abiotrophia defectiva*

Question #5

Would you be interested in sharing your experience with AI's role in answering the LKA questions during a group discussion?

A. Yes
B. No

If there is enthusiasm for discussing it, a time a place will be set at the beginning or end of a course day

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Let's Begin!

1 Introduction

Speaker: John Bennett, MD and Henry Masur, MD

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Saturday, August 22, 2026

02

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

Robin Patel, MD

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

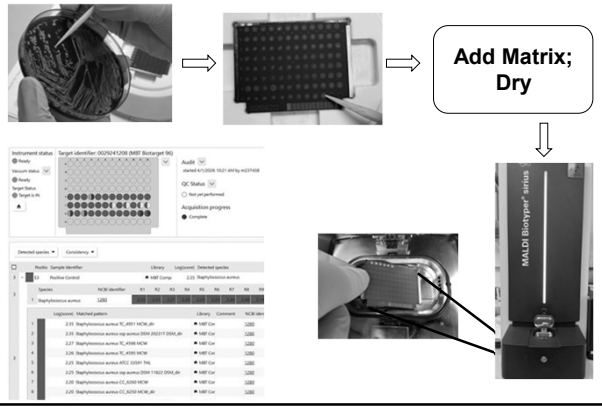
Robin Patel, MD
Mayo Clinic

4/18/2026

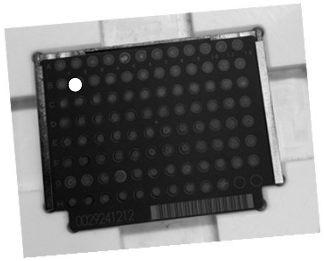
Disclosures of Financial Relationships with Relevant Commercial Interests

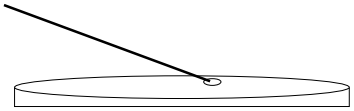
- Consulting: PhAST, Iterum Therapeutics, DEEPULL DIAGNOSTICS, Claryx, Inc., Nostics, CARB-X
- Grant Funding: MicuRx Pharmaceuticals, ImmuCell
- Patent: Bordetella pertussis/parapertussis PCR; a device/method for sonication (royalties paid by Samsung to Mayo Clinic); Anti-biofilm substance; PET imaging of bacterial infection with a PET probe filed
- Honoraria: UpToDate

MALDI ToF Mass Spectrometry

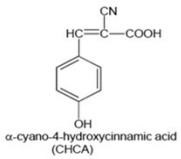


MALDI ToF Mass Spectrometry





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



α-cyano-4-hydroxycinnamic acid (CHCA)

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

3. **Dry – room air 5 min**

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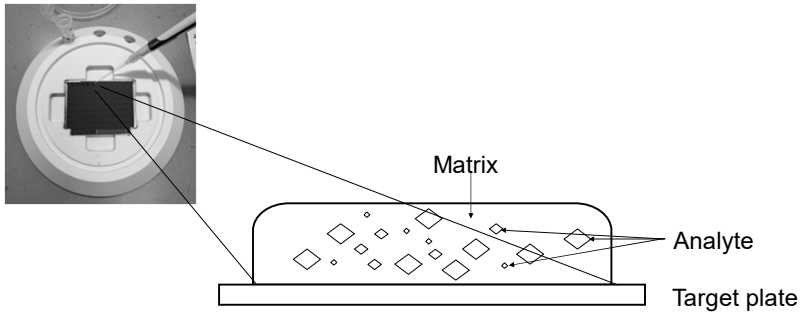
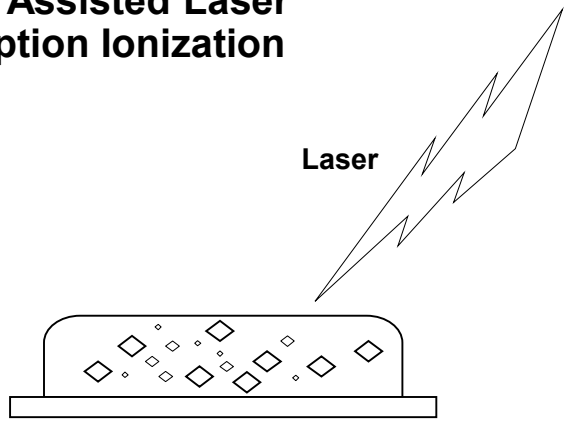
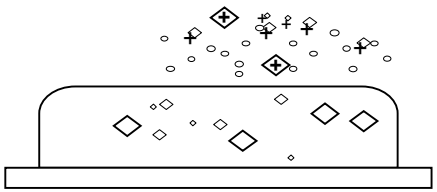
Matrix Assisted Laser Desorption Ionization



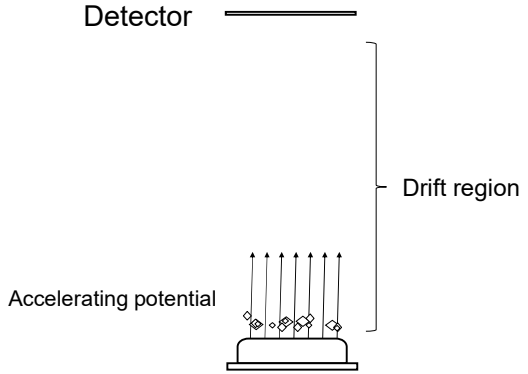
Matrix Assisted Laser Desorption Ionization



Matrix Assisted Laser Desorption Ionization



Time of Flight



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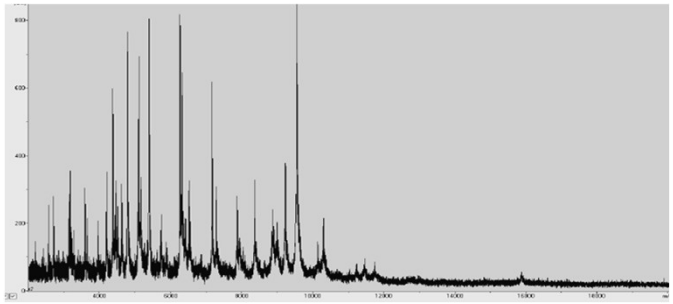
Mass Spectrum Generated Compared with Library (Database)



Question #1

Which of the following will not grow on sheep blood, chocolate and/or MacConkey agar?

A. Granulicatella adiacens
B. Bordetella pertussis
C. Brucella melitensis
D. Vibrio cholerae
E. Abiotrophia defectiva

Bacteria Requiring Specialized Media

- *Bordetella pertussis*
- *Brucella* species (+/-)
- *Burkholdheria pseudomallei* (+/-)
- *Campylobacter* species
- *Francisella tularensis* (+/-)
- *Helicobacter pylori*
- *Legionella* species
- *Mycoplasma* species (+/-)
- *Ureaplasma* species

Question #2

Which of the following bacteria may stain acid-fast positive?

A. Rhodococcus species
B. Cutibacterium species
C. Finegoldia species
D. Microbacterium species
E. Wolbachia species

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Acid-fast Bacteria (Mycolic Acids)

- *Mycobacterium* species
  - "Modified" acid fast stain positive
    - Weaker decolorizing agent (0.5-1% sulfuric acid in place of 3% acid-alcohol); do not stain well with Ziehl-Neelsen or Kinyoun stain
      - *Nocardia* species
      - *Rhodococcus* species
      - *Gordonia* species
      - *Tsukamurella* species
      - *Dietzia* species
- *Legionella micdadei* and some *Corynebacterium species*
  - [But not *Cutibacterium* species]

Question #3

A laboratory technologist who has a longstanding history of diabetes mellitus inadvertently opens the lid of an agar plate growing an organism which is subsequently determined to be *Burkholdheria pseudomallei*.

You are asked to make a recommendation regarding postexposure prophylaxis.

Which of the following would you recommend?

A. Trimethoprim-sulfamethoxazole
B. Amoxicillin
C. Streptomycin
D. Cephalexin
E. None

Burkholderia pseudomallei

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

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

Question #4

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

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

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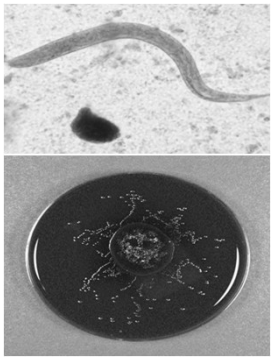
Strongyloides stercoralis

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

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



Laboratory- Acquired Bacterial, Fungal and Parasitic Infections (Selected)

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

Organisms about which the Laboratory Should be Notified if Suspected

- Avian influenza
- *Bacillus anthracis*
- *Brucella* species
- *Burkholdheria pseudomallei*
- *Burkholdheria mallei*
- *Clostridium botulinum*
- *Coxiella burnetii*
- *Coccidioides immitis/posadasii*
- Hemorrhagic fever viruses

  (e.g.., Ebola, Marburg, Chapare, Crimean-congo, Guanarito, Hanta, Junin, Kayasnur Forest Disease, Lassa Fever, Lujo, Machupo, Omsk Hemorrhagic Fever, Sabia)
- *Francisella tularensis*
- Measles
- MERS, SARS-COV
- Nipah virus, Hendra virus
- Smallpox
- *Yersinia pestis*

FDA-Approved/Cleared Multiplex Panels for Gastrointestinal Pathogens in Stool
(For Reference)

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

SEE ENLARGED SLIDE FOLLOWING ENTIRE PRESENTATION0

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Gastroenteritis Panel Testing Key Points

- If available, use culture independent method
- Indications: Dysentery, moderate-to-severe disease, symptoms lasting >7 days
  - Not recommended for chronic diarrhea
  - If *C. difficile* main consideration, test for C. difficile alone
- What's missing?
  - Some bacteria (e.g., Aeromonas species)
  - Fungi (e.g., microsporidia)
  - Some parasites (e.g., *Strongyloides stercoralis*)
    - Not all panels include same parasites (e.g., *Cyclospora cayetanensis*)
  - Some viruses (e.g., cytomegalovirus)

Meningitis/Encephalitis Panels [BIOFIRE FILMARRAY & QIAstat-Dx QIAGEN*] (For Reference)

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

Meningitis/Encephalitis Panel Key Points

- Doesn't nullify need for cell count, differential, protein, glucose, Gram stain, culture
- Cryptococcal antigen more sensitive than PCR
- Streptococcus pneumoniae antigen plus HSV, enterovirus ±VZV PCR an alternative
- May be helpful with current/recent antibiotic treatment
- HHV-6 & CMV may not be clinically significant
- What's missing?
  - Some bacteria (e.g., *Capnocytophaga canimorsus*)
  - Some fungi (e.g., *Aspergillus species*)
  - Some parasites (e.g., *Toxoplasma gondii*)
  - Some viruses (e.g., West Nile virus)

Question #5

A 73-year-old man with a history of coronary artery disease, hypercholesterolemia and colon cancer presents to the Emergency Department with a 4-day history of fever, non-productive cough, and shortness of breath.

Physical examination reveals an ill-appearing man in respiratory distress, pulse 120/min, blood pressure 110/70, respiratory rate 24/min, temperature 39oC, O2 sat on room air 89.

Chest x-ray shows bilaterial pulmonary infiltrates.

Blood cultures, urine Legionella and pneumococcal antigen, CBC, basic chemistries are collected. Sputum is submitted for Gram stain and culture but rejected due to poor specimen quality. A pneumonia panel, which includes Legionella pneumophila, is performed on the sputum and returns a negative result for all organisms on the panel. Urine Legionella and pneumococcal antigen return negative.

He is started on intravenous ceftriaxone and nasal cannula O2 and transferred to the intensive care unit where he is ultimately intubated and mechanically ventilated.

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Question #5

Which of the following is the most appropriate empiric antibiotic to add to this patient's treatment?

A. Gentamicin
B. Daptomycin
C. Trimethoprim-sulfamethoxazole
D. Vancomycin
E. Azithromycin

Lower Respiratory Tract Panels (For Reference)

	Curetis Unyvero	BioFire		Curetis Unyvero	BioFire
Bacteria			Viruses		
Acinetobacter spp.	✓		Influenza A		✓
Acinetobacter calcoaceticus-baumannii complex		✓	Influenza B		✓
Chlamydia pneumoniae	✓	✓	Respiratory Syncytial Virus		✓
Citrobacter freundii	✓		Human Rhinovirus/Enterovirus		✓
Klebsiella aerogenes		✓	Human Metapneumovirus		✓
Enterobacter cloacae complex	✓	✓	Parainfluenza virus		✓
Escherichia coli	✓	✓	Adenovirus		✓
Haemophilus influenzae	✓	✓	Coronavirus (non-SARS-CoV)		✓
Klebsiella oxytoca	✓	✓	Fungi		
Klebsiella pneumoniae	✓		Pneumocystis jirovecii	✓	
Klebsiella pneumoniae group		✓	Resistance genes		
Klebsiella variicola	✓		bla_{KPC}	✓	✓
Legionella pneumophila	✓	✓	bla_{NDM}	✓	✓
Moraxella catarrhalis	✓	✓	bla_{IMP}		✓
Morganella morganii	✓		bla_{OXA-23}	✓	
Mycoplasma pneumoniae	✓	✓	bla_{OXA-24}	✓	
Proteus spp.	✓	✓	bla_{OXA-48}	✓	
Pseudomonas aeruginosa	✓	✓	bla_{OXA-58}		
Serratia marcescens	✓	✓	$bla_{OXA-48-like}$		✓
Staphylococcus aureus	✓	✓	bla_{VIM}	✓	✓
Stenotrophomonas maltophilia	✓		bla_{CTX-M}	✓	✓
Streptococcus agalactiae		✓	bla_{TEM}	✓	
Streptococcus pneumoniae	✓	✓	*mecA*	✓	
Streptococcus pyogenes		✓	*mecA/C and MREJ*		✓

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Lower Respiratory Tract Panels Key Points

- Perform alongside Gram stain and culture
- Deploy with antimicrobial stewardship guidance
- Detection of members of the usual respiratory microbiota may be clinically insignificant
- **What's missing?**
  - Fungi ALL (except one includes *Pneumocystis jirovecii*)
  - Some parasites (e.g., *Toxoplasma gondii*)
  - Some viruses (e.g., varicella zoster virus)
  - Some bacteria (e.g., *Burkholderia cepacia* complex, *Streptococcus dysgalactiae*, non-*pneumophila Legionella* species) - one includes *Stenotrophomonas maltophilia*

Question #6

You are asked to see a 62-year-old man with a positive blood culture to advise on management.

Gram stain of the positive blood culture bottle shows Gram positive cocci in clusters.

A rapid PCR panel performed on the positive blood culture bottle contents detects *Staphylococcus aureus*, *Staphylococcus epidermidis* as well as *mecA/C* but not *mecA/C* and MREJ.

Which of the following is the interpretation of this finding?

A. Methicillin-susceptible *S. aureus* and methicillin-resistant *S. epidermidis*
B. Methicillin-susceptible *S. aureus* and methicillin-susceptible *S. epidermidis*
C. Methicillin-resistant *S. aureus* and methicillin-resistant *S. epidermidis*
D. Methicillin-resistant *S. aureus* and methicillin-susceptible *S. epidermidis*

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

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

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FDA-Approved Multiplex Panels for Detection of Gram-Positive Bacteria in Positive Blood Cultures
(For Reference), cont.

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

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*Detected as *Enterobacter* species

FDA-Approved Multiplex Panels for Detection of Selective Resistance Genes in Positive Blood Cultures
(For Reference), cont.

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

FDA-Approved Multiplex Panels for Detection of Fungi in Positive Blood Cultures
(For Reference), cont.

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

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Staphylococci Methicillin Resistance

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

BioFire Joint Infection Panel (Synovial Fluid)

Anaerococcus prevotii/vaginalis
Clostridium perfringens
Cutibacterium avidum/granulosum
Enterococcus faecalis
Enterococcus faecium
Finegoldia magna
Parvimonas micra
Peptoniphilus
Peptostreptococcus anaerobius
Staphylococcus aureus
Staphylococcus lugdunensis
Streptococcus species
Streptococcus agalactiae
Streptococcus pneumoniae
Streptococcus pyogenes

Bacteroides fragilis
Citrobacter
Enterobacter cloacae complex
Escherichia coli
Haemophilus influenzae
Kingella kingae
Klebsiella aerogenes
Klebsiella pneumoniae group
Morganella morganii
Neisseria gonorrhoeae
Proteus spp.
Pseudomonas aeruginosa
Salmonella spp.
Serratia marcescens

Candida spp.
Candida albicans

bla_{IMP}
bla_{KPC}
bla_{NDM}
$bla_{OXA-48-like}$
bla_{VIM}
bla_{CTX-M}
mecA/C & MREJ
vanA/B

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Joint Infection Panel Key Points

- Only synovial fluid
- Doesn't nullify need for culture, cell count/differential, crystal assessment
- Used for gonococcal septic arthritis
- Gaps for periprosthetic joint infection (e.g., *Staphylococcus epidermidis*)

Periprosthetic Joint Infection Unified Definition

- STANDALONE CRITERIA – CONFIRMED PJI = One criterion
- Clinical features
  - Sinus tract
- Microbiology
  - Two positive cultures - phenotypically indistinguishable organism from periprosthetic tissue
  - One positive synovial or sonicate fluid culture PLUS one positive periprosthetic tissue culture- phenotypically indistinguishable organism
- Inflammatory markers and histology
  - Synovial fluid leukocyte count >3000 cells/μL
  - Synovial fluid polymorphonuclear cells >75%
  - Positive histology: 5 or more neutrophils in each of 5 or more high power fields (400x)
- SUPPORTIVE CRITERIA – PROBABLE PJI = One microbiology PLUS one inflammatory or imaging criterion
- Microbiology
  - Single positive synovial fluid, sonicate fluid or periprosthetic tissue culture
  - Positive molecular test for any organism in synovial fluid, periprosthetic tissue or sonicate fluid
- Imaging
  - Positive WBC-scintigraphy
  - Positive [18F]-FDG-PET/CT when performed more than 6 months after index arthroplasty
- Inflammatory markers
  - Synovial fluid leukocyte count 1500 - 2999 cells/μL
  - Synovial fluid polymorphonuclear cells 65-74%
  - Any alternative positive synovial fluid biomarker

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Wouthuysen-Bakker et al. N Engl J Med. In Press.

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Question #7

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

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

The *bla*$_{KPC}$ gene product would be expected to confer resistance to which of the following?

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

Typical Susceptibility of a *bla*$_{KPC}$-Producer

Klebsiella pneumoniae

Ampicillin	>16 R	Ampicillin/Sulbactam	>16/8 R	Piperacillin/Tazobactam	64/4 R
Cefazolin	>16 R	Oral cephalosporins	R	Cefepime	>16 R
Ceftazidime	>16 R	Ceftriaxone	>32 R	Ertapenem	>1 R
Meropenem	>8 R	Aztreonam	>16 R	Ciprofloxacin	>2 R
Levofloxacin	4 I	Amikacin	>32 R	Gentamicin	>8 R
Tobramycin	4 S	Tigecycline	2 S	TMP/SMX	>2/38 R

Typical Susceptibility of an ESBL-Producer

Escherichia coli

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

*Not currently recommended for infection outside of urinary tract

Typical Susceptibility of Inducible, Chromosomally-Encoded AmpC β-lactamase Producer

*Enterobacter cloacae**

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

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

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Question #8

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

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

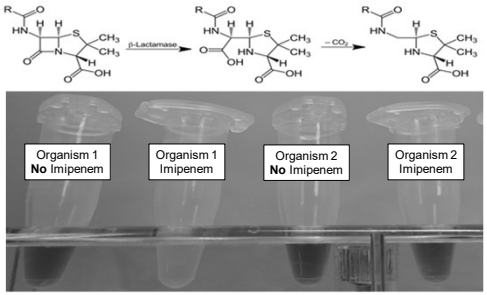
Question #9

Which of the following tests for carbapenemase production?

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

Lateral Flow Assay
***bla*$_{KPC}$, *bla*$_{OXA-48-like}$, *bla*$_{VIM}$, *bla*$_{IMP}$, *bla*$_{NDM}$**

Carbapenemase Production Test
Carba NP Test



Positive = Carbapenemase Producer

Negative = Carbapenemase Non-Producer

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

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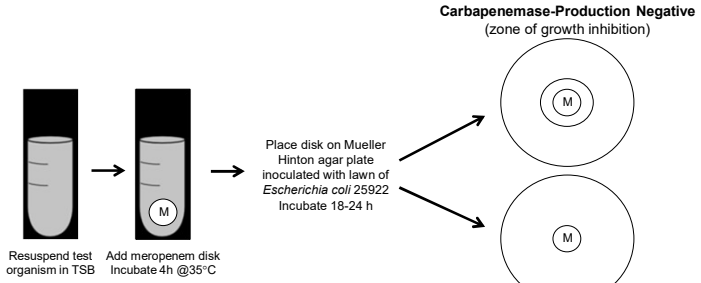
Carbapenemase Production Test
Modified Carbapenem Inactivation



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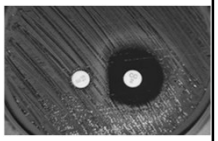
Question #10

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



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

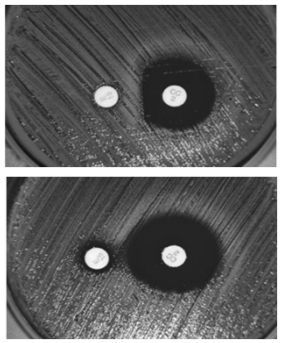
A. Erythromycin susceptibility, inducible clindamycin resistance
B. Erythromycin resistance, constitutive clindamycin resistance
C. Erythromycin resistance, inducible clindamycin resistance
D. Erythromycin susceptibility, constitutive clindamycin resistance

Inducible Clindamycin Resistance (D-Test)

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

Inducible Clindamycin Resistance (D-Test)

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



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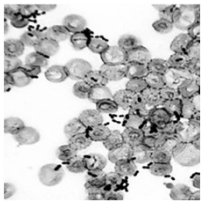
Question #11

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



Question #11

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

A. Enterococcus gallinarum
B. Enterococcus faecium
C. Enterococcus faecalis
D. Enterococcus casseliflavus
E. Enterococcus avium

Enterococci Vancomycin Susceptibility Testing

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

Question #12

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

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

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

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

A. Cefepime
B. Ceftriaxone
C. Trimethoprim-sulfamethoxazole
D. Azithromycin
E. Doxycycline

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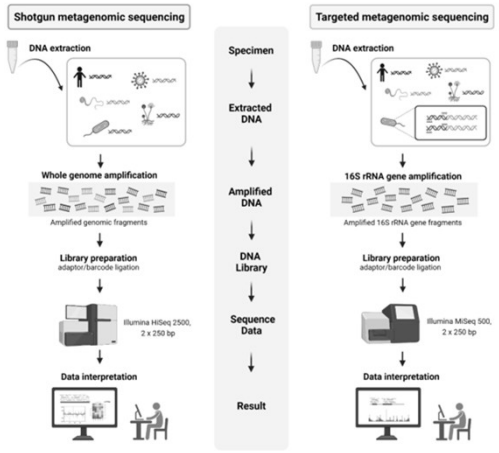
Mycoplasma hominis

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

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



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

Shotgun Metagenomic Sequencing - CSF

- May identify CNS infection not found with conventional diagnostics
  - e.g., hepatitis E virus, St. Louis encephalitis virus, Taenia solium
- Not always positive in CNS infection
  - Infections for which serology preferred (e.g., syphilis, Lyme)
  - Low pathogen titer in CSF
  - Diagnosis from samples other than CSF (tissue)
- May detect microorganisms not causing clinical syndrome
  - e.g., HHV-6, EBV

Plasma Shotgun Metagenomic Sequencing (Cell Free DNA)

- 18,690 reports; 15,165 patients; 22,792 detections
- 701 unique taxa
  - 75% bacteria
  - 15% fungi
  - 7% viruses (herpesviruses, BK virus, adenovirus, torque teno virus)
  - 3% parasites

Park et al. J Clin Microbiol. 2023;61:e01855

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Plasma Shotgun Metagenomic Sequencing (Cell Free DNA)

- *Legionella*-like bacteria (80), 40% *Legionella pneumophila*
- *Nocardia* detections (76), 25% *Nocardia cyriacigeorgica*
- *Mycobacterium* species detections (156)
- Zoonotic and vector-borne bacteria detections (247)
  - *Bartonella henselae, Bartonella quintana, Bartonella clarridgeiae, Bartonella vinsonii*
  - *Rickettsia typhi, Rickettsia rickettsii, Rickettsia felis*
  - *Ehrlichia chaffeensis, Ehrlichia muris, Anaplasma phagocytophilum, Borrelia hermsii, Borrelia burgdorferi*
  - *Coxiella burnetii, Streptobacillus moniliformis, Capnocytophaga canimorsus*
  - *Leptospira kirschneri, Leptospira interrogans, Leptospira santarosai, Leptospira borgpetersenii, Leptospira noguchii*
  - *Francisella tularensis, Brucella melitensis*
- 632 candidal, 374 Aspergillus species, 196 Mucorales, 78 dimorphic and 33 dematiaceous fungal detections
- 9 microsporidia
- 57 protozoa - 68% Toxoplasma gondii, 14% pathogenic amoebae
- 7 helminths - 4 *Strongyloides stercoralis*, 2 *Echinococcus multilocularis*, 1 *Schistosoma mansoni*

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Park et al. J Clin Microbiol. 2023;61:e01855

2023 Duke-International Society For Cardiovascular Infectious Diseases Criteria For Infective Endocarditis (IE)

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

SEE ENLARGED SLIDE FOLLOWING ENTIRE PRESENTATION

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

Question #13

You are consulted to advise on the course of action for a 57-year-old female liver transplant recipient (transplant for alcoholic steatohepatitis; CMV D^+/R^+) who has a whole blood HHV-6 viral load of $3.6x10^6$ copies/ml at three months post-transplant. The test was performed because of a report of subjective fever of four days' duration. She has no other new symptoms.

The patient received one month of acyclovir prophylaxis post-transplant and is currently receiving mycophenolate mofetil, prednisone and trimethoprim-sulfamethoxazole. Her post-transplant course was complicated by one episode of treated rejection on day 30 post transplant. Physical examination is unremarkable, and she is afebrile.

Question #13

Which of the following would you recommend?

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

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Chromosomally Integrated Human Herpesvirus-6

- High HHV-6 levels in whole blood
  - (>5.5 log10 copies/ml)
  - Suggest chromosomally integrated HHV-6
- 1:1 ratio of viral to human genomes

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

Question #14

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

Which of the following COVID-19 tests is recommended?

A. Antigen
B. Serology
C. NAAT

COVID-19 Diagnostics

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

IDSA Guidelines on the Diagnosis of COVID-19

Question #15

A 22-year-old man presents to an urgent care clinic with a cough of 9 day's duration. Prior to the onset of cough, he experienced a runny nose for a couple of days. He has not had fever. The cough is keeping him up at night and has caused him to vomit on two occasions. He has not received any vaccinations since he was a baby. Physical examination is unremarkable, except that he looks tired.

Which of the following is the test of choice for this patient?

A. Nasopharyngeal swab antigen
B. Nasopharyngeal swab culture
C. Nasopharyngeal swab NAAT
D. Serology

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Question #16

A 60-year-old man presents to an emergency department in Texas with a maculopapular rash that began 7 days prior to presentation. The rash started on his face and subsequently spread to his neck, chest and then arms and legs, and has been accompanied by fever. Before onset of the rash, he had two days of rhinorrhea and red eyes.

Which of the following is recommended?

A. Throat or nasopharyngeal swab NAAT and serum IgM test
B. Serum IgM test
C. Urine NAAT and serum IgG test
D. Throat or nasopharyngeal swab culture and serum IgM test

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FDA-Approved/Cleared Multiplex Panels for Gastrointestinal Pathogens in Stool
(For Reference)

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

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Lower Respiratory Tract Panels (For Reference)

	Curetis Unyvero	BioFire		Curetis Unyvero	BioFire
Bacteria			Viruses		
Acinetobacter spp.	✓		Influenza A		✓
Acinetobacter calcoaceticus-baumannii complex		✓	Influenza B		✓
Chlamydia pneumoniae	✓	✓	Respiratory Syncytial Virus		✓
Citrobacter freundii	✓		Human Rhinovirus/Enterovirus		✓
Klebsiella aerogenes		✓	Human Metapneumovirus		✓
Enterobacter cloacae complex	✓	✓	Parainfluenza virus		✓
Escherichia coli	✓	✓	Adenovirus		✓
Haemophilus influenzae	✓	✓	Coronavirus (non-SARS-CoV)		✓
Klebsiella oxytoca	✓	✓	Fungi		
Klebsiella pneumoniae	✓		Pneumocystis jirovecii	✓	
Klebsiella pneumoniae group		✓	Resistance genes		
Klebsiella variicola	✓		bla_{KPC}	✓	✓
Legionella pneumophila	✓	✓	bla_{NDM}	✓	✓
Moraxella catarrhalis	✓	✓	bla_{IMP}		✓
Morganella morganii	✓		bla_{OXA-23}	✓	
Mycoplasma pneumoniae	✓	✓	bla_{OXA-24}	✓	
Proteus spp.	✓	✓	bla_{OXA-48}	✓	
Pseudomonas aeruginosa	✓	✓	bla_{OXA-58}		
Serratia marcescens	✓	✓	$bla_{OXA-48-like}$		✓
Staphylococcus aureus	✓	✓	bla_{VIM}	✓	✓
Stenotrophomonas maltophilia	✓		bla_{CTX-M}	✓	✓
Streptococcus agalactiae		✓	bla_{TEM}	✓	
Streptococcus pneumoniae	✓	✓	*mecA*	✓	
Streptococcus pyogenes		✓	*mecA/C and MREJ*		✓

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

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

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FDA-Approved Multiplex Panels for Detection of Gram-Positive Bacteria in Positive Blood Cultures (For Reference), cont.

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

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*Detected as *Enterobacter* species

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FDA-Approved Multiplex Panels for Detection of Fungi in Positive Blood Cultures
(For Reference), cont.

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

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BioFire Joint Infection Panel (Synovial Fluid)

Anaerococcus prevotii/vaginalis
Clostridium perfringens
Cutibacterium avidum/granulosum
Enterococcus faecalis
Enterococcus faecium
Finegoldia magna
Parvimonas micra
Peptoniphilus
Peptostreptococcus anaerobius
Staphylococcus aureus
Staphylococcus lugdunensis
Streptococcus species
Streptococcus agalactiae
Streptococcus pneumoniae
Streptococcus pyogenes

Bacteroides fragilis
Citrobacter
Enterobacter cloacae complex
Escherichia coli
Haemophilus influenzae
Kingella kingae
Klebsiella aerogenes
Klebsiella pneumoniae group
Morganella morganii
Neisseria gonorrhoeae
Proteus spp.
Pseudomonas aeruginosa
Salmonella spp.
Serratia marcescens

Candida spp.
Candida albicans

bla_{IMP}
bla_{KPC}
bla_{NDM}
$bla_{OXA-48-like}$,
bla_{VIM}
bla_{CTX-M}
mecA/C & MREJ
vanA/B

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Periprosthetic Joint Infection
Unified Definition

- STANDALONE CRITERIA – CONFIRMED PJI = One criterion
- Clinical features
  - Sinus tract
- Microbiology
  - Two positive cultures - phenotypically indistinguishable organism from periprosthetic tissue
  - One positive synovial or sonicate fluid culture PLUS one positive periprosthetic tissue culture- phenotypically indistinguishable organism
- Inflammatory markers and histology
  - Synovial fluid leukocyte count >3000 cells/µL
  - Synovial fluid polymorphonuclear cells >75%
  - Positive histology: 5 or more neutrophils in each of 5 or more high power fields (400x)
- SUPPORTIVE CRITERIA – PROBABLE PJI = One microbiology PLUS one inflammatory or imaging criterion
- Microbiology
  - Single positive synovial fluid, sonicate fluid or periprosthetic tissue culture
  - Positive molecular test for any organism in synovial fluid, periprosthetic tissue or sonicate fluid
- Imaging
  - Positive WBC-scintigraphy
  - Positive [18F]-FDG-PET/CT when performed more than 6 months after index arthroplasty
- Inflammatory markers
  - Synovial fluid leukocyte count 1500 - 2999 cells/µL
  - Synovial fluid polymorphonuclear cells 65-74%
  - Any alternative positive synovial fluid biomarker

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Wouthuysen-Bakker et al. N Engl J Med. In Press.

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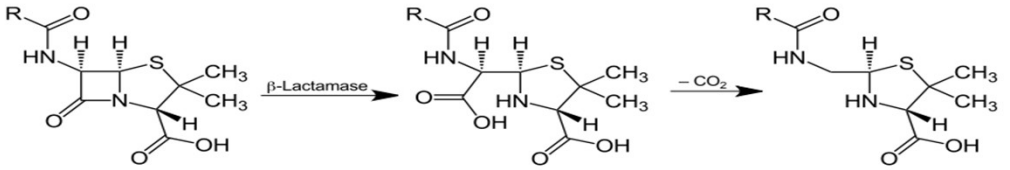
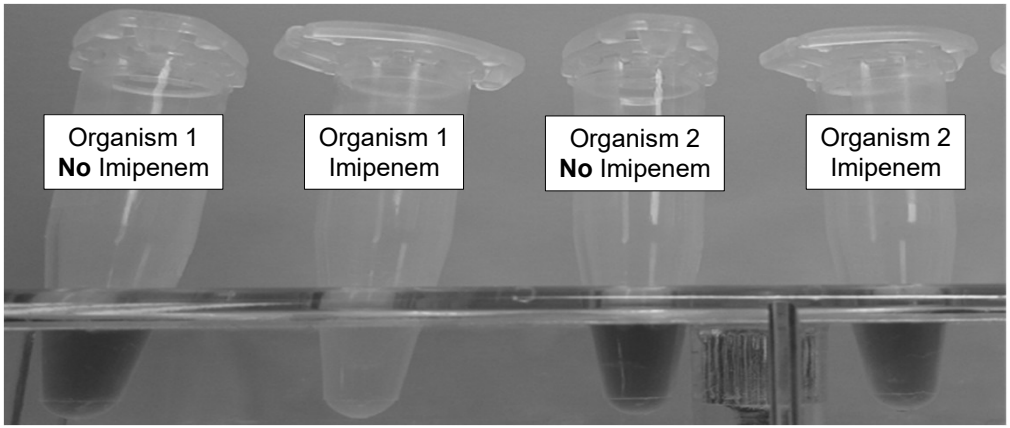
Carbapenemase Production Test
Carba NP Test





Positive = Carbapenemase Producer

Negative = Carbapenemase Non-Producer

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

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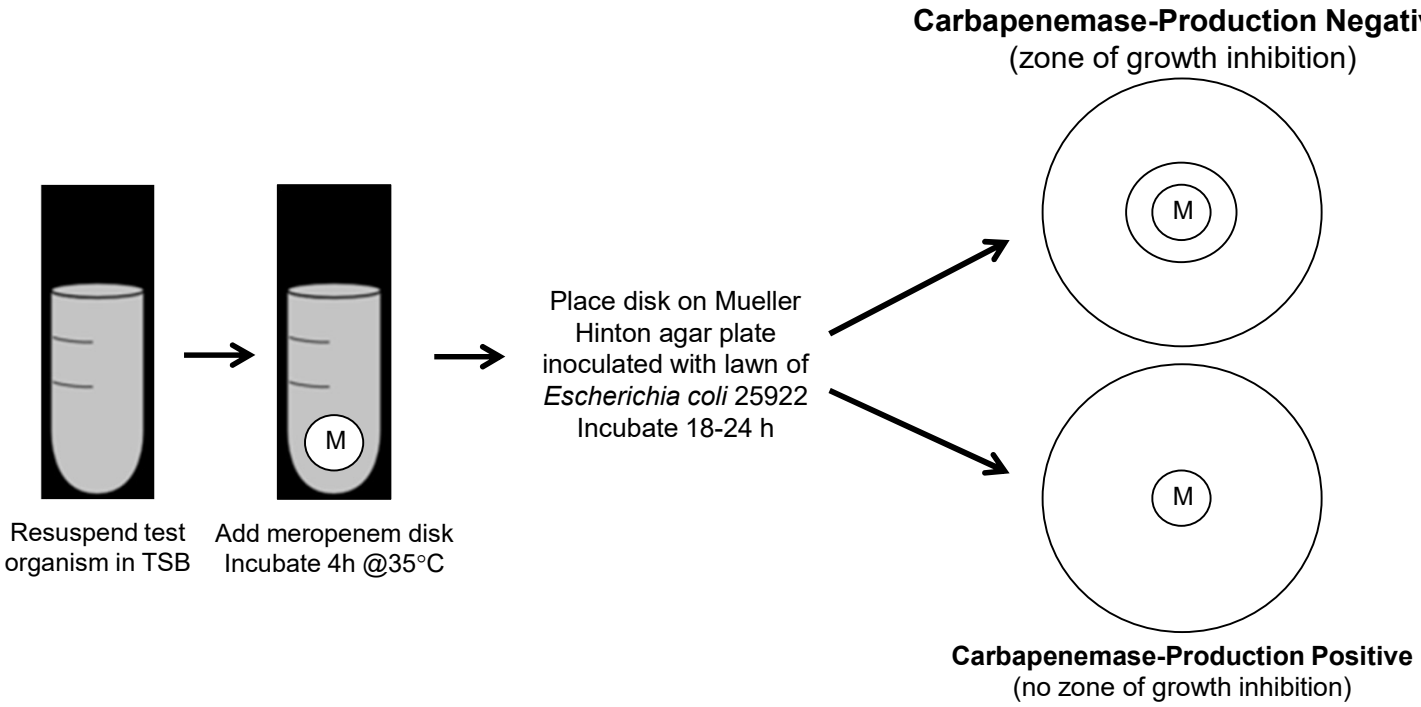
Carbapenemase Production Test
Modified Carbapenem Inactivation



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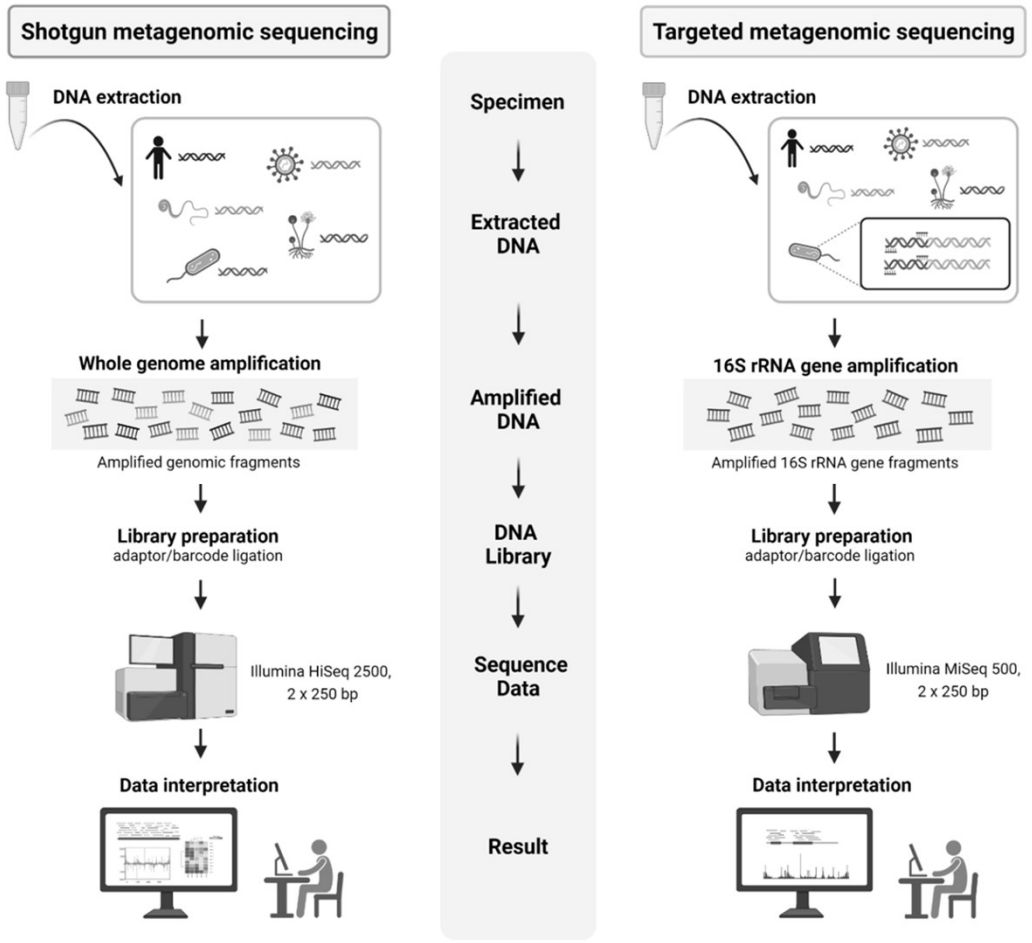

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Hong et al. Clin Infect Dis. 2023;76:e1456-e62

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Plasma Shotgun Metagenomic Sequencing (Cell Free DNA)

- *Legionella*-like bacteria (80), 40% *Legionella pneumophila*
- *Nocardia* detections (76), 25% *Nocardia cyriacigeorgica*
- *Mycobacterium* species detections (156)
- Zoonotic and vector-borne bacteria detections (247)
  - *Bartonella henselae, Bartonella quintana, Bartonella clarridgeiae, Bartonella vinsonii*
  - *Rickettsia typhi, Rickettsia rickettsii, Rickettsia felis*
  - *Ehrlichia chaffeensis, Ehrlichia muris, Anaplasma phagocytophilum, Borrelia hermsii, Borrelia burgdorferi*
  - *Coxiella burnetii, Streptobacillus moniliformis, Capnocytophaga canimorsus*
  - *Leptospira kirschneri, Leptospira interrogans, Leptospira santarosai, Leptospira borgpetersenii, Leptospira noguchii*
  - *Francisella tularensis, Brucella melitensis*
- 632 candidal, 374 Aspergillus species, 196 Mucorales, 78 dimorphic and 33 dematiaceous fungal detections
- 9 microsporidia
- 57 protozoa - 68% Toxoplasma gondii, 14% pathogenic amoebae
- 7 helminths - 4 *Strongyloides stercoralis*, 2 *Echinococcus multilocularis*, 1 *Schistosoma mansoni*

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Park et al. J Clin Microbiol. 2023;61:e01855

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2023 Duke-International Society For Cardiovascular Infectious Diseases Criteria For Infective Endocarditis (IE)

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

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

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Saturday, August 22, 2026

03

Core Concepts: Antibacterial Drugs I Approach to Resistant Gram-Negative Bacilli

Pranita Tamma, MD

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Core Concepts: Antibacterial Drugs I Approach to Resistant Gram-Negative Bacilli

Pranita D. Tamma, MD, MHS
University of Pennsylvania Perelman School of Medicine

8/8/2026

Disclosures of Financial Relationships with Relevant Commercial Interests

- None

Objectives

- Review the antibiotic treatment for infections caused by:
  - Extended-spectrum β-lactamase producing Enterobacterales (ESBL-E)
  - AmpC β-lactamase producing Enterobacterales (AmpC-E)
  - Carbapenem-resistant Enterobacterales (CRE)

Clinical Infectious Diseases
IDSA GUIDELINES

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

Infectious Diseases Society of America 2026 Guidance on the Treatment of Antimicrobial-Resistant Gram-Negative Infections

Pranita D. Tamma,[1,•] Robert A. Bonomo,[2] Emily L. Heil,[3] Julie Ann Justo,[4] Michael J. Satlin,[5] and Amy J. Mathers[6]

Provides guidance on the treatment of:

- Extended-spectrum beta-lactamase producing Enterobacterales (ESBL-E)
- AmpC beta-lactamase producing Enterobacterales (AmpC-E)
- Carbapenem-resistant Enterobacterales
- *Pseudomonas aeruginosa* with difficult-to-treat resistance
- Carbapenem-resistant *Acinetobacter baumannii* complex
- *Stenotrophomonas maltophilia* infections

www.idsociety.org/practice-guideline/amr-guidance/

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ESBL-E Infections

Clinical Case

- 18-year-old female
- Renal transplant secondary to focal segmental glomerulosclerosis
- Multiple urinary tract infections in the past including <1 month ago
- Dysuria, fevers, rigors, and hypotension
- ICU to initiate vasopressors
- Urine and blood cultures growing Escherichia coli

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

*Applying Clinical and Laboratory Standards Institute 2026 breakpoints

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

*Applying Clinical and Laboratory Standards Institute 2026 breakpoints

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Question #1

Which of the following is the preferred initial agent for a women presenting with bacteremia secondary to a urinary tract infection caused by ESBL-producing Escherichia coli?

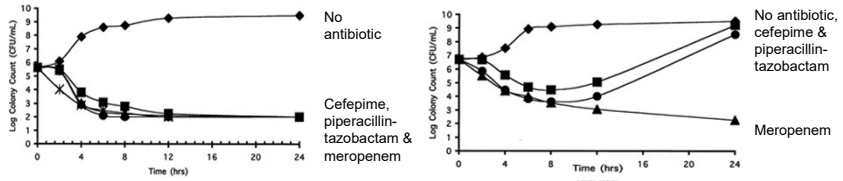
A. Ceftriaxone
B. Piperacillin-tazobactam
C. Cefepime
D. Meropenem
E. Ceftazidime-avibactam

A Primer on ESBL-E

- ESBLs are enzymes that inactivate penicillins, cephalosporins, and aztreonam
  - Do not inactivate non-β-lactam agents (e.g., aminoglycosides, TMP-SMX, ciprofloxacin, doxycycline)
  - Organisms carrying ESBL genes often harbor antimicrobial resistance determinants to a broad range of antibiotics
- Most commonly produced by *Escherichia coli, Klebsiella pneumoniae*, & *Klebsiella oxytoca*
  - Less than **10%** of other Enterobacterales species produce ESBL enzymes
- Routine ESBL testing not performed by most clinical microbiology laboratories on all specimens; if performed often limited to blood isolates
  - **Ceftriaxone MICs ≥2 µg/mL** for the above species often used as a surrogate by clinicians for ESBL production (limited specificity and perhaps overly sensitive)
- CTX-M enzymes are the most common ESBLs
  - About **10-15%** of ESBL enzymes are not CTX-M enzymes

Piperacillin-Tazobactam (PTZ): Inoculum Effect

Caveat: Relevance to clinical practice?



Low inoculum ESBL growth curve **High inoculum ESBL growth curve**

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Burgess D, et al. Diag Microbiol Infect Dis 2004; 49:41.

What are Some Concerns with Tazobactam as an ESBL Inhibitor?

- Designed to inhibit SHV and TEM ESBL variants and not CTX-M ESBLs
- Tazobactam effectiveness may be diminished with increased expression of ESBL enzymes, multiple ESBLs, or presence of other β-lactamases (e.g., OXA-1, AmpC enzymes)
  - Only 8:1 ratio of piperacillin to tazobactam compared to 2:1 ratio of ceftolozane to tazobactam
- Piperacillin-tazobactam breakpoint for Enterobacterales exclusively based on pharmacokinetic-pharmacodynamic considerations of piperacillin and not tazobactam

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JAMA

Research

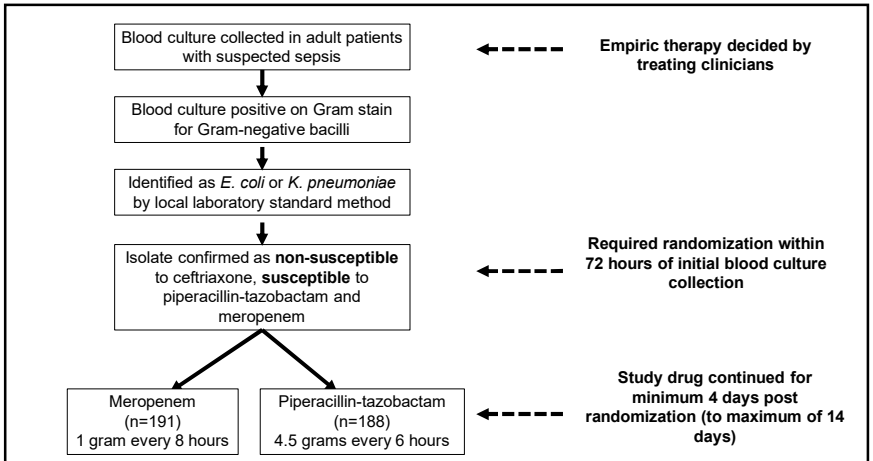
JAMA | Original Investigation

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

A Randomized Clinical Trial

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

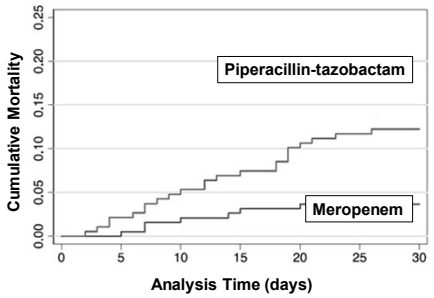
Harris PNA, et al. JAMA. 2018; 320:984-994.



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

Results

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



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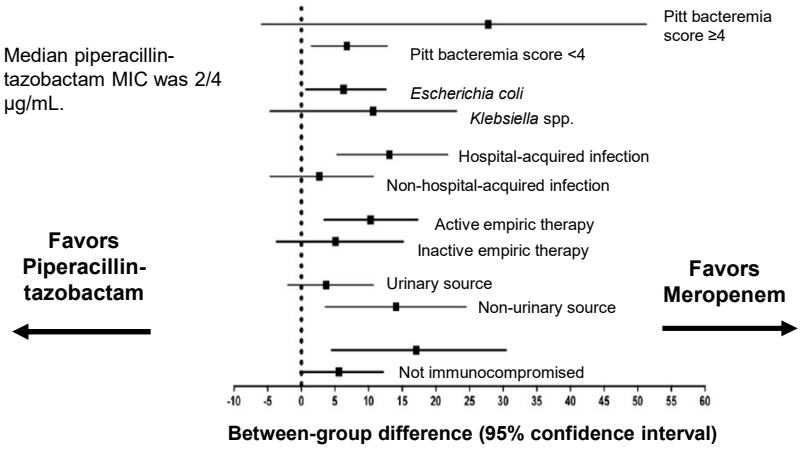
Median piperacillin-tazobactam MIC was 2/4 µg/mL.



3 Core Concepts: Antibacterial Drugs I
Approach to Resistant Gram-Negative Bacilli
Speaker: Pranita Tamma, MD, MHS

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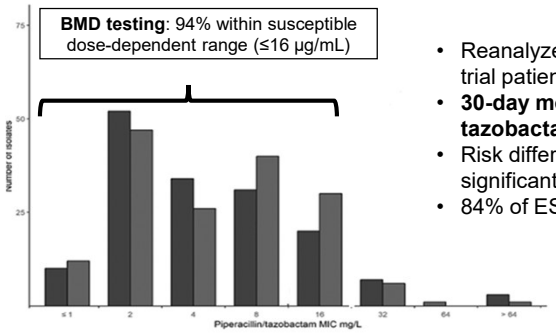
MERINO Trial: MICs for Piperacillin-Tazobactam by BMD



- Reanalyzed data from 320 of 391 trial patients
- **30-day mortality: 9% (piperacillin-tazobactam) vs. 4% (meropenem)**
- Risk difference not statistically significant (95% CI: −1% to 11%)
- 84% of ESBL genes were *bla*$_{CTX-M}$

Blue = Meropenem arm
Green = Piperacillin-tazobactam arm

SEE ENLARGED SLIDE FOLLOWING ENTIRE PRESENTATION

Henderson A, et al. Clin Infect Dis. 2021;73:e3842-e3850.

Selecting the Right Carbapenem

Critically Ill

- Meropenem and imipenem have shorter half-lives allowing for more frequent dosing, optimizing T>MIC
- Critically ill patients may have altered drug metabolism (e.g., augmented renal clearance), leading to suboptimal ertapenem drug levels

Hypoalbuminemia

- Ertapenem is highly protein bound (~90%), prolonging serum half-life
- With hypoalbuminemia, the free fraction of ertapenem increases, increasing ertapenem clearance
- 30-day mortality greater than 4 times higher with ertapenem compared to meropenem/imipenem for patients with hypoalbuminemia

Cefepime for ESBL-E Infections

- CTX-M enzymes generally hydrolyze cefepime
- No clinical trials comparing cefepime and carbapenems for ESBL-E bloodstream infections
- Poorer outcomes with cefepime compared to carbapenems for the treatment of ESBL-E bloodstream infections in multiple comparative effectiveness studies

Returning to the Clinical Case

- 18-year-old female
- Renal transplant secondary to focal segmental glomerulosclerosis
- Multiple urinary tract infections in the past including <1 month ago
- Dysuria, fevers, rigors, and hypotension
- ICU to initiate vasopressors
- Urine and blood cultures growing Escherichia coli

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

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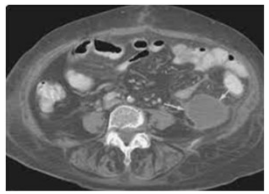
Take-Home Points
ESBL-E Bloodstream Infections

- Bloodstream infections
  - Preferred: **Meropenem/imipenem** (preferred over ertapenem while patient critically ill or with low albumin; otherwise ertapenem reasonable)
  - Alternate: Cefepime-enmetazobactam
  - Oral transition options: TMP-SMX, ciprofloxacin, levofloxacin
- Complicated UTIs
  - Preferred: **TMP-SMX, ciprofloxacin, or levofloxacin, cefepime-enmetazobactam, or carbapenems** (ertapenem, meropenem, imipenem, oral tebipenem)
  - Alternates: IV fosfomycin, aminoglycosides, and piperacillin-tazobactam
  - Oral transition options: Sulopenem

AmpC-E Infections

Clinical Case

- 21-year-old male with colon cancer
- Fevers, abdominal pain, and mental status changes one week after partial colectomy
- Multiple intra-abdominal abscesses
- Blood cultures growing Enterobacter cloacae complex



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Cefepime	≤1 µg/mL	S
Ceftriaxone	**1 µg/mL**	**S**
Ciprofloxacin	0.25 µg/mL	S
Ertapenem	0.5 µg/mL	S
Gentamicin	2 µg/mL	R
Meropenem	0.5 µg/mL	S
Piperacillin/tazobactam	4/4 µg/mL	S
Tobramycin	2 µg/mL	S
Trimethoprim/sulfamethoxazole	≥4/76 µg/mL	R

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Question #2

Which of the following is the preferred regimen for a patient with an intra-abdominal abscess in the setting of Enterobacter cloacae bacteremia, with E. cloacae exhibiting susceptibility to ceftriaxone, cefepime, piperacillin-tazobactam, and meropenem?

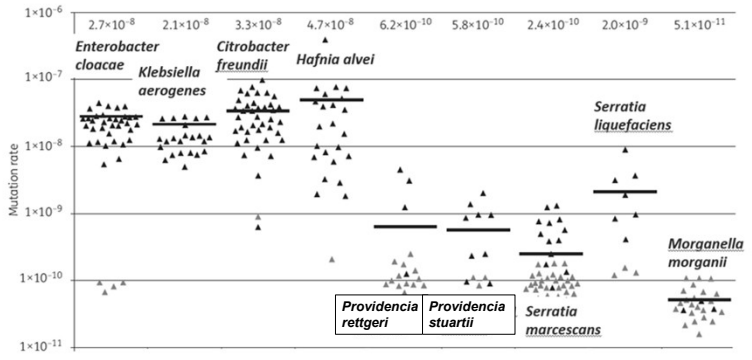
A. Cefepime plus metronidazole
B. Ceftriaxone plus metronidazole
C. Ceftazidime-avibactam
D. Meropenem-vaborbactam
E. Piperacillin-tazobactam

Three Main Mechanisms of Excessive AmpC Production

- **Inducible chromosomal *ampC* expression**
  - Inducible *ampC* expression often in the presence of specific antibiotics
- **Stable chromosomal *ampC* de-repression**
  - Some Enterobacterales isolates (e.g., some E. coli) contain mutations in promoters or attenuators of *ampC* or other regulatory genes (e.g., *ampD*), stably de-repressing *ampC* gene expression
- **Plasmid-mediated (sometimes chromosomal) *ampC* gene expression**
  - *ampC* genes carried on plasmids (and integrated into chromosome of some species)
  - Examples: bla_{CMY}, bla_{FOX}, bla_{DHA}, bla_{ACT}, bla_{MIR}

Overview of AmpC-E

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



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Kohlmann R, et al. J Antimicrob Chemother 2018; 73: 1530–1536.

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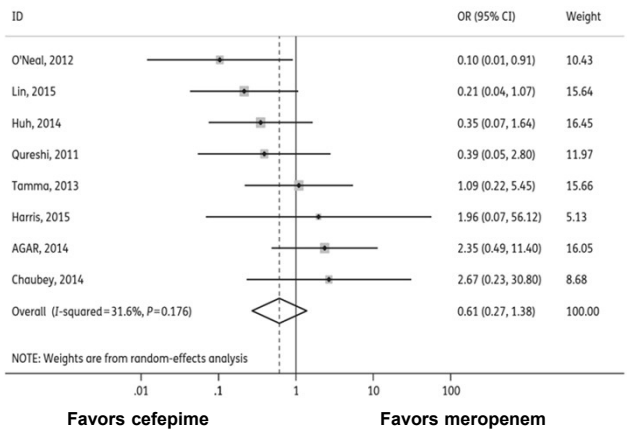
Changes with Antibiotic MICs with Increases AmpC Production

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

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

Cefepime

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



30 day mortality cefepime (9%) vs. meropenem (15%)

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Piperacillin-Tazobactam

- Tazobactam is significantly less effective at inhibiting AmpC hydrolysis in vitro than newer β-lactamase inhibitors, such as avibactam, relebactam, and vaborbactam
- The role of piperacillin-tazobactam in treating Enterobacterales at risk for clinically significant AmpC production remains uncertain, but is not suggested according to the IDSA AMR Treatment Guidance

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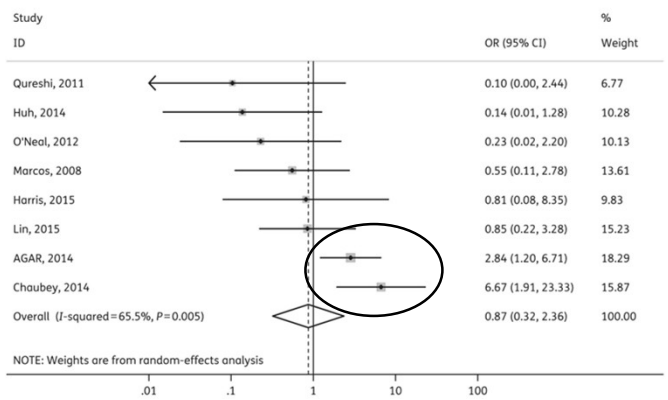

30 day mortality piperacillin-tazobactam (11%) vs. meropenem (15%)

2 additional observational studies: (n=184) with significantly higher mortality in piperacillin-tazobactam group

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Tobramycin	2 µg/mL	S
Trimethoprim-sulfamethoxazole	≥4/76 µg/mL	R

Take-Home Points: AmpC-E Infections

- Ceftriaxone is generally not suggested for the treatment of infections caused by AmpC-E, outside of uncomplicated cystitis
  - Most concerning organisms: *E. cloacae, K. aerogenes, C. freundii, H. alvei*
- For organisms at lower risk of moderate AmpC production (e.g., *S. marcescens*) ceftriaxone is generally sufficient
- Cefepime is generally an effective treatment option for AmpC-E infections
- Data less favorable for piperacillin-tazobactam for AmpC-E infections
- Save the carbapenems for infections where there are fewer options!
- Fluoroquinolones, aminoglycosides, trimethoprim-sulfamethoxazole, and doxycycline, are not substrates for AmpC hydrolysis and remain treatment options for AmpC-E infections

CRE Infections

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Defining Carbapenem-Resistant Enterobacterales (CRE)

- Enterobacterales resistant to at least one carbapenem antibiotic
- Often produce a carbapenemase enzyme
  - *Klebsiella pneumoniae* carbapenemases (KPCs)
  - New Delhi metallo-β-lactamases (NDMs)
  - Verona integron-encoded metallo-β-lactamases (VIMs)
  - Imipenem-hydrolyzing metallo-β-lactamases (IMPs)
  - Oxacillinases (OXA-48-like)

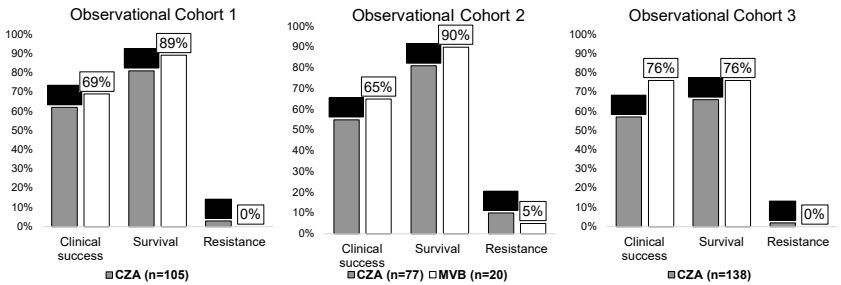
Metallo-β-lactamases (MBLs)

KPC-Producing Enterobacterales

- Most common carbapenemases in the United States
- Can occur with any Enterobacterales; not unique to K. pneumoniae
- **Treatment options**
  - Preferred: **Meropenem-vaborbactam** > **ceftazidime-avibactam** > imipenem-cilastatin-relebactam
  - Alternative: Cefiderocol

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

Ceftazidime-Avibactam Versus Meropenem-Vaborbactam



Karaba SM, Antimicrob Agents Chemother. 2026 May 6;70(5):e0160225.. Ackley R, et al. AAC 2020; e02313-19. Tumbarello M, et al. JAR AMR 2022;4(1):dlac022. Tumbarello M, et al. Clin Infect Dis. 2019; 68(3):355-364. Shields RK, et al. Antimicrob Ag Chemother. 2018; 62(5):e02487-17. Shields RK, et al. Clin Infect Dis. 2020;71(3):667-671.

NDM-Producing Enterobacterales

- Rare but increasing in the United States
- Main risk factor: previous medical care in Indian subcontinent; but clear risk factors not always present
- **Treatment options**
  - Preferred: **aztreonam-avibactam** (or if not available, ceftazidime-avibactam PLUS aztreonam); **cefiderocol**
  - Comparative effectiveness studies between the two agents not available

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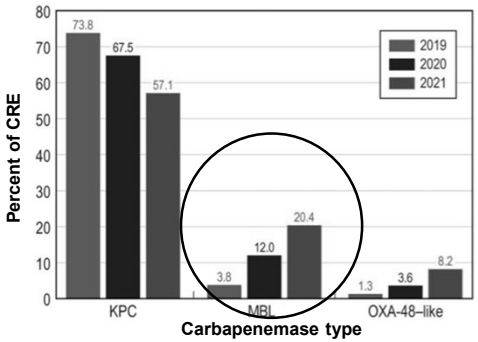
NDM-Enterobacterales are Rapidly Rising in the United States



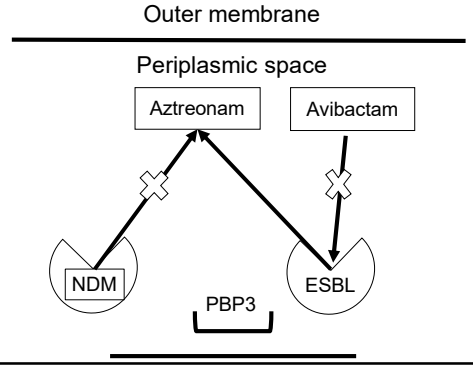
- Data from 74 United States medical centers
- NDM represent 88% of metallo-beta-lactamases
  - Most commonly *K. pneumoniae*

Sader HS, et al. Open Forum Infect Dis. 2023;10(2):ofad046.

A Brief Overview of NDM-Producing Enterobacterales

- bla_{NDM} detected in 2008 in *K. pneumoniae* and *E. coli* isolates from a patient returning to Sweden from India
  - By 2010, NDM-producing bacteria in drinking water in New Delhi
- Over 60 different variants of NDM circulating
- Require zinc at their active site for β-lactam hydrolysis
  - Variants with lower zinc requirements emerging, enabling them to thrive in settings of relative zinc scarcity, which is common in states of human infection
- Easy transferability of bla_{NDM} between bacterial species via mobile genomic elements

Aztreonam-Avibactam Mechanism of Action



Cefiderocol

- Innate immune system minimizes free iron in response to bacterial infections
  - Most iron bound to hemoglobin, myoglobin, or iron binding proteins
- Bacteria upregulate production of their native siderophores
  - Iron-chelating compounds that scavenge for free iron
- Cefiderocol is a siderophore (competing with bacterial siderophores) conjugated to a cephalosporin
- "Trojan Horse" approach to enter bacteria through iron transport channels
  - Not impacted by porins or efflux pumps
  - Once across outer membrane, cefiderocol dissociates from iron molecule and binds to PBP3, disrupting cell wall synthesis

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Emergence of Resistance to Aztreonam-Avibactam & Cefiderocol

- Aztreonam and cefiderocol bind primarily to PBP3
- 4 amino acid PBP3 insertions result in inactivity of aztreonam-avibactam and cefiderocol MICs, particularly when present with CMY (i.e., AmpC) enzymes
- Represent ~90% of NDM-producing E. coli in India
  - Now present in all regions of the world

CRE: Take-Home Points

- KPC: most common carbapenemase globally
- NDM: hint medical care in South Asia
- **Preferred treatment**
  - KPC-producers: meropenem-vaborbactam > ceftazidime-avibactam > imipenem-cilastatin-relebactam
  - NDM-producers: cefiderocol = aztreonam-avibactam (if not available, ceftazidime-avibactam PLUS aztreonam)
    - May 2026: cefepime-zidebactam FDA-approved

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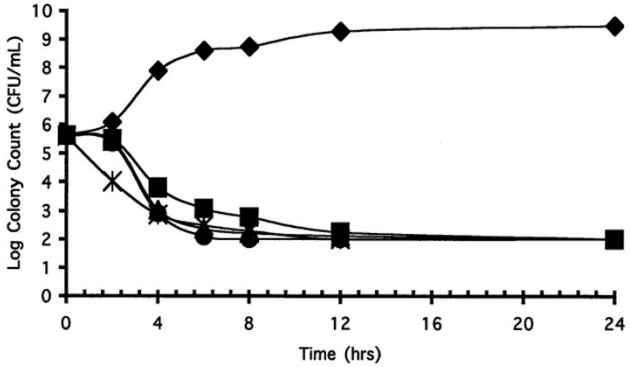
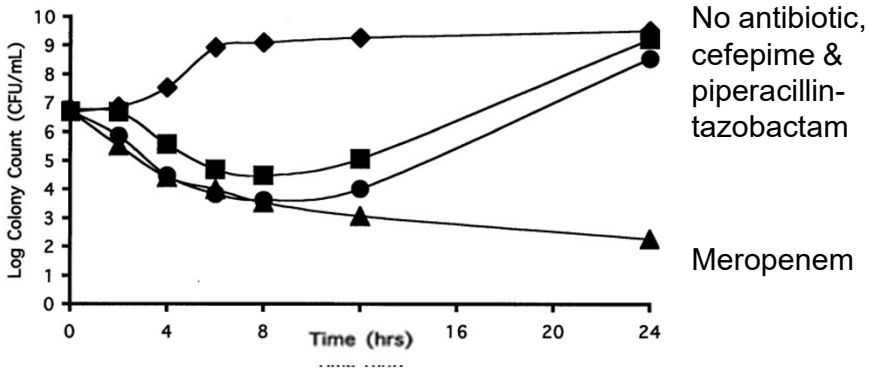
Piperacillin-Tazobactam (PTZ): Inoculum Effect

Caveat: Relevance to clinical practice?



Low inoculum ESBL growth curve



High inoculum ESBL growth curve

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Burgess D, et al. Diag Microbiol Infect Dis 2004; 49:41.

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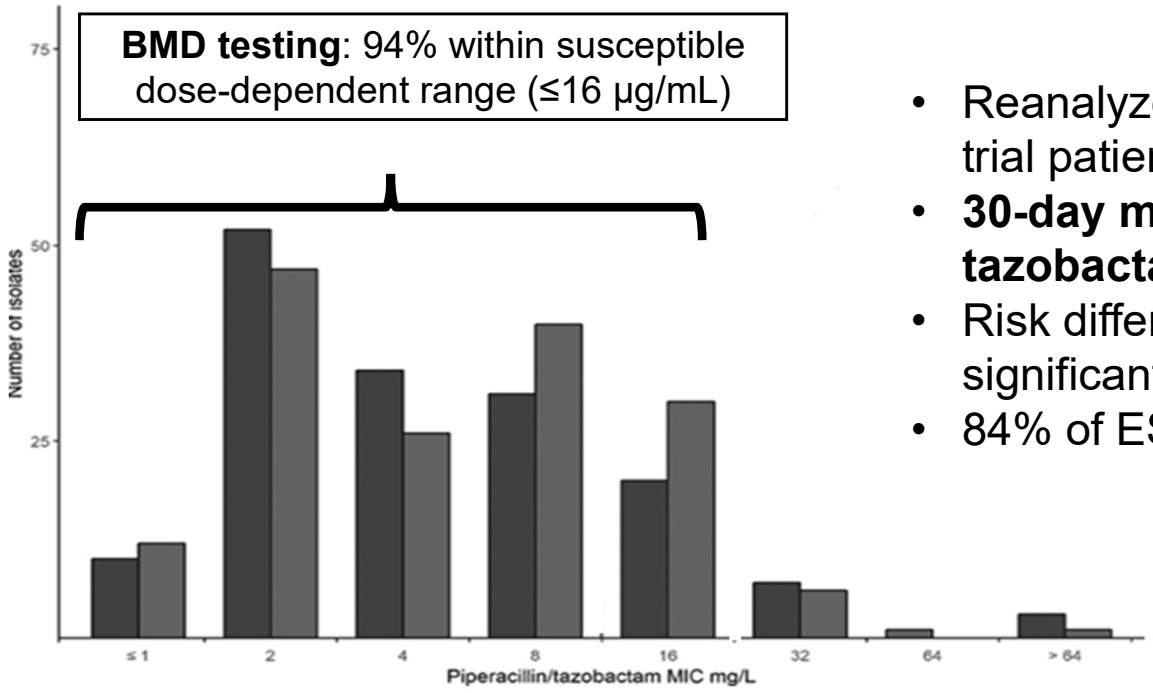
MERINO Trial: MICs for Piperacillin-Tazobactam by BMD

BMD testing: 94% within susceptible dose-dependent range (≤16 µg/mL)



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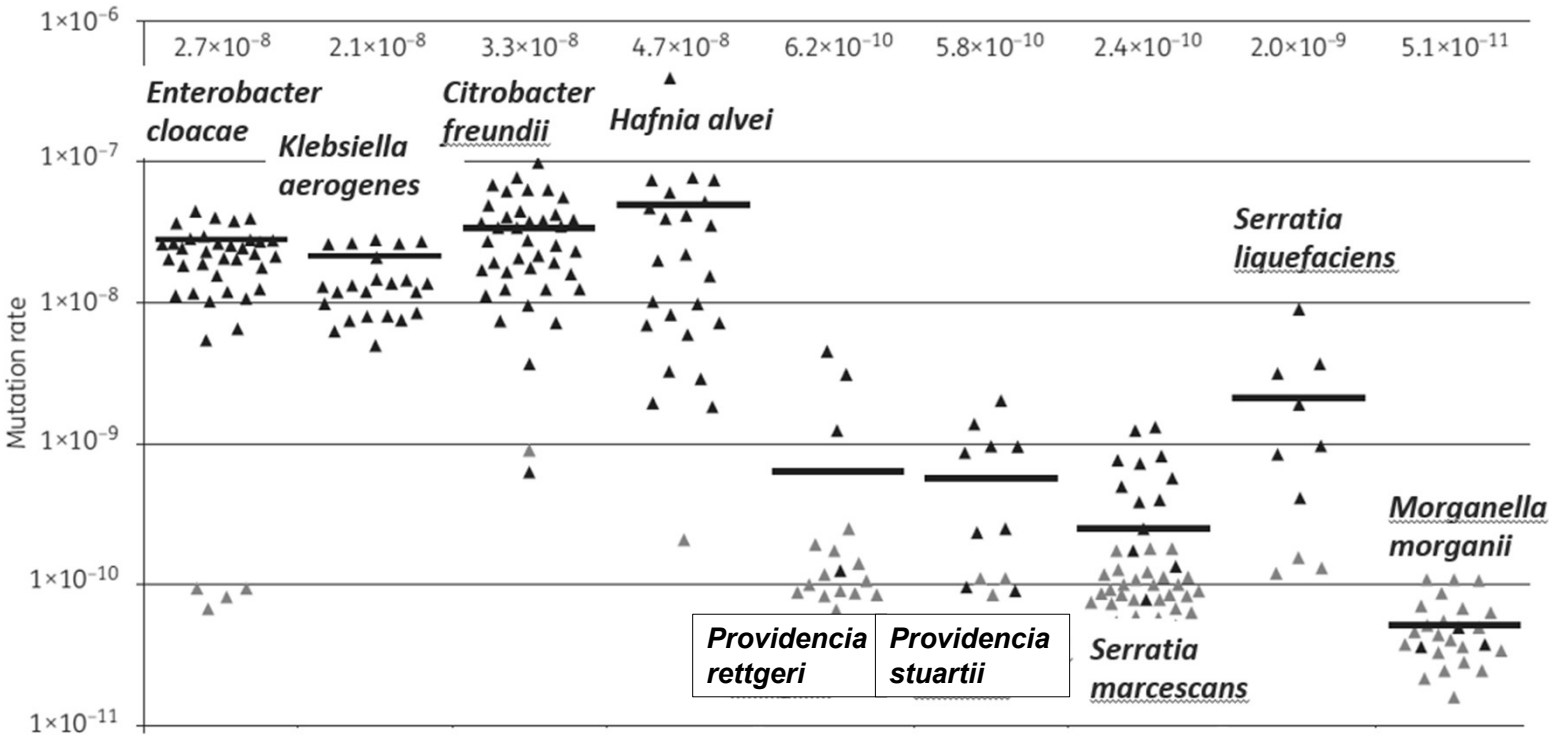

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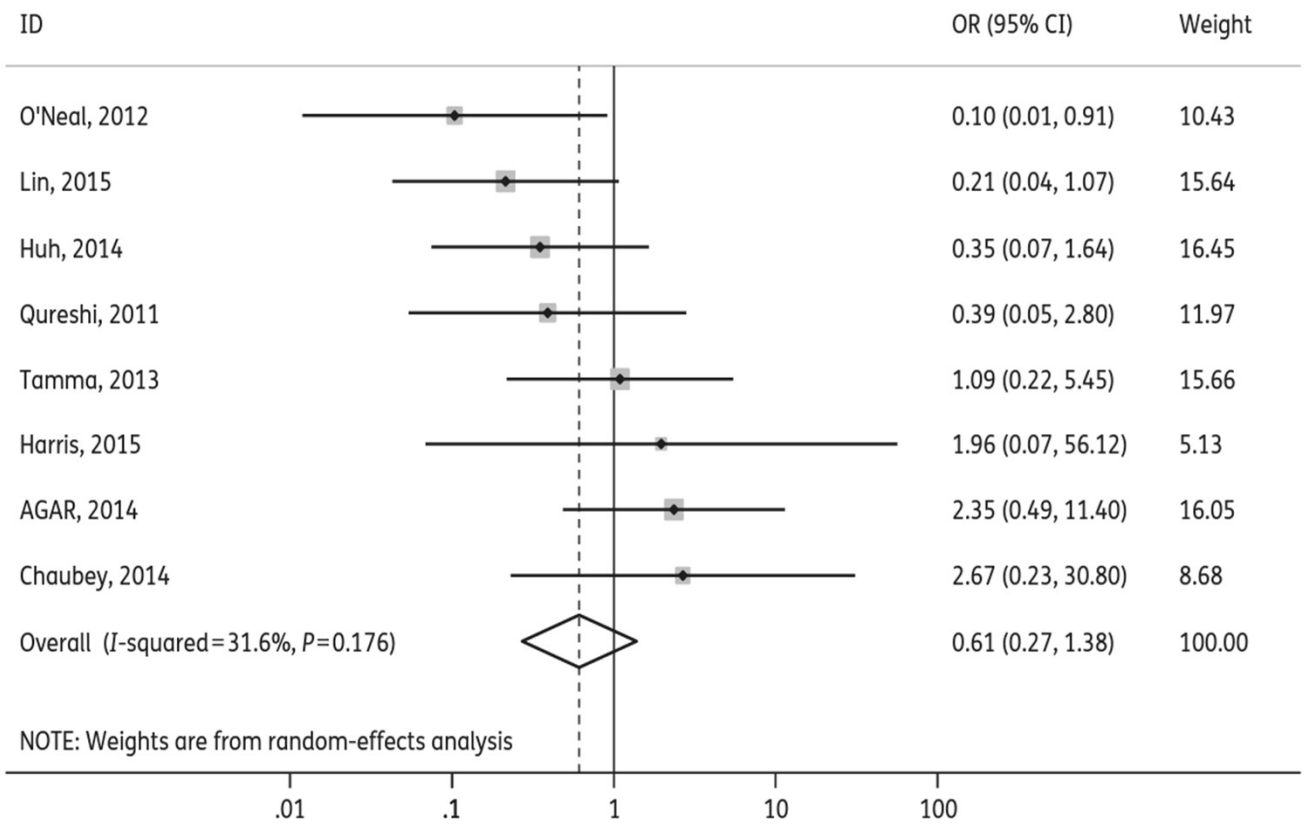

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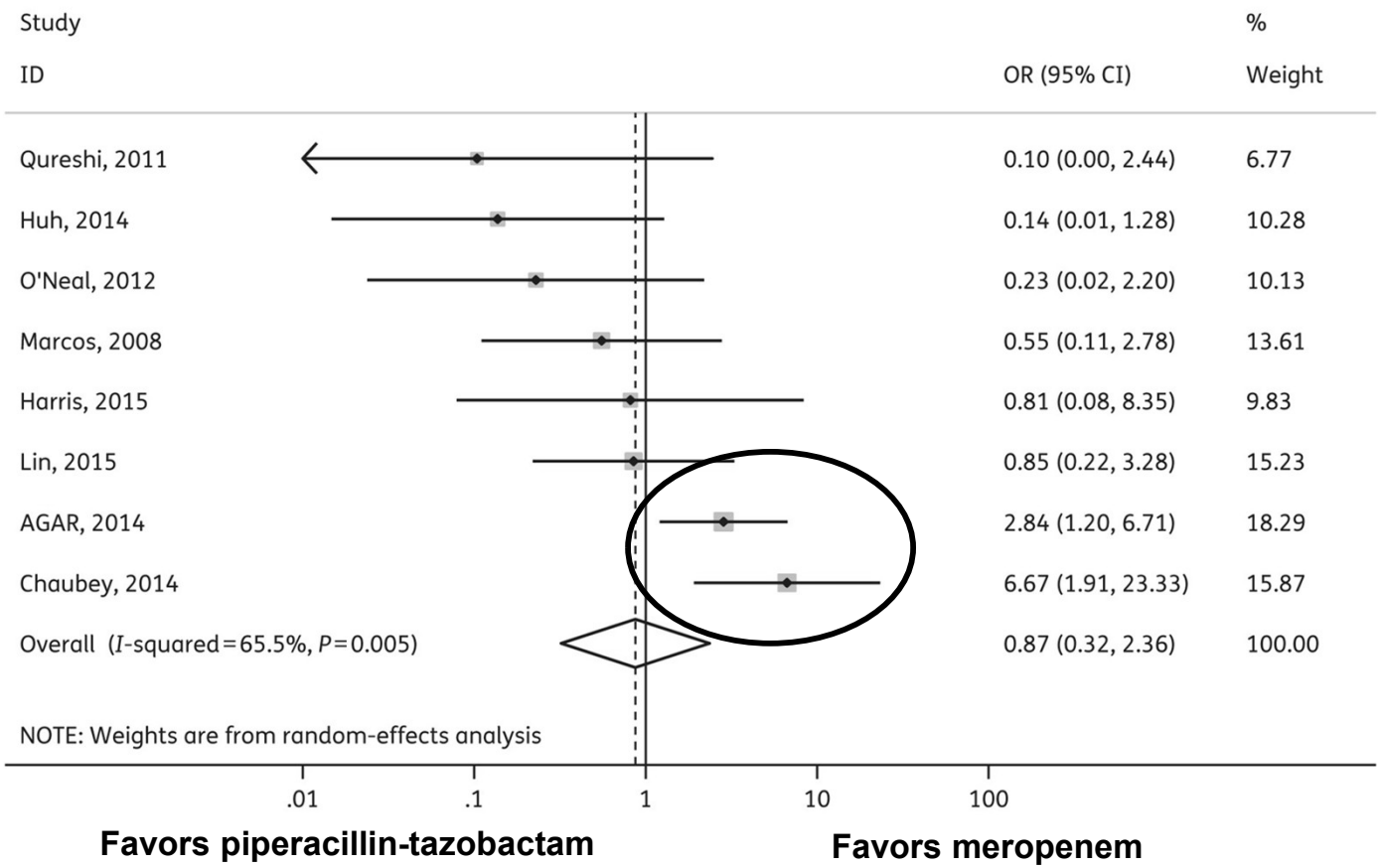

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Saturday, August 22, 2026

04

Infections in Hematopoietic Stem Cell Recipients

Jennifer Saullo, MD

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Infections in Hematopoietic Stem Cell Recipients

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Associate Professor of Medicine
Transplant Infectious Diseases
Duke University Medical Center
Durham, NC

8/5/2026

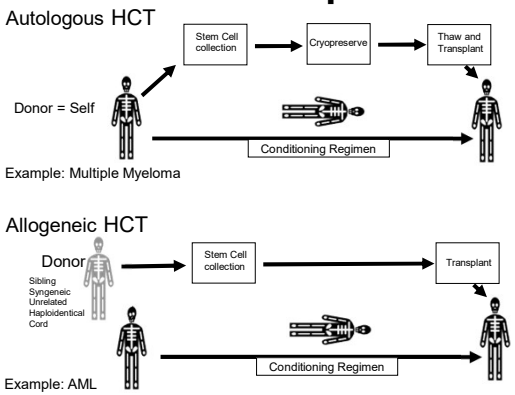
Disclosures of Financial Relationships with Relevant Commercial Interests

- None

Objectives

- Review fundamental concepts of hematopoietic cell transplantation (HCT)
- Review of common infectious complications in HCT
  - Relevance of transplant variables, risks and timeline
  - Differentiation of non-infectious mimics
  - Primary and secondary prophylaxis + recognition of breakthrough infections

Fundamental Concepts



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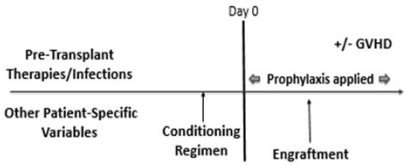
Fundamental Concepts
Transplant Variables and Infection Risk

- Transplant type
  - Autologous vs Allogeneic
- Underlying disease, prior infection
- Donor/recipient age
- HLA matching
  - MRD, MUD, MMRD and UCD
- Conditioning regimen
  - Myeloablative, non-myeloablative and
- Source of stem cells
  - Bone marrow, peripheral blood, cord bl
- Graft manipulation
- Graft versus host disease



Matched-related donor, MRD; Matched-unrelated donor, MUD; Mismatched-related donor, MMRD; UCD, umbilical cord donor; GVD, graft versus host disease.CD

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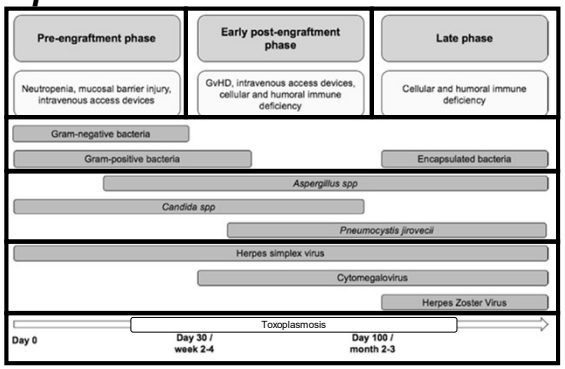
Fundamental Concepts
Transplant Timeline



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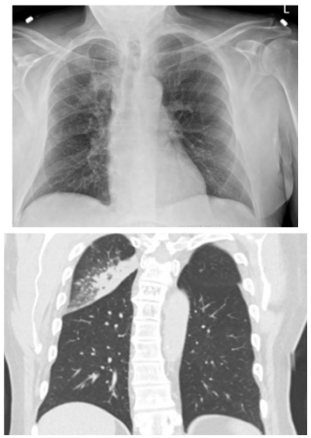
Adapted from: Akhmedov M. Clin Transplant. 2021;35(2):e14172.

Question #1

- 42-year-old male, d+20 following a matched unrelated donor (MUD), non-myeloablative (NMA) HCT develops fevers, cough and a new pulmonary infiltrate.
- Pre-transplant serologies: CMV D+/R-, Toxo D-/R-; recipient otherwise HSV/VZV+
- Exam: T 38.3, BP 120/70, HR 115, SaO2 98% on 1L, rhonchi on R
- Labs: Cr 1.5, ANC 1200/μL, platelets 43. Current prophylaxis includes acyclovir and fluconazole.



Question #1

What is the most likely etiology of his current process?

A. Candida albicans
B. Pseudomonas aeruginosa
C. Cytomegalovirus
D. Parainfluenza virus
E. Hemorrhage

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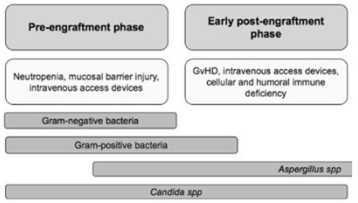
Pulmonary Complications
Hematopoietic Cell Transplant

- Key elements of the question stem
  - Timing post transplant
  - Applied prophylaxis
  - Donor/recipient serologies
- Differential
  - Infection (bacterial, fungal, viral, parasitic)
  - Non-infectious "mimics"

Pulmonary Complications
Infections

- Bacterial pathogens
  - E. coli, P. aeruginosa, S. pneumoniae, S. aureus, K. pneumoniae
  - Aspiration events, particularly with mucositis
- Fungal infections
  - Aspergillus most common (early & late post-transplant)
  - PJP – uncommon early, typically late + consider lapses in prophylaxis, suboptimal regimens



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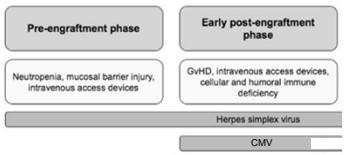
Pulmonary Complications
Infections

- Viral pathogens
  - Community acquired respiratory viruses
    - Influenza, Parainfluenza, RSV, Human metapneumovirus, Adenovirus, Rhinovirus, SARS-CoV-2
    - Increased risk for lower respiratory tract involvement
  - Herpesvirus
    - CMV >> HSV/VZV
    - CMV typically occurs post-engraftment, onset further delayed with primary CMV prophylaxis
- Other (Toxoplasmosis, Strongyloidiasis)



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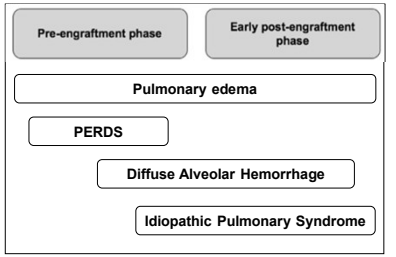
Pulmonary Complications
Non-infectious

- Early non-infectious considerations
  - **Pulmonary edema**
  - **Engraftment syndrome / PERDS**
    - Fever, rash, diffuse pulmonary opacities
  - **Diffuse alveolar hemorrhage**
    - Heterogenous etiology – infection, GVHD, alveolar injury, medications
    - Progressively hemorrhagic return on bronchoalveolar lavage
  - **Idiopathic pulmonary syndrome**
    - Dry cough, hypoxia, diffuse infiltrates



Peri-engraftment respiratory distress syndrome, PERDS.

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Adapted from: Astashchanka A et al. J Clin Med. 2021;10(15):3227.

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Question #2

- A 46-year-old male **18 months** s/p HLA mismatched allogeneic HCT
  - HCT course complicated by GVHD involving the skin, GI tract, and lungs. Treated with steroids 3 months ago
  - One month ago, he had Parainfluenza 3 with chest CT demonstrating tree-in-bud opacities in LLL. Received levofloxacin for 10 days.
  - Now presents with increasing shortness of breath and cough

Question #2
Different Cuts on Same CT

Question #2

Blood cultures are negative. Sputum cultures grow oropharyngeal flora. Serum galactomannan is negative.

What is the ***most likely* etiology of his current process?**

A. Cryptococcus neoformans
B. Escherichia coli
C. Staphylococcus aureus
D. Aspergillus fumigatus
E. Fusarium spp.

Invasive Aspergillosis in HCT

- Most common invasive mold (allogeneic > autologous HCT)
- Pulmonary involvement (IPA) predominates
- Look for specific risks in the question stem
- Bi-modal distribution (d<100, d+180)
- Primary prevention
  - High risk allogeneic HCT- mold-active prophylaxis through at least d +75
  - GVHD (posaconazole A-I; alternative is voriconazole (B-I), isavuconazole also utilized)
- Diagnostic pearls - negative aspergillus GM does NOT exclude IA if on mold-active prophylaxis or non-neutropenic
- Treatment – generally a minimum of 3 months, radiographic resolution + clinical improvement

Risks for Invasive Aspergillosis
Pre-transplant IA
Specific comorbidities – hematologic malignancy, diabetes, Fe overload
Prolonged neutropenia
GVHD
Community acquired respiratory viral infections; CMV reactivation
Environmental exposures (construction, gardening, marijuana)

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Dadwal SS et al. Transplant Cell Ther. 2021;27(3):201.

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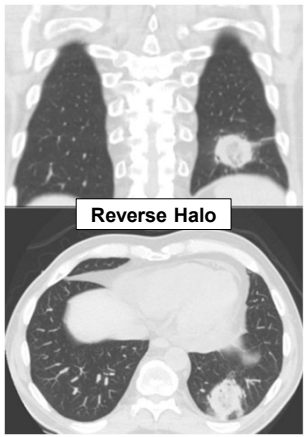
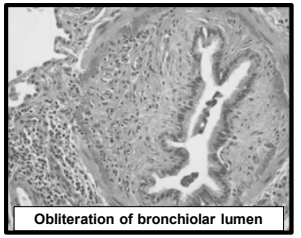
Pulmonary Complications
Late/Post Engraftment +

- Infectious
  - Fungal - Aspergillus, PJP, other molds
  - Bacterial (encapsulated, Nocardia), Mycobacteria
  - Respiratory viruses, CMV
- Non-infectious
  - Organizing pneumonia
  - Bronchiolitis obliterans syndrome

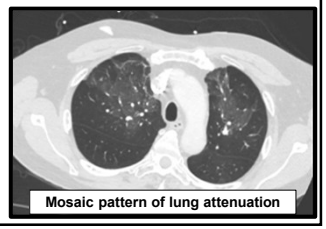


Pulmonary Complications
Bronchiolitis Obliterans

- Chronic GVHD of the lungs
- Inflammatory and fibroproliferative process focused on the terminal bronchioles
- Clinical presentation - cough, increasing shortness of breath and dyspnea on exertion
- Diagnostics
  - PFTs: narrowing of the bronchiolar lumen → airflow obstruction
  - CT imaging: air trapping, "mosaicism"



From: Williams KM et al. JAMA 2009;302(3):306.



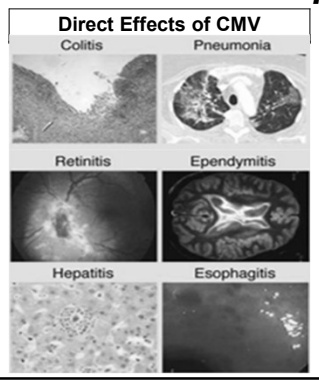
Question #3

50-year-old female with refractory AML is set to receive a matched unrelated donor allogeneic HCT with fludarabine/busulfan and post-transplant cyclophosphamide. CMV serostatus of the donor and recipient is positive.

What is the most appropriate preventative approach?

A. Pre-emptive therapy with letermovir
B. Primary prophylaxis with letermovir
C. Primary prophylaxis with (val)ganciclovir
D. Primary prophylaxis with foscarnet
E. None of the above, the patient is not at risk for CMV infection

CMV Infection in HCT
The "Troll of Transplant"



Indirect Effects of CMV
Bacteremia
Graft versus host disease
Invasive fungal infections
Non-relapse mortality

Figure left, adapted from: Boeckh M, Geballe AP. J Clin Invest 2011;121:1673, Hakki M et al. Transplant Cell Ther. 2021;27(9):707.

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CMV Infection in HCT
The "Troll of Transplant"

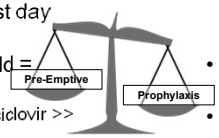
Risks for CMV in HCT
CMV Seropositive recipient (R+ >>> D+/R- >> D-/R-)
Graft versus host disease and applied therapies (e.g., prednisone > 1 mg/kg/day equivalent)
T-cell depletion (e.g., alemtuzumab, ATG)
Cord blood transplant
Haploidentical, mismatched or unrelated donors
Lymphopenia
Older age

Hakki M et al. Transplant Cell Ther. 2021;27(9):707.

CMV Infection in HCT
Prevention[1]

Pre-Emptive

- Weekly CMV DNA PCR monitoring through at least day +100
- CMV DNAemia > threshold = initiation of antiviral
  - Typical therapy – (val)ganciclovir >> foscarnet
  - Induction dosing ~ 2 weeks and until DNAemia clearance



Primary Prophylaxis

- Initiated by day +28 through at least day +100 in highest risk (R+)2
- Extension through day +200 can be considered high risk patients3
- Letermovir (FDA-approved)
  - Lacks side effects - cytopenias and nephrotoxicity
  - Lacks activity against HSV/VZV
  - Relevant DDI (azoles - vori, calcineurin inhibitors)

Hakki M et al. Transplant Cell Ther. 2021;27(9):707.
Marty FM et al. N Engl J Med. 2017; 21;377(25):2433.
Russo D et al. Lancet Haematol. 2024;11(2):e127.

CMV Infection in HCT
Refractory / Resistant CMV

Refractory CMV Infection

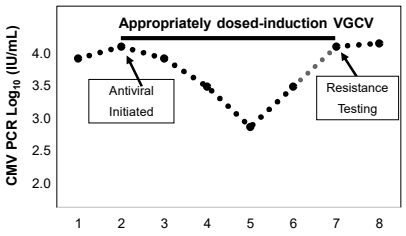
CMV viremia that increases (i.e., >1 log10) OR persists (i.e., ≤1 log10 increase or decrease) after at least 2 weeks of appropriate antiviral therapy

Refractory CMV End-Organ Disease

Worsening signs and symptoms or progression to end-organ disease OR lack of improvement after at least 2 weeks of appropriately dosed antiviral therapy

Resistant CMV Infection

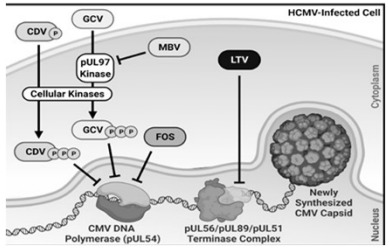
Refractory CMV infection AND viral genetic alteration decreasing susceptibility to 1 or more antiviral drugs



Ljungman P, et al. Clin Infect Dis. 2024;26;79(3):787.

CMV Infection in HCT
Treatment of Infection +/- Resistant / Refractory CMV

- Induction therapy typically with (val)ganciclovir
- Resistance to (val)ganciclovir is rare (compared to SOT)
  - Most failures due to profound immunocompromise – e.g. steroids, other T cell depletion
  - Clues for resistance - long exposure to suboptimal doses, poor cellular immunity
  - Resistant and refractory disease
    - Foscarnet, Maribavir
    - Letermovir is for CMV prevention NOT treatment



CDV, cidofovir; CMV, cytomegalovirus; FOS, foscarnet; GCV, ganciclovir; LTV, letermovir; MBV, maribavir.

Figure from: Saullo JL, Miller RA. Annu Rev Med. 2023;74:89.

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Pneumocystis jirovecii in HCT

- Allogeneic >> Autologous
  - Shift with routine prophylaxis – now a late complication
  - Risks – steroids, T-cell depletion
- Prophylaxis applied at least 6 months post-transplant
  - Primary – sulfamethoxazole-trimethoprim (SMX-TMP)
  - Non SMX-TMP alternatives (less effective, potential for breakthrough)
    - Atovaquone
    - Dapsone
    - Aerosolized pentamidine
- Tropism for lungs, rare disseminated infection
- Radiograph findings – "any and none", most commonly diffuse radiographic infiltrates

Toxoplasmosis in HCT

- Seroprevalence higher in in NE US (30%), foreign born (25-50%)
- Risk in allogeneic HCT >>> autologous HCT
- 90% of cases within the first 6 months post-HCT
  - Most occur between post-transplant months 2 thru 4
  - Over 2/3 represent reactivation in seropositive recipients
- Presentation with fever, pneumonia, encephalitis (recognize the lack of prophylaxis in the question stem)
- Uncommon but deadly - high mortality, diagnosis often delayed

Gajurel K et al. Curr Opin Infect Dis. 2015;28(4):283.

Question #4

35-year-old female, d+80 after allogeneic HCT presenting with **5 days of anorexia, nausea, epigastric pain, and diarrhea**. CMV D-/R+, HSV+, VZV+.

Exam: afebrile, faint maculopapular rash on upper body.

Antimicrobials: acyclovir, letermovir, TMP-SMX and fluconazole.

Labs: ANC 1200, ALC 250. Hepatic panel within normal limits. Stool PCR for norovirus and *C. difficile* negative. Plasma quantitative CMV PCR negative.

What is the most appropriate initial work-up and management?

A. Perform serum varicella zoster virus (VZV) PCR
B. Empiric corticosteroid treatment
C. Blood lipase and amylase
D. Upper and lower endoscopy

Graft Versus Host Disease

- Immune cells from the donor graft recognize host cells as "foreign"
- 3 forms exist: acute, chronic and GVHD overlap (NIH consensus criteria)
- Acute – typically early post transplant
  - Rash +/- fever
  - GI manifestations (nausea, vomiting, anorexia, diarrhea), acute hepatitis
- Chronic – typically later post transplant
  - Can affect virtually any organ
    - Skin - lichen planus, scleroderma-like
    - Liver - hepatitis, cholestatic picture
    - GI tract - nausea, vomiting, chronic diarrhea, weight loss
    - Lungs - bronchiolitis obliterans syndrome
    - Eyes - dry, painful eyes

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GVHD in HCT
GI Manifestations (Infection Mimic)

Hepatitis

- GVHD
- Herpesviruses (CMV, VZV, HSV)
- Other viral hepatitis
  - Hepatitis B (less common A/C/E)
  - Adenovirus

Diarrhea

- GVHD
- CMV
- *C. difficile*
- Norovirus (chronic diarrhea)
- Adenovirus

Question #5

40-year-old male, d+60 following allogeneic HCT from a MUD presents with bloody urine for 6 days. Also has skin GVHD with recent initiation of high-dose prednisone (1 mg/kg/day) with ongoing taper.

Exam demonstrates a faint diffuse erythematous rash.

Cr 1.2, hepatic panel within normal limits. CMV quantitative plasma PCR is negative.

What is the most likely etiology?

A. Cyclophosphamide
B. Cytomegalovirus
C. Epstein-Barr virus
D. BK virus
E. HHV-6

Hemorrhagic Cystitis in HCT

- Early occurrence
  - Following conditioning regimen
  - Therapy-related (e.g., cyclophosphamide, busulfan)
- Later occurrence
  - Post-engraftment
  - Viral infection (e.g., BK virus, adenovirus)

Question #6

68-year-old male with CMML (CMV, HSV and VZV seropositive) underwent a reduced intensity allogeneic HCT with multiple complications including pneumonia, BK cystitis and acute graft versus host of the GI tract requiring recent initiation of high dose steroids. He presents with fever, lethargy, confusion and appreciable weakness.

- Head CT is non-focal but brain MRI reveals mild flair hyperintensity with diffusion restriction in the right hippocampus and parahippocampal gyrus
- Plasma HHV6 PCR is 1600 copies/mL

What are the best next steps in management?

A. Initiation of IV acyclovir for HHV-6 encephalitis, no further diagnostic work-up required
B. Initiation of IV ganciclovir for HHV-6 encephalitis, no further diagnostic work-up required
C. Initiation of empiric IV ganciclovir and pursue additional diagnostics with lumber puncture
D. Initiation of IV foscarnet for HHV-6 encephalitis, no further diagnostic work-up required
E. Initiation of empiric IV letermovir and pursue additional diagnostics with brain biopsy

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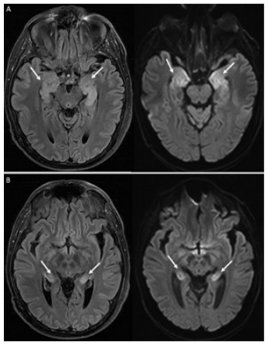
Human Herpes Virus-6 (HHV-6)

- Ubiquitous herpesvirus, seroprevalence > 95% after age 2
- Viremia common post-allogeneic HCT (~ 40-70%)
- Clinical associations - rash, fever, myelosuppression, hepatitis, pneumonitis
- **Meningoencephalitis**** (most testable manifestation; HHV-6B)
  - Nonspecific presentation (confusion, memory loss, seizures)
  - Generally early post-transplant (before day +100), uncommon (1-3% allo HCT)
  - Risks - mismatched/unrelated donors, umbilical cord blood, T-cell depletion, GVHD and steroids
  - Diagnosis via history, MRI/EEG (temporal region), PCR of CSF
- Chromosomal integration (1%)
- Treatment: ganciclovir, foscarnet >> cidofovir (acyclovir resistant, letermovir lacks activity)



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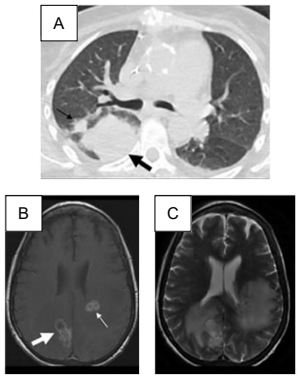
Marcelis S et al. J Belg Soc Radiol. 2022;06(1):93.

Neurologic Syndromes in HCT

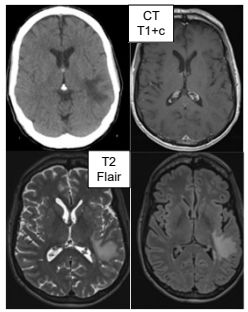
- Infection
  - Pulmonary – CNS lesions
    - Invasive fungal infections
    - Nocardia
    - Toxoplasmosis
  - Viral pathogens
    - Herpes viruses – HSV, VZV, CMV, **HHV-6***, EBV
    - West Nile virus
    - **JCV – PML***



Progressive Multifocal Leukoencephalopathy (PML)

- Demyelinating CNS infection due to reactivation of JC virus
- Rare, described in multiple populations - malignant hematology (HL, CLL), HIV, SOT/HCT, inflammatory/autoimmune disorders (including multiple sclerosis)
- Specific risks include applied immunomodulatory therapies - **monoclonal antibodies, specifically natalizumab**; others rituximab, efalizumab, eculizumab, belatacept, ibrutinib*
- Clinical presentation
  - Months to years after HCT
  - Progressive, subacute neurological deficits - cognitive impairment, limb and gait ataxia, weakness, visual changes, hemiparesis, aphasia
- Diagnostics - CNS imaging (*asymmetry, periventricular/subcortical, non-contrast enhancing, spares grey matter), CSF PCR, brain biopsy
- Treatment - no effective treatment; immune restoration key

*list not all-inclusive



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Neurologic Syndromes in HCT

- Infection
  - Viral pathogens
    - Herpes viruses
    - West Nile virus
    - JCV
- Pulmonary – CNS lesions
  - Invasive fungal infections
  - Nocardia
  - Toxoplasmosis
- Non-Infectious
  - Antibiotics – carbapenems, cefepime
  - Posterior reversible encephalopathy syndrome (PRES)

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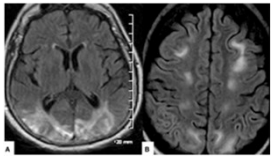
Posterior Reversible Encephalopathy Syndrome (PRES)

- AKA reversible posterior leukoencephalopathy syndrome (RPLS)
- Uncommon overall in HCT (<10%)
- Risks / conditions include hypertension, renal disease, autoimmune disorders and applied immunosuppressive / immunomodulatory therapies (CNI, cyclophosphamide)
- Clinical presentation – acute to sub-acute, altered consciousness, headaches, visual disturbances, seizures
- Diagnostics – neuroimaging (CT/MRI)
  - Cortical and subcortical involvement (image A)
  - Bilateral vasogenic edema in occipital and parietal regions +/- watershed areas (image B)
- Treatment – supportive, reversal of associated culprit +/- antiseizure medications



From: Shankar J, Banfield J. Can Assoc Radiol J. 2017;68(2):147

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Other Viral Infections in HCT *HSV/VZV**

Herpes Simplex Virus (HSV)

- Risk generally greatest early post-transplant
- Clinical presentation
  - Mucositis /esophagitis most common
  - Visceral, neurologic and ocular less common
- Resistance emergence (acyclovir/valacyclovir)
  - Uncommon (3.5-10%)
  - Mechanism: altered thymidine kinase (UL23 mutation) >>> altered DNA polymerase (UL30 mutation)

Varicella Zoster Virus (VZV)

- Risk generally late post-transplant
- Clinical presentation
  - Cutaneous most common
  - Visceral (pneumonitis, hepatitis), neurologic and ocular less common
    - Can occur without skin lesions (consider in case of severe abdominal pain, transaminitis & without rash)
- Resistance rare

*Think about "holes" in prophylaxis, breakthrough/resistance

Pearls

- Fundamentals – Risks (temporality, prophylaxis)
  - Early – mucositis, neutropenia
  - Late – GVHD (steroids, asplenia, T cell dysfunction and other delays in IRC)
- Syndromes
  - Early pulmonary syndromes
    - Bacterial, fungal pneumonia
    - Non-infectious: Alveolar hemorrhage, IPS, engraftment
  - Late pulmonary syndromes
    - CMV, respiratory viruses, fungal infections
    - Non-infectious: BO, organizing pneumonia
- Hemorrhagic cystitis
  - BK >> adenovirus
  - Non-infectious: conditioning
- Diarrhea – colitis – hepatitis
  - Herpesviruses
  - Non-infectious: GVHD
- Neurologic syndromes
  - Herpesviruses (+HHV-6), West Nile, angioinvasive molds, toxoplasmosis
  - PML
  - Non-infectious: PRES, antibiotics

Thank You

Questions/Comments:
jennifer.horan@duke.edu

Special Thanks to Kieren Marr, MD

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Additional References

- Vaccinations and HCT
  - Carpenter PA, Englund JA. How I vaccinate blood and marrow transplant recipients. Blood. 2016 Jun 9;127(23):2824-32.
  - Pergam SA, Englund JA, Kamboj M, Gans HA, Young JH, Hill JA, Savani B, Chemaly RF, Dadwal SS, Storek J, Duchin J, Carpenter PA. Preventing Measles in Immunosuppressed Cancer and Hematopoietic Cell Transplantation Patients: A Position Statement by the American Society for Transplantation and Cellular Therapy. Biol Blood Marrow Transplant. 2019 Nov;25(11):e321-e330.

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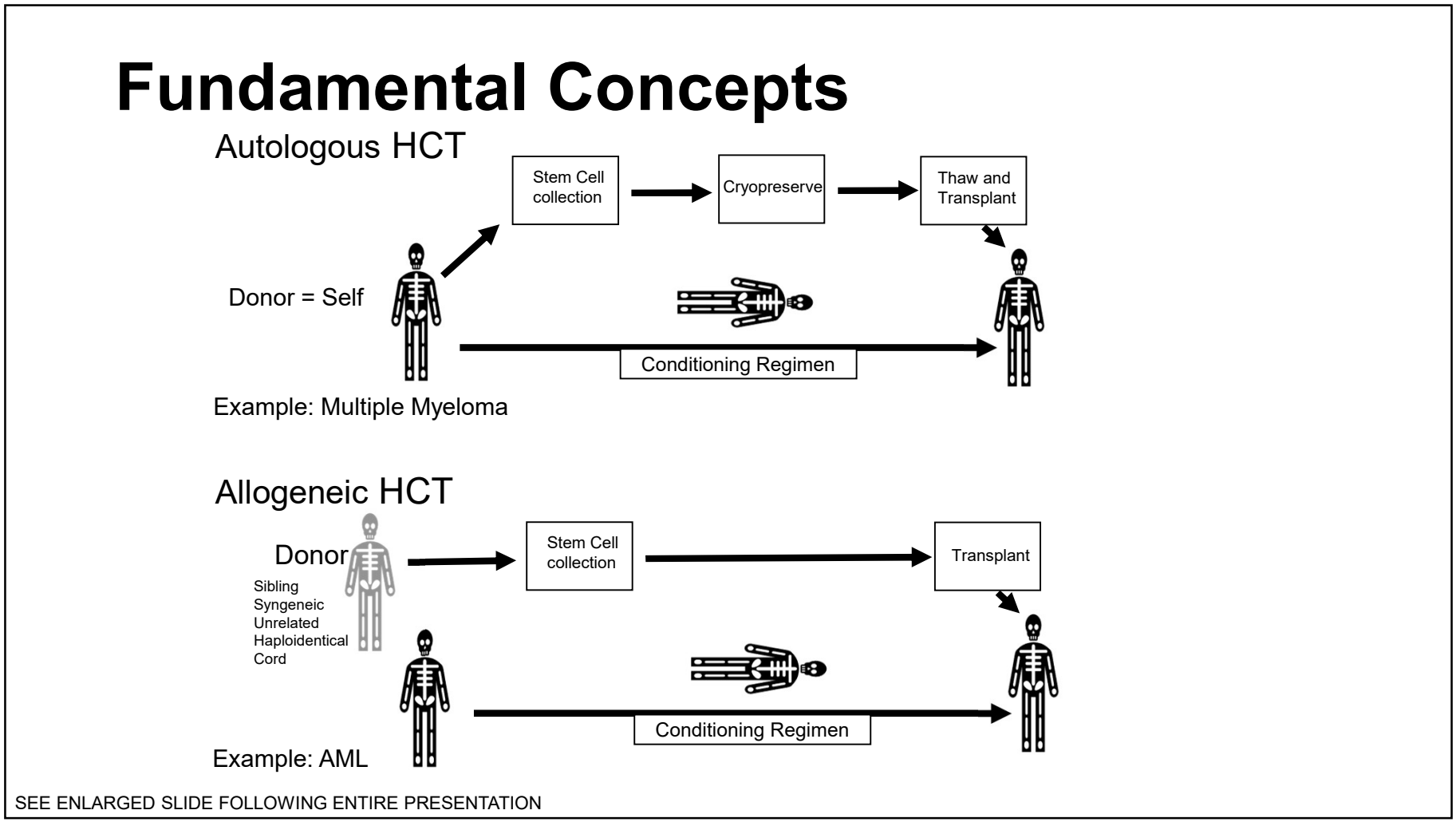
Fundamental Concepts



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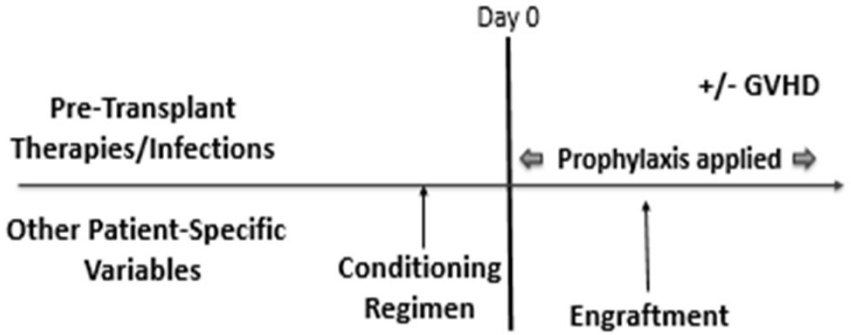
Fundamental Concepts
Transplant Variables and Infection Risk

- Transplant type
  - Autologous vs Allogeneic
- Underlying disease, prior infection
- Donor/recipient age
- HLA matching
  - MRD, MUD, MMRD and UCD
- Conditioning regimen
  - Myeloablative, non-myeloablative and
- Source of stem cells
  - Bone marrow, peripheral blood, cord b
- Graft manipulation
- Graft versus host disease



Matched-related donor, MRD;
Matched-unrelated donor, MUD;
Mismatched-related donor, MMRD;
UCD, umbilical cord donor; GVD, graft versus host disease.CD

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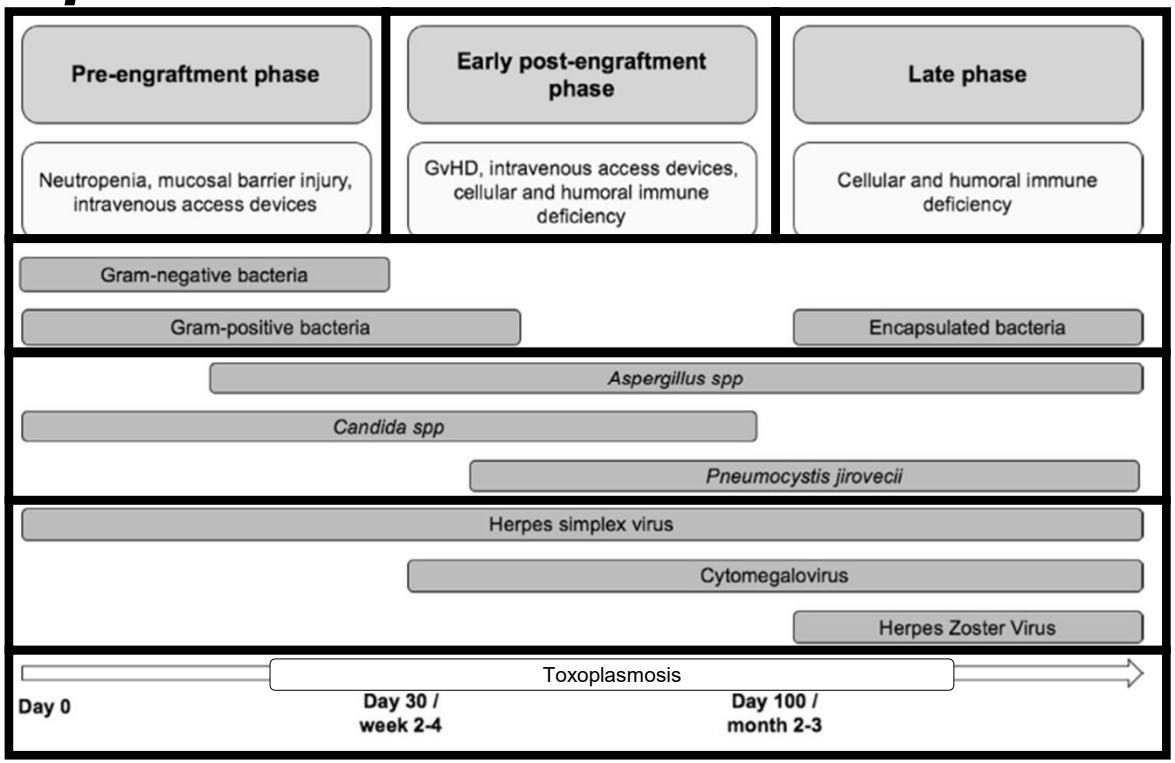
Fundamental Concepts
Transplant Timeline



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Adapted from: Akhmedov M. Clin Transplant. 2021;35(2):e14172.

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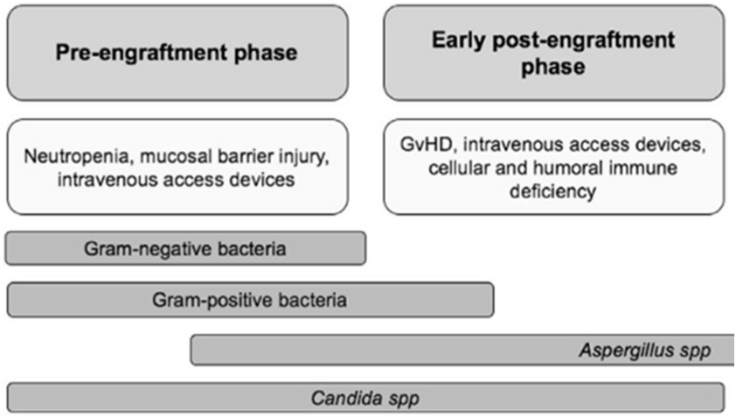
Pulmonary Complications
Infections

- Bacterial pathogens
  - E. coli, P. aeruginosa, S. pneumoniae, S. aureus, K. pneumoniae
  - Aspiration events, particularly with mucositis
- Fungal infections
  - Aspergillus most common (early & late post-transplant)
  - PJP – uncommon early, typically late + consider lapses in prophylaxis, suboptimal regimens



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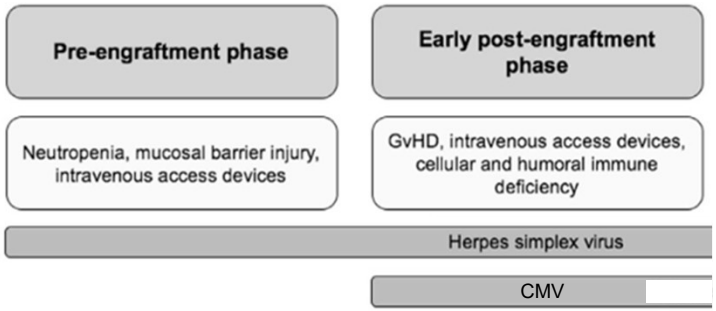
Pulmonary Complications
Infections

- Viral pathogens
  - Community acquired respiratory viruses
    - Influenza, Parainfluenza, RSV, Human metapneumovirus, Adenovirus, Rhinovirus, SARS-CoV-2
    - Increased risk for lower respiratory tract involvement
  - Herpesvirus
    - CMV >> HSV/VZV
    - CMV typically occurs post-engraftment, onset further delayed with primary CMV prophylaxis
- Other (Toxoplasmosis, Strongyloidiasis)



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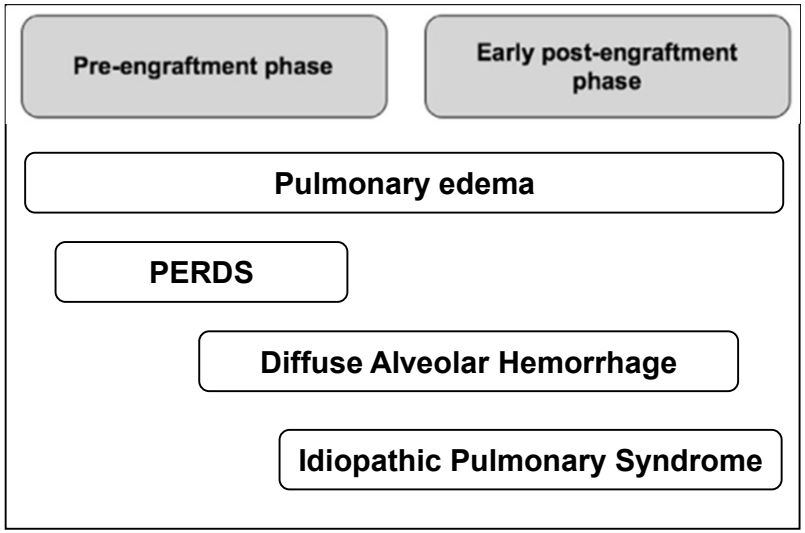
Pulmonary Complications
Non-infectious

- Early non-infectious considerations
  - **Pulmonary edema**
  - **Engraftment syndrome / PERDS**
    - Fever, rash, diffuse pulmonary opacities
  - **Diffuse alveolar hemorrhage**
    - Heterogenous etiology – infection, GVHD, alveolar injury, medications
    - Progressively hemorrhagic return on bronchoalveolar lavage
  - **Idiopathic pulmonary syndrome**
    - Dry cough, hypoxia, diffuse infiltrates



Peri-engraftment respiratory distress syndrome, PERDS.

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Adapted from: Astashchanka A et al. J Clin Med. 2021;10(15):3227.

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Invasive Aspergillosis in HCT

- Most common invasive mold (allogeneic > autologous HCT)
- Pulmonary involvement (IPA) predominates
- Look for specific risks in the question stem
- Bi-modal distribution (d<100, d+180)
- Primary prevention
  - High risk allogeneic HCT- mold-active prophylaxis through at least d +75
  - GVHD (posaconazole A-I; alternative is voriconazole (B-I), isavuconazole also utilized)
- Diagnostic pearls - negative aspergillus GM does NOT exclude IA if on mold-active prophylaxis or non-neutropenic
- Treatment – generally a minimum of 3 months, radiographic resolution + clinical improvement

Risks for Invasive Aspergillosis
Pre-transplant IA
Specific comorbidities – hematologic malignancy, diabetes, Fe overload
Prolonged neutropenia
GVHD
Community acquired respiratory viral infections; CMV reactivation
Environmental exposures (construction, gardening, marijuana)

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Dadwal SS et al. Transplant Cell Ther. 2021;27(3):201.

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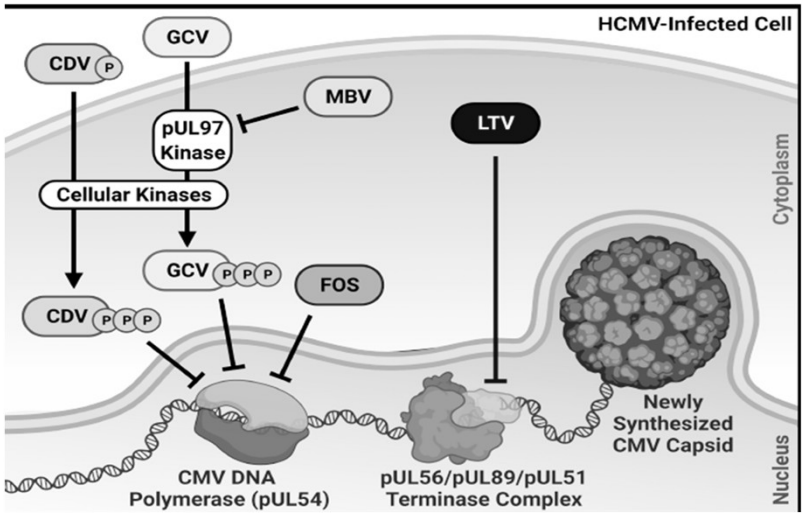
CMV Infection in HCT

Treatment of Infection +/- Resistant / Refractory CMV

- Induction therapy typically with (val)ganciclovir
- Resistance to (val)ganciclovir is rare (compared to SOT)
  - Most failures due to profound immunocompromise – e.g. steroids, other T cell depletion
  - Clues for resistance - long exposure to suboptimal doses, poor cellular immunity
  - Resistant and refractory disease
    - Foscarnet, Maribavir
    - Letermovir is for CMV prevention NOT treatment



CDV, cidofovir; CMV, cytomegalovirus; FOS, foscarnet; GCV, ganciclovir; LTV, letermovir; MBV, maribavir.

Figure from: Saullo JL, Miller RA. Annu Rev Med. 2023;74:89.

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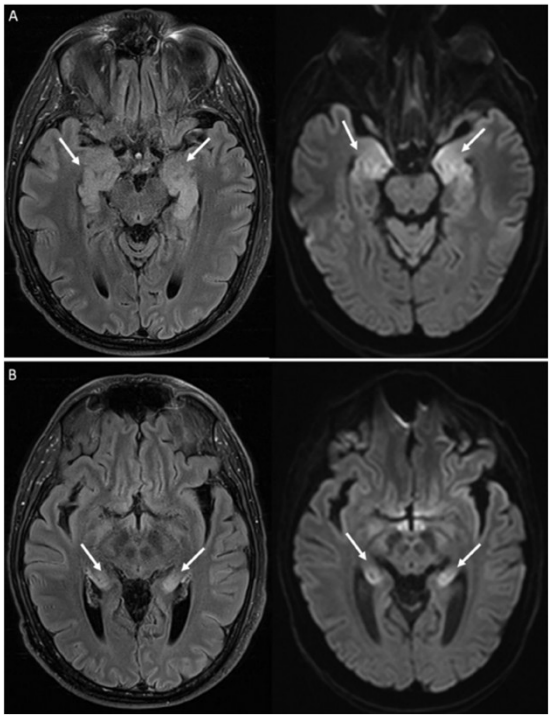
Human Herpes Virus-6 (HHV-6)

- Ubiquitous herpesvirus, seroprevalence > 95% after age 2
- Viremia common post-allogeneic HCT (~ 40-70%)
- Clinical associations - rash, fever, myelosuppression, hepatitis, pneumonitis
- **Meningoencephalitis**** (most testable manifestation; HHV-6B)
  - Nonspecific presentation (confusion, memory loss, seizures)
  - Generally early post-transplant (before day +100), uncommon (1-3% allo HCT)
  - Risks - mismatched/unrelated donors, umbilical cord blood, T-cell depletion, GVHD and steroids
  - Diagnosis via history, MRI/EEG (temporal region), PCR of CSF
- Chromosomal integration (1%)
- Treatment: ganciclovir, foscarnet >> cidofovir (acyclovir resistant, letermovir lacks activity)



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Marcelis S et al. J Belg Soc Radiol. 2022;06(1):93.

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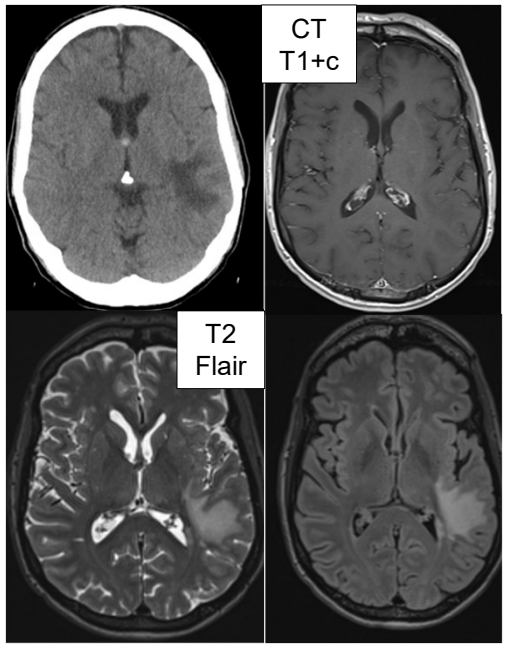
Progressive Multifocal Leukoencephalopathy (PML)

- Demyelinating CNS infection due to reactivation of JC virus
- Rare, described in multiple populations - malignant hematology (HL, CLL), HIV, SOT/HCT, inflammatory/autoimmune disorders (including multiple sclerosis)
- Specific risks include applied immunomodulatory therapies **- monoclonal antibodies, specifically natalizumab**; others rituximab, efalizumab, eculizumab, belatacept, ibrutinib*
- Clinical presentation
  - Months to years after HCT
  - Progressive, subacute neurological deficits - cognitive impairment, limb and gait ataxia, weakness, visual changes, hemiparesis, aphasia
- Diagnostics - CNS imaging (*asymmetry, periventricular/subcortical, non-contrast enhancing, spares grey matter), CSF PCR, brain biopsy
- Treatment - no effective treatment; immune restoration key

*list not all-inclusive



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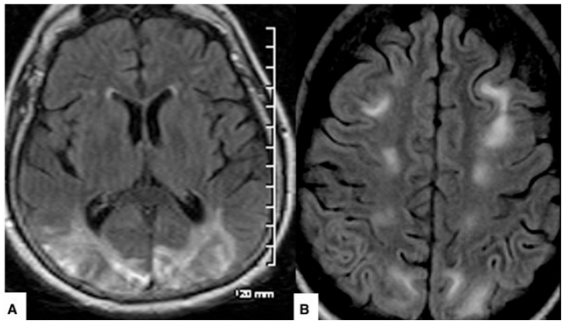
Posterior Reversible Encephalopathy Syndrome (PRES)

- AKA reversible posterior leukoencephalopathy syndrome (RPLS)
- Uncommon overall in HCT (<10%)
- Risks / conditions include hypertension, renal disease, autoimmune disorders and applied immunosuppressive / immunomodulatory therapies (CNI, cyclophosphamide)
- Clinical presentation – acute to sub-acute, altered consciousness, headaches, visual disturbances, seizures
- Diagnostics – neuroimaging (CT/MRI)
  - Cortical and subcortical involvement (image A)
  - Bilateral vasogenic edema in occipital and parietal regions +/- watershed areas (image B)
- Treatment – supportive, reversal of associated culprit +/- antiseizure medications



From: Shankar J, Banfield J. Can Assoc Radiol J. 2017;68(2):147

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Saturday, August 22, 2026

BR1

Board Review Day 1

Drs. Patel (Moderator),
Alexander, Pavia, Saullo, and Tamma

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Board Review: Day 1

Moderator: Robin Patel, MD

Faculty: Drs. Alexander, Pavia, Saullo, and Tamma

7/29/2026

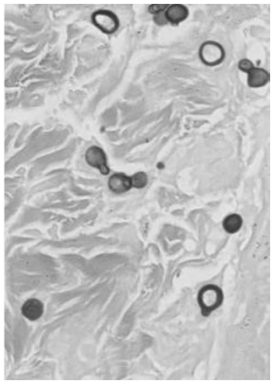
#1 **A CMV seronegative renal transplant recipient received an allograft from a CMV seropositive donor. Valganciclovir prophylaxis was started. After one month, he developed refractory leukopenia despite optimal dosing of valganciclovir for renal function and stopping mycophenolate.**

What is the best option for CMV prophylaxis?

A. **Stop valganciclovir; start every other week preemptive monitoring with a blood-based CMV PCR test**
B. **Stop valganciclovir and start valacyclovir**
C. **Stop valganciclovir and start letermovir**
D. **Stop valganciclovir and start maribavir**
E. **Decrease to half dose valganciclovir**

#2 **A 32-year-old woman in Wisconsin who worked as a farmer, presents to her family physician in June with a 3-week history of low-grade fever, myalgias, and a productive cough, and a skin lesion on her arm that developed over the previous week. The physician found an infiltrate on chest x-ray and collected sputum and a biopsy from the skin lesion for culture and histopathology.**

The organisms shown here were seen when the tissue was stained with a silver stain. After 14 days, a mold grew in the fungal culture.



#2 **Which of the following is the most likely pathogen?**

A. ***Blastomyces* species**
B. ***Candida* species**
C. ***Coccidioides* species**
D. ***Cryptococcus* species**
E. ***Histoplasma* species**

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#3 A 72-year-old retired firefighter who has a history of chronic obstructive lung disease is seen in the emergency department because of 96 hours of cough, chills, sore throat, and body aches. He lives in an assisted care facility where he has his own room but takes meals in a congregate dining room.

He reports that several other residents and servers in the dining room have been coughing. In the emergency department, a test for influenza is positive. He is hypoxemic and admitted to the intensive care unit.

#3 Regarding treatment for influenza, what should he receive?

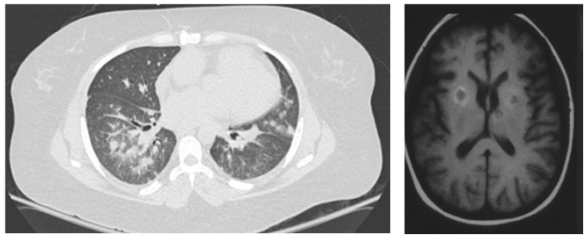
A. No specific anti-viral because the patient has been ill for substantially more than 48 hours
B. Baloxavir
C. Peramivir
D. Oseltamivir
E. Zanamivir

#4 A 50-year-old woman is admitted with 1 month of fever, dyspnea, and confusion. She underwent heart transplantation 15 months ago from a donor who was seropositive for cytomegalovirus (CMV), Epstein-Barr virus (EBV), and *Toxoplasma*, while she was seropositive for CMV but seronegative for EBV and *Toxoplasma*.

She completed 3 months of valganciclovir prophylaxis and 12 months of sulfamethoxazole-trimethoprim prophylaxis and is on chronic immunosuppression with tacrolimus, prednisone, and mycophenolate.

On presentation: T 39.0°C, HR 130, BP 100/60, and RR 30, SpO_2 82% on room air.

#4 Relevant computed tomography (CT) imaging of the lungs (left) and brain magnetic resonance imaging (MRI, right) are below.



Initial microbial testing, including blood cultures, serum cryptococcal antigen, and CMV quantitative plasma PCR, is negative.

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BOARD REVIEW DAY 1

#4 Which of the following prophylactic antimicrobial therapies would most likely have prevented this complication?

A. Acyclovir
B. Valganciclovir
C. Letermovir
D. Fluconazole
E. Sulfamethoxazole-trimethoprim

3 of 4

BOARD REVIEW DAY 1

#5 A 46-year-old man presents for follow-up after being diagnosed with non-purulent cellulitis of the lower leg. Three days ago, he was started on cephalexin. At that time, he had fever, localized erythema, and tenderness over the anterior shin.

Today, he reports that his fever and malaise have resolved, and that his leg is less painful. On examination, the affected area remains warm and erythematous. The area of erythema is slightly larger than at the initial visit. There are no bullae, fluctuance, or necrosis, and vital signs are normal.

1 of 3

BOARD REVIEW DAY 1

#5 Which of the following is the most appropriate next step in management?

A. Switch to intravenous antibiotics
B. Continue the current oral antibiotic regimen to complete a 5-day course
C. Add trimethoprim–sulfamethoxazole for MRSA coverage
D. Refer the patient to the emergency department for further evaluation
E. Continue the current oral antibiotic regimen to complete a 10-day course

2 of 3

BOARD REVIEW DAY 1

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

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

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

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

1 of 4

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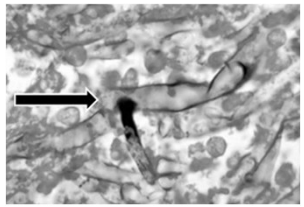
#6 1,3 beta D glucan had fallen to 216 pg/ml and serum galactomannan was negative.

Bronchoalveolar lavage fluid cultures were negative and the bronchoalveolar lavage fluid galactomannan was negative.

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



Grocott-Gömöri methenamine silver (GMS) 400x

#6 What is the most likely pathogen?

A. *Cryptococcus neoformans*
B. *Aspergillus terreus*
C. *Scedosporium apiospermum* complex
D. *Cunninghamella bertholletiae*
E. *Fusarium solani*

#7 A 64-year-old man with a prosthetic aortic valve presents with fever and general malaise of four weeks duration. He lives in an urban area of the US and has no unusual exposures.

He denies having taken any recent antibiotics.

Echocardiography shows a 2 mm vegetation on his aortic valve with mild aortic regurgitation.

Three sets of blood cultures are negative after five days of incubation.

#7 Which of the following is most likely to be helpful?

A. Serologic testing for *Bartonella* species and *Coxiella burnetii*
B. Fungal and mycobacterial blood cultures
C. Three further sets of blood cultures
D. Blood PCR for *Tropheryma whipplei*
E. Serologic testing for *Mycoplasma pneumoniae* and *Legionella* species

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#8 A 42-year-old Tennessee farmer is seen for fever that has been present for five days. He is also experiencing pronounced fatigue and intermittent diarrhea.

For the two weeks before he became ill, he had been working in a field clearing brush and reported removing numerous ticks from his body on an almost daily basis. His exam is unremarkable except for fever.

He is leukopenic, thrombocytopenic, and has elevated aminotransferases. A presumptive diagnosis of ehrlichiosis is made.

PCR studies for *Ehrlichia* and *Anaplasma* are sent, and he is given doxycycline. After five days of doxycycline therapy, he is not improved.

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

A. Phlebovirus
B. Babesia
C. Scrub typhus (*Orientia tsutsugamushi*)
D. *Rickettsia typhi* (Murine typhus)
E. Adenovirus

#9 A 30-year-old woman with acute myelogenous leukemia underwent allogeneic hematopoietic cell transplantation from a matched unrelated donor. She has myeloid engraftment on day 10 but post-transplant course has been complicated by skin graft-versus-host disease for which she has been receiving high-dose corticosteroids and tacrolimus.

Her prophylaxis includes acyclovir, letermovir, inhaled pentamidine, and posaconazole.

She is admitted on post-transplant day +45 with progressive confusion and irritability. She is initially afebrile with stable vitals, but soon after admission develops a generalized tonic-clonic seizure.

#9 MRI demonstrates bilateral symmetric hyperintensities in the medial temporal lobes.

Labs demonstrate a sodium of 126 mEq/L, creatinine of 0.7 mg/dL, a normal hepatic panel, and a WBC of 1.9 x 10^3/μL.

Lumbar puncture demonstrates a normal opening pressure and a lymphocyte-predominant pleocytosis (30 nucleated cells/μL – 95% lymphocytes), a mildly elevated CSF protein, and normal CSF glucose. Additional CSF studies are pending.

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#9 **Which of the following is the most appropriate next step in management?**

A. Intravenous liposomal amphotericin B plus flucytosine
B. Intravenous IV foscarnet
C. Cessation of tacrolimus
D. Intravenous IV acyclovir
E. Rituximab

#10 **A 63-year-old man with type 2 diabetes mellitus and peripheral neuropathy presents with several weeks of progressive left foot pain, intermittent fevers, and a chronic plantar ulcer.**

On admission, his temperature is 38.3°C, heart rate is 102 beats/min, blood pressure is 132/76 mm Hg, and oxygen saturation is 98% on room air.

Examination demonstrates a 2-cm ulcer over the plantar aspect of the left first metatarsal with surrounding erythema and probing to bone.

Laboratory studies reveal a white blood cell count of 10,800 cells/μL, erythrocyte sedimentation rate of 84 mm/hour, serum creatinine of 0.9 mg/dL, and normal liver enzyme levels.

#10 **MRI of the left foot demonstrates osteomyelitis involving the first metatarsal. Bone biopsy cultures grow *Escherichia coli* and *Bacteroides fragilis*. Blood cultures remain negative.**

Because the patient declines surgical amputation, he is treated medically with a planned 6-week course of intravenous ceftriaxone plus oral metronidazole for chronic diabetic foot osteomyelitis.

Four weeks after initiating therapy, he returns to the infectious diseases clinic with several days of progressive gait instability, dizziness, slurred speech, and increasing confusion noted by his family.

#10 **He denies headache, fever, or new focal weakness. Vital signs are normal. Neurologic examination demonstrates dysarthria and truncal and gait ataxia without focal motor or sensory deficits.**

Complete blood count, comprehensive metabolic panel, serum glucose, and renal and hepatic function are unchanged from baseline.

MRI of the brain demonstrates bilateral symmetric T2/FLAIR hyperintense lesions involving the cerebellar dentate nuclei without evidence of acute infarction or mass effect.

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#10 **Which of the following is the most appropriate next step in management?**

A. Discontinue ceftriaxone
B. Discontinue metronidazole
C. Obtain blood cultures
D. Perform lumbar puncture

#11 **A 62-year-old patient with end stage renal disease requiring hemodialysis is scheduled for a living related kidney transplant in one month.**

He is referred to you for a positive interferon-gamma release assay. He denies fevers, weight loss, cough, or shortness of breath.

CXR showed a calcified pulmonary granuloma.

#11 **What would you recommend?**

A. Isoniazid plus pyridoxine daily for 9 months starting now
B. Isoniazid plus pyridoxine daily for 9 months beginning one month after transplant
C. Pyrazinamide plus rifampin daily for 2 months
D. Levofloxacin daily for 6 months

#12 **A 34-year-old man who underwent renal transplantation for end stage renal disease due to focal sclerosing glomerulonephritis two months prior to presentation, presents to the Emergency Department in January with headache and fever of five days duration.**

His post-transplant course was uncomplicated, and he is receiving prednisone, tacrolimus, mycophenolate mofetil and trimethoprim-sulfamethoxazole.

He and his donor were cytomegalovirus and Epstein-Barr virus seropositive.

BR1 Board Review - Day 1
Moderator - Robin Patel, MD

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#12 **He lives in Minnesota and has been at home since the transplant. He has no personal history of or exposure to tuberculosis.**

There is no history of travel to the desert Southwest of the United States, or outside of the United States and no animal exposure.

A lumbar puncture is performed revealing 50 cells/ml (90% lymphocytes, 10% neutrophils), a protein of 75 mg/dL and a glucose of 35 mg/dL. Gram stain of cerebrospinal fluid is negative, and bacterial cultures are in progress.

His cerebrospinal fluid is submitted to testing with a multiplex PCR panel, and returns the results shown below (i.e., all results are negative).

#12

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

#12 **Which test is most urgent to perform on his cerebrospinal fluid next?**

A. Mycobacterial culture
B. West Nile virus PCR
C. Zika virus PCR
D. Cryptococcal antigen
E. Smear for *Naegleria fowleri*

#13 **A 29-year-old man is admitted with rapid onset of shortness of breath and hypoxemia. He reports that about a week ago he developed a headache, fevers, myalgias and abdominal pain. He was seen in an urgent care clinic where influenza, and COVID-19 testing was negative.**

Three weeks ago, he returned from a prolonged trip to South America where he was backpacking and climbing in Chile and Argentina.

The rest of his exposure history is hard to obtain because of his dyspnea.

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#13 On exam, he is tachypneic and tachycardic with diffuse rales.

- Chest Xray shows diffuse fluffy infiltrates
- O_2 saturation could not be maintained on high flow oxygen, and he was intubated and placed on mechanical ventilation

Laboratory studies reveal the following:

- HCT: 52%
- WBC: 9000 cells/μl with 50% immature neutrophils and 2+ atypical lymphocytes
- Platelet count: 70,000/μl
- PT/INR 19/1.9
- AST/ALT: 90/105 U/L

#13 What is the most likely cause of this syndrome?

A. Dengue
B. Malaria
C. *Staphylococcus aureus* pneumonia
D. Hantavirus pulmonary syndrome
E. Argentine hemorrhagic fever virus

#14 A 47-year-old male arrives for clinic follow-up. He alerts you that five days ago, his brother and 10-year-old niece came to stay with him in his home. Yesterday, his niece was diagnosed with measles after developing high fevers, cough, conjunctivitis, and a rash.

The patient has acute myelogenous leukemia and underwent a matched-related donor allogeneic hematopoietic cell transplant 2 months ago.

His course has been complicated by skin and gastrointestinal graft-versus-host disease, for which he is on tapering doses of high-dose prednisone and tacrolimus.

The patient was up to date on all vaccines prior to transplant, including 2 doses of the measles, mumps, and rubella (MMR) vaccine.

#14 What is the best next step in management?

A. Administer the MMR vaccine immediately
B. Administer intravenous immunoglobulin immediately
C. Start prophylactic vitamin A immediately
D. Check measles serologies, and if negative, then administer intravenous immunoglobulin
E. No intervention required as the window has passed for any preventative measures. Closely monitor the patient for signs or symptoms of measles

BR1 Board Review - Day 1
Moderator - Robin Patel, MD

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#15 A 42-year-old woman presents to a primary care clinic with nasal congestion, facial pressure, and purulent nasal discharge that began 11 days ago.

She initially had symptoms of a common cold, including sore throat and rhinorrhea. Although most of her symptoms have improved slightly, right sided nasal congestion and facial pressure have worsened. She denies shortness of breath or chest pain.

Her temperature is 37.2°C (99.0°F).

Physical examination reveals right maxillary sinus tenderness and purulent nasal drainage from the right nares.

#15 What is the most appropriate next step in management?

A. Supportive care with decongestants and saline nasal lavage
B. Obtain a plain film of the sinuses
C. Refer to otolaryngology for sinus cultures
D. Start empiric antibiotics

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Saturday, August 22, 2026

05

Antifungal Drugs

Barbara Alexander, MD

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Antifungal Drugs

Barbara D. Alexander, MD, MHS, FIDSA
Duke University

8/8/2026

Disclosures of Financial Relationships with Relevant Commercial Interests

- Consultant: Scynexis/GSK, HealthTrackRx, DevleBio, Anvil Diagnostics
- Research Grant to My Institution: Karius
- Clinical Trials (Site PI/Study PI): Scynexis, F2G, Basilea
- Royalties: UpToDate, Biomeme

Agenda

1. Review of Antifungals
   - Antifungal Classes / Mechanisms of Action
   - Distinguishing properties of most common drugs
2. Questions on antifungals with answers
3. New stuff (not on boards)

Reasons for Treatment Failure

"<u>Clinical</u>"
Host defense inadequate
- Underlying disease uncontrolled
- Persistent neutropenia / Immunosuppressive drug use

Drug exposure inadequate
- Toxicity / Non-compliance / Not absorbing
- Persistent nidus / Protected site
- Drug interactions

"<u>Microbiologic</u>"
Microbial resistance
- Intrinsic - present for all members of the species despite lack of drug exposure
- Acquired - develops after exposure to a drug

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Antifungal Resistance
Altered Target Enzymes

1. AZOLE RESISTANCE IN CANDIDA and ASPERGILLUS
   - Fungus modifies drug target: 14-α-sterol demethylase
     - Changes in ERG11 gene (yeasts), cyp51A gene (molds)
   - Azoles no longer block synthesis of ergosterol, which is necessary for cytoplasmic membrane function
   - Cross resistance varies with specific mutation and azole
2. ECHINOCANDIN RESISTANCE IN CANDIDA
   - Fungus modifies drug target: glucan synthase
     - Changes in **FKS1 & FKS2 genes**
   - Echinocandins no longer block synthesis of beta-D-glucan, which is necessary for cell wall synthesis/stability
   - Cross resistance between echinocandins is usual

Antifungal Resistant Species

- Amphotericin B resistant: *Scedosporium apiospermum complex, Lomentosporum (Scedosporium) prolificans*, *Purpureocillium (Paecilomyces) lilacinum*, *Aspergillus terreus;* variable in *Candida lusitaniae, C. auris, Fusarium* species
- Fluconazole resistant: All molds, *Rhodotorula* species*, Candida krusei;* variable in *Candida auris (~90%), Candida haemulonii,* some *Candida glabrata (~20%)*
- Voriconazole resistant: Mucorales; higher MIC's for cryptic *Aspergillus* species (*A. lentulus, ustus, calidoustus*)
- Posaconazole, Isavuconazole resistance: Similar to voriconazole, but more activity against Mucorales
- Echinocandin resistance: *Cryptococcus, Rhodotorula,Trichosporon, Mucorales*

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

Amphotericin B

- Compromises cell membrane (leaky)
- Induces proinflammatory cytokines: fever, myalgias
- Azotemia (less with saline loading), hypokalemia, renal tubular acidosis, anemia (erythropoietin loss)
  - Amph B deoxycholate (conventional)
  - Liposomal Ampho B (LAMB) - less toxic

Azoles

ALL AZOLES ARE TERATOGENIC; CYP3A4 DRUG INTERACTIONS

- Fluconazole: *Candida, Cryptococcus, Coccidioides*
  - Good concentration in urine & CSF
- Itraconazole: *Histoplasma, Blastomyces*, ringworm
  - Check blood levels
- Voriconazole: *Aspergillus,* molds other than *Mucorales*, *Candida*
  - Check blood levels; IV formula with cyclodextrin
- Posaconazole: *Aspergillus,* variable *Mucorales*
  - Check blood levels; IV formula with cyclodextrin
- Isavuconazole: *Aspergillus*, variable *Mucorales*
  - Fewer drug interactions, less QTc Prolongation than other azoles
  - Water soluble so no cyclodextrin

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Fluconazole
THE FUNDAMENTALS

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

*Good Board Questions!

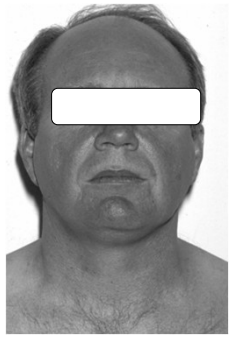
Voriconazole
THE FUNDAMENTALS

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

*Good Board Questions!

Voriconazole Side Effects
Photosensitivity

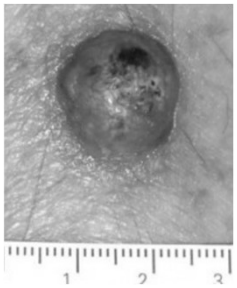
…driving in my "Beamer with the ragtop down"….
Jason Aldean

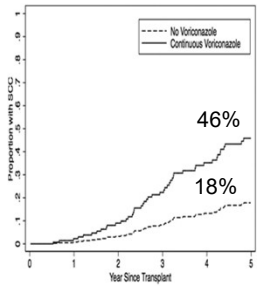


…love you more than that feeling when the bass hits the hook…
Morgan Wallen

Voriconazole Side Effects
Skin Cancer

N=327 Lung transplant Recipients:
50 with SCC, 277 Controls





Voriconazole Prophylaxis

- 2.6-fold increased risk for SCC
- Impact dose-dependent: risk increased by 5.6% with each 60-day, 200mg BID exposure
- 28% absolute risk increase @ 5 yrs

Singer JP, et al. Journal of Heart and Lung Transplantation. 2012;31:694-69

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Voriconazole Side Effects

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

Wermers, et al. CID 2011

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

Posaconazole
THE FUNDAMENTALS

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

*Good Board Questions!

Isavuconazole
THE FUNDAMENTALS

- Approved for**:** Invasive Aspergillosis (noninferior to vori); Mucorales (use is controversial)
- Not approved for Invasive Candidiasis*(inferior to caspofungin for candidemia)
- No good data on prophylaxis
- Distribution: no drug in CSF* or urine; long half life (5.4 days)
- Drug interactions: fewer than vori or posa*
- Isavuconazonium 372mg = Isavuconazole 200 mg
- Load with 200 mg q8h X 6 doses then 200 mg qd, IV or PO
- No dose change for renal* or moderate liver failure

*Good Board Questions!

Echinocandins

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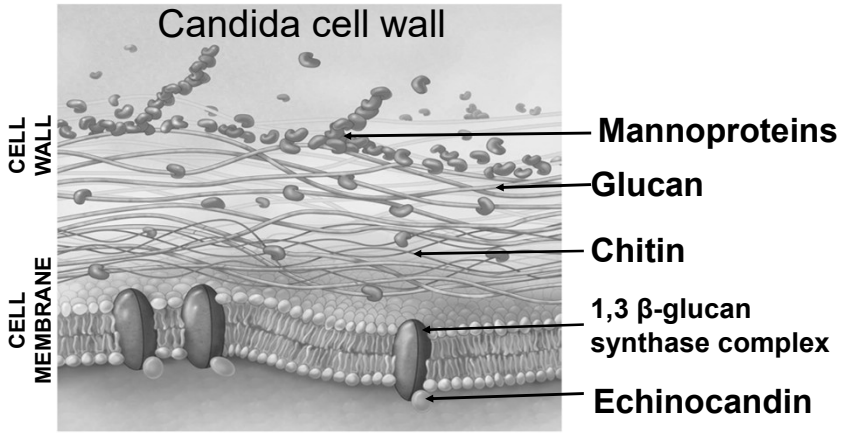

Caspofungin, Micafungin, Anidulafungin, Rezafungin

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

*Good Board Questions!

Flucytosine

- Indications: Cryptococcal Meningitis, Invasive Candidiasis
- Distribution: Capsule only; Bioavailability 100%; good levels in CSF, eye, urine*
- Drug resistance arises during monotherapy; typically used in combination with ampho B*
- Side Effects*: Accumulates in azotemia: bone marrow suppression, hepatitis, colitis
- Measure blood levels/dose adjust (target ~40-60 mcg/ml)

*Good Board Questions!

Now For A Few Questions

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Question #1

A 47-year-old male with known HIV, poorly compliant with ARV, last CD4 20/mcl, presents with low grade fever and headache. Blood culture is growing a yeast, not yet identified.

Starting micafungin would be a poor choice if the isolate is which of the following?

A. Candida parapsilosis
B. Cryptococcus gattii
C. Candida auris
D. Candida krusei
E. Candida glabrata

Question #2

A 72-year-old man with diabetes mellitus, renal failure and a central venous catheter developed fever and hypotension. Blood cultures grew Candida lusitaniae.

On day 5 of liposomal amphotericin B 5 mg/kg he remained febrile, and his creatinine rose from 4.5 to 6.0 mg/dl.

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

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

Question #3

What is the mechanism of action of the echinocandin class of antifungals?

A. Inhibits synthesis of membrane sterols
B. Damages cytoplasmic membrane
C. Interferes with synthesis of fungal cell wall glucans
D. Inhibits fungal DNA synthesis
E. Interfere with synthesis of fungal cell wall chitin

Question #4

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

Which of the following would be most appropriate?

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

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Question #5

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

According to the IDSA guidelines and literature, what would you recommend?

A. Itraconazole solution
B. Posaconazole
C. Rezafungin
D. Voriconazole
E. Caspofungin

Question #6

45-year-old male 6 weeks post stem cell transplant for myelodysplasia, with a history of chronic hepatitis C was discharged home to Florida on cyclosporine, mycophenylate, prednisone, bactrim (TMP/SMZ), citalopram and voriconazole. Diffuse nonpruritic erythema developed over his sun exposed skin.

What was the most probable cause?

A. Porphyria cutanea tarda
B. Graft versus host disease
C. Drug interaction
D. Voriconazole
E. Bactrim allergy

Question #7

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

Which of the following would be preferred?

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

Question #8

65-year-old admitted with cryptococcal meningitis, seizures, diabetes mellitus and granulomatosis with polyangiitis. Given conventional amphotericin B, flucytosine, phenytoin, glipizide, prednisone and cyclophosphamide.

By the end of the first week of treatment, his creatinine had risen from 1.6 to 3 mg/dl.

By the end of the second week his WBC count had fallen to 1.2K, platelets 60K and diarrhea began.

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

A. Flucytosine
B. Phenytoin
C. Glipizide
D. Cyclophosphamide
E. Cytomegalovirus

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Take Home Messages…

- Ampho: NOT for *Scedosporium/Lomentosporum, Candida lusitaniae,* or *Asperillus terreus*
- Only use ampho B as first line for mucormycosis
- Fluconazole: NOT *Candida krusei or Candida auris;* *+/- Candida glabrata*
- Echinocandins: NOT for *Trichosporon, Rhodotorula* or *Crypto*
- Know mechanisms of action:
  - Ergosterol synthesis – azoles
  - Glucan synthesis – echinocandins
  - Ergosterol binding / leaky cell membrane – Amphotericin B
  - DNA synthesis – Flucytosine
- Flucytosine: leuko- and thrombo-cytopenias, diarrhea, hepatitis

Take Home, continued…

- Voriconazole: phototoxicity, periostitis, skin cancer, visual disturbances and hallucinations
- Azole drug interactions:
  - Increases other drug levels: cyclosporine, tacrolimus, sirolimus, warfarin, midazolam, steroids, etc.
  - Some drugs decrease azole levels: phenytoin, rifampin, etc.

Thank You

barbara.alexander@duke.edu

New Oral Antifungals Approved for Vulvovaginal Candidiasis

Ibrexafungerp – novel ORAL glucan synthase inhibitor (triterpenoid)

- Acute infection: 300mg 12 hours apart on same day
  - Cost: $ 475
- Recurrent infection: 300mg bid monthly for 6 months
  - Cost: $2,992

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

- Recurrent infection (in women not breastfeeding/capable of childbearing)
- One week of fluconazole or otesaconazole then otesaconazole once a week for 11 weeks
  - Cost: $2,966

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Investigational Antifungals in Clinical Trials

- **Olorofim**. Orotomide; Inhibits DHODH* (pyrimidine, cell wall synthesis)
  - PO
  - *Aspergillus, Coccidioides*, *Scedosporium, Lomentospora* (not Mucorales or yeast)
- **Fosmanogepix**. Oxazole; Inhibits GWT1** (mannoprotein transport & anchoring)
  - PO, IV
  - *Candida* (not *C. krusei*), *Aspergillus, Fusarium, Scedosporium*, (not Mucorales)
- **Encochleated amphotericin B**: PO. Multilayered sheets of lipids.
  - *Crytpococcus, Aspergillus*
- **Opelconazole**: Aerosol. Prophylaxis; Chronic aspergillosis

*DHODH – Dihydroorotate dehydrogenase
**GWT1 - Glycosylphosphatidylinositol-anchored Wall protein Transfer 1

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Saturday, August 22, 2026

06

Infections in Solid Organ Transplant Recipients

Barbara Alexander, MD

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Infections in Solid Organ Transplant Recipients

Barbara D. Alexander, MD, MHS, FIDSA
Duke University

8/8/2026

Disclosures of Financial Relationships with Relevant Commercial Interests

- Consultant: Scynexis/GSK, HealthTrackRx, DevleBio, Anvil Diagnostics
- Research Grant to My Institution: Karius
- Clinical Trials (Site PI/Study PI): Scynexis, F2G, Basilea
- Royalties: UpToDate, Biomeme

Infections in Solid Organ Transplant (SOT) Recipients

- SOT is a life-saving intervention
  - 1,068,934 sots performed in U.S. Since 1988
  - 49,065 sots performed in 2025
  - ~40% increase over past decade
- SOT recipients are unique
  - Compromised immunity / increased infection risk
  - Targets for common, emerging & opportunistic pathogens encountered pre- and post-transplant
  - Atypical infection presentation owing to decreased inflammatory response
  - Complex medical regimens; drug interactions common

Data from Organ Procurement and Transplantation Network database as of March 2, 2026

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
  - Calcineurin inhibitors and TTP & PRES (altered mentation, fever)
  - Sirolimus associated pneumonitis (mimics viral lower respiratory infection)

TTP - Thrombotic Thrombocytopenic Purpura
PRES - Posterior Reversible Encephalopathy Syndrome

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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
  - *Candida, Aspergillus, Scedosporium*, 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 *freshwater 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 on posaconazole prophylaxis planted vegetable garden 2 weeks prior 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	Chest/Lung
Liver	1.86	10-23	29	4.7	Abdomen/ Biliary tract
Heart	1.36	8-11	25	3.4	Lung
Kidney	0.98	5-10	8	1.3	Urinary tract

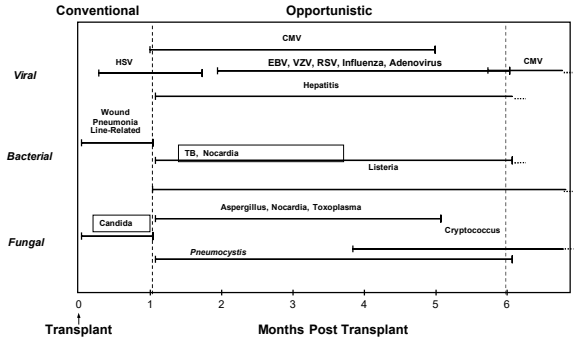
*CMV, Cytomegalovirus; CMV disease rates in the absence of routine antiviral prophylaxis

Table Modified from: Principles and Practices of Infectious Diseases, 8th Edition. Chapter 313: Infections in Solid-Organ Transplant Recipients by Nina Singh and Ajit Limaye. Editors: Bennett JE, Dolin R, and Blaser MJ. Elsevier Saunders, Philadelphia, PA, 2015.
Pappas P et al. CID. 2010:50:1101-1111

Classic Timing of Infections Following Solid Organ Transplantation

Timing altered by:

- Enhanced immunosuppression
- Prophylaxis regimen
- Unique exposures



SEE ENLARGED SLIDE FOLLOWING ENTIRE PRESENTATION

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"Early" Bacterial Infections Following SOT

- Type & site of early bacterial infection varies based on organ transplanted, surgical approach/technique & transplant center
  - Risk of peritoneal soilage/infection greater in liver transplantation with Roux-en-Y biliary drainage
  - Recipient colonization with resistant organisms (e.g., MRSA, VRE, CRE) pre-transplant, confers risk of post-transplant infection
  - Cluster with unusual pathogen - environmental problem? (e.g., *Legionella, M. abscessus* from hospital water distribution systems)

"Late" Bacterial Infections Following SOT

80% of Late Bacterial Infections are Community Acquired

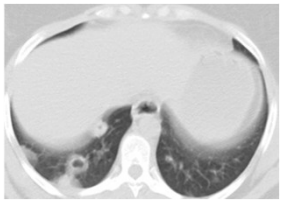
- *Streptococcus pneumoniae*
  - Incidence significantly > in SOT (146/100,000) vs general population (12/100,000)
  - Vaccination recommended
- *Listeria monocytogenes*
  - Bacteremia (Gram + Rods) / Diarrhea / Meningitis
  - Ampicillin treatment of choice
  - High relapse rate, treat for at least 3-6 wks

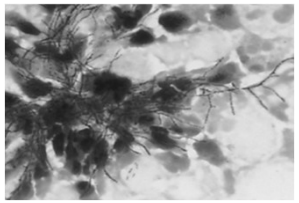
Kumar D et al., *Am J of Transplant* 2007;7:1209

"Late" Bacterial Infections (Cont.)

***Nocardia* species**

- 1%-6% of all SOT recipients
- Presents most often as pulmonary nodules, CNS (15-20%), skin (15%), or bone (2-5%) lesions
- Diagnosis: Culture and/or histopathology
  - Branching, filamentous Gram + Rods
  - Partially acid-fast by modified Kinyoun stain
  - *Nocardia* is *Neurotropic*; brain imaging critical
- Treatment:
  - High dose TMP-SMX drug of choice
  - Otherwise, based on susceptibility data & site of infection
- TMP-SMX dose used for PCP prophylaxis not protective





CMV Disease After SOT
Indirect and Direct Effects

- INDIRECT Effects:
- Acute and Chronic Rejection
- Opportunistic Super-Infections (Gram Negative Bacteria & Molds)
- DIRECT Effects:
- CMV Syndrome – Most Common Presentation
  - CMV in blood + fever + malaise, leukopenia, atypical lymphocytosis, thrombocytopenia
- Tissue Invasive Disease
  - Evidence of CMV on biopsy + compatible signs/symptoms

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Risk of CMV Disease After SOT

CMV Serologic Status	Risk Category	Incidence of Disease (%)
D+/R-	High	50+
D+ or D- /R+	Intermediate	10-15
D-/R-*	Low	0
ALA Therapy (R+)		
Induction	Intermediate	25-30
Rejection	High	65

D, Donor; R, Recipient; ALA, Antilymphocyte Antibody

*Should receive leukocyte depleted blood products

CMV Disease After SOT Prophylactic Approaches

UNIVERSAL

All SOT recipients receive therapy during highest risk periods

- Expensive
- May induce resistance
- Some pts exposed unnecessarily

PREEMPTIVE

Treatment based on asymptomatic viral replication in blood

- Optimal viral threshold for initiating therapy not well defined
- Requires serial weekly monitoring with detection assay

NOTE: Typically, Valganciclovir or IV Ganciclovir used for prophylaxis
Letermovir now approved for use after Renal Transplant

CMV Prophylaxis After SOT

- Bottomline:
- D+/R- or ALA for rejection → Universal
  - First 3-6 months post-transplant
  - At least 1 month post-ALA for rejection
- R+ → Universal or Preemptive
  - First 3-6 months post-transplant

CMV Disease After SOT

- Typically occurs 1-3 months post-transplant
  - Or after prophylaxis is stopped (“late onset”)
- Disease of GI Tract and Eye may not have concurrent viremia
  - Diagnosis often requires biopsy/aspiration
- Valganciclovir or IV Ganciclovir are first line therapy
- Viral load may continue to rise during first 2 weeks of Rx
  - Don’t repeat PCR until Day 10-14 of treatment, then weekly until negative
- Treat for 2-3 weeks…
  - Resolution of symptoms AND clearance of CMV DNAemia
  - DO NOT STOP TIL VIREMIA CLEARs (high risk for relapse)

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CMV Disease After SOT
Ganciclovir Resistance

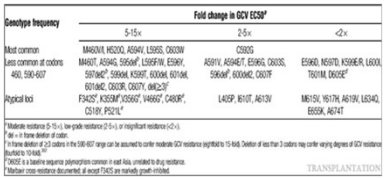
- **Suspect resistance if prolonged (> 6 weeks) (val)ganciclovir exposure AND:**
  - No reduction in viral load after 10-14 days of treatment
  - No clinical improvement after 10-14 days of treatment
- **Management of suspected ganciclovir resistance:**
  - Reduce immunosuppression
  - Switch to Maribavir 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



Genotype frequency	Fold change in GCV EC50*		
	5-15×	2-5×	<2×
Most common	M460I/I, H520Q, A594V, L595S, C603W	C592G	
Less common at codons 460, 590-607	M460T, A594G, 595del[†], L595F/W, E596Y, 597del[†], 599del, K599T, 600del, 601del, 601del2, C603R, C607Y, del≥3[‡]	A591V, A594E/T, E596G, C603S, 596del[†], 600del2, C607F	E596D, N597D, K599E/R, L600, T601M, D605E[†]
Atypical loci	F342S[†], K359M[†]/D360[†], V466G[†], C480R[†], C519Y, P521L[‡]	L405P, I510T, A613V	M615I, Y617N, A619V, L634Q, E655K, A674T

*Moderate resistance (5-15×), low-grade resistance (2-5×), or insignificant resistance (<2×).
†del = in frame deletion of codon.
‡In frame deletion of ≥3 codons in the 590-607 range can be assumed to confer moderate GCV resistance (eighfold to 15-fold). Deletion of less than 3 codons may confer varying degrees of GCV resistance but fold to 10-fold.[30]
§V466 is a baseline sequence polymorphism common in east Asia, unrelated to drug resistance.
||Marbavir cross-resistance documented, all except T342S are markedly growth-inhibited.

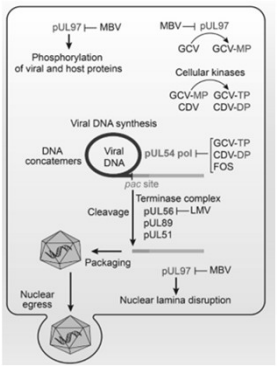
TRANSPLANTATION

- UL54 CMV DNA Polymerase gene mutations
  - May confer resistance to ganciclovir, foscarnet, & cidofovir

SEE ENLARGED SLIDE FOLLOWING ENTIRE PRESENTATION

Lurain et al JID 2002; Limaye et al Lancet 2000; Limaye et al JID 2002; Kotton et al. Transplantation 2018;102(6):900-931. Torre-Cisneros 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 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)
  - Add acyclovir

SEE ENLARGED SLIDE FOLLOWING ENTIRE PRESENTATION

Piret J, Boivin G. Antiviral Research 2019;163:91-105.
Avery RK, et al. Clin Infect Dis. 2021 Dec: Online ahead of print.

Question #1

54-year-old 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.

What is the most appropriate treatment for this condition?

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

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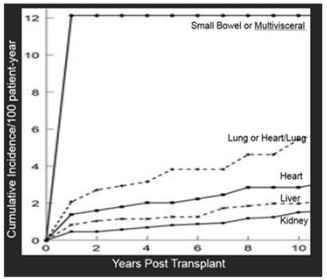
Epstein Barr Virus: Post Transplant Lymphoproliferative Disorder (PTLD)

- Virus establishes latency in B-lymphocytes which serve as lifelong reservoirs
- EBV transformed B-lymphocytes give rise to PTLD (a few cases may arise from T-lymphocytes)
- Risk factors:
  - 1° EBV infection
  - Donor seropositive, Recipient seronegative
  - Anti-lymphocytic 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



SEE ENLARGED SLIDE FOLLOWING ENTIRE PRESENTATION

Olagne, J, et al. Am J Transplant. 2011 Jun;11(6):1260-9.

Epstein Barr Virus: Post Transplant Lymphoproliferative Disorder (PTLD)

Clinical manifestation - wide range

- Febrile mononucleosis-like illness with lymphadenopathy
- Solid tumors
  - Often involve transplanted graft
  - 50% are extranodal masses
  - 25% involve CNS

Definitive diagnosis requires tissue biopsy

- WHO Pathology Classification based is gold standard for diagnosis
- Molecular (PCR) tests available
  - WHO Standard for Assay Calibration available
  - Whole Blood vs Plasma controversial
  - Misses EBV-negative and some localized cases
  - Used as an aid for Diagnosis and Pre-emptive monitoring with stepwise reduction in immunosuppression to reduce PTLD rates

Petit B et al. Transplantation. 2002;73(2):265.
Peters AC et al. Transplantation. 2018; 102(9):1553.

Epstein Barr Virus: Post Transplant Lymphoproliferative Disorder (PTLD)

Treatment:

- Antivirals not effective on latently infected lymphocytes (antivirals only work in lytic phase)
- Reduce Immunosuppression (Response ~ 45%)
- Rituximab: Anti-CD20 monoclonal antibody (Response ~ 55%)
- Cytotoxic Combination (CHOP, ACVBP) Chemotherapy
  - Reserved for non-responsive disease
  - High treatment associated mortality (13%-50%)
- Adoptive Immunotherapy (EBV cytotoxic T-cells)
  - Under study

Allen et al. Clin Transplant. 2019;33(9):e13652.

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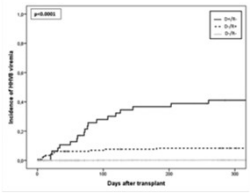
HHV-8 After Solid Organ Transplant

- Seroprevalence in U.S. considered low overall
- High seroprevalence among certain populations:
  - 68% among MSM w/ HIV ; 37% among MSM
  - 36% among women who inject drugs
- U.S. OPTN DTAC* 2018-2020 data:
  - 6 cases of HHV-8 transmission/KS from deceased organ donors
  - 6 donors -> 22 recipients -> 14 w/ post transplant HHV-8 infection
    - 6 developed KS; 4 died due to KS or associated complications
- Post-transplant KS Incidence: 12.4 per 100,000 person years



*OPTN DTAC – Organ Procurement Transplant Network, Disease Transmission Advisory Committee

SEE ENLARGED SLIDE FOLLOWING ENTIRE PRESENTATION

Knights SM, et al. Open Forum Infect Dis. 2023 Mar 24;10(4):ofad160. Salyards M, et al. J Infect Dis. 2024 May 15;229(5):1387-1392. Cannon MJ, et al. N Engl J Med. 2001 Mar 1;344(9):637-43. Dollard, SC, et al. *American Journal of Transplantation*. 2021: 21(2), 681–688. Cahoon EK et al.. Int J Cancer. 2018 Dec 1;143(11):2741-2748. Mularoni A, et al. American Journal of Transplantation. 2025; 25(5):10070-1085.

HHV-8 Oncovirus Presentations

- Kaposi Sarcoma
  - Skin, oral lesions
  - Visceral involvement
- Primary effusion lymphoma; other large cell lymphomas
  - Cytopathology alone may be insufficient for dx
  - Flow cytometry and special staining required
  - HHV-8 NAT from blood/fluid can be clue to dx
- Multicentric Castleman Disease (polyclonal B cell lymphoproliferative disorder)
- Kaposi Sarcoma Herpesvirus (KHSV) Inflammatory Cytokine Syndrome (KICS):
  - Systemic inflammatory syndrome, often severe with shock/ multiorgan failure
  - Most often occurs concurrently w/ KS
  - Poor prognosis

KICS could show up on the Boards!

Question #2

- 52-year-old female S/P cadaveric renal transplant receiving tacrolimus, prednisone and mycophenolate
- 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

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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

Polyomavirus
BK Virus Nephropathy

- 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 PCR
  - Detection in urine: Low PPV but High NPV

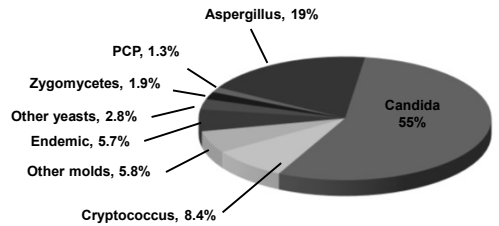
Hirsch et al, Transplantation 2005;79:1277-1286; Nickeleit et al, NEJM 2000;342 (18):1309-1315; Ramos et al. *J Am Soc Nephrol* 2002;13:2145

BK Virus Nephropathy Treatment

- Reduce immunosuppression
  - Case series with variable success using:
  - Low-dose cidofovir
- Leflunomide
- New drugs & randomized controlled trials needed
- Preemptive monitoring up to 2 years post-transplant & stepwise immunosuppression decrease 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 varies depending on organ transplanted

Pappas P et al. CID. 2010:50:1101-1111.

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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.
Aslam S, Rotstein C. AST ID COP. *Am J Transpl.* 2019;33:e13623.
Husain S, Camargo J. AST ID COP. *Am J Transpl.* 2019;33:213544.

Tuberculosis

- 34-74-fold higher risk of active disease in SOT recipients than general population
- Incidence 1% - 6% (up to 15% in endemic areas)
- Median onset 9 months post-tx (0.5-144 months)
- 33% of infections are disseminated at diagnosis
- Treatment
  - Rifampin-based regimens associated with graft loss/rejection in 25%
- Mortality ~30%
- Treat latent TB prior to transplant when possible

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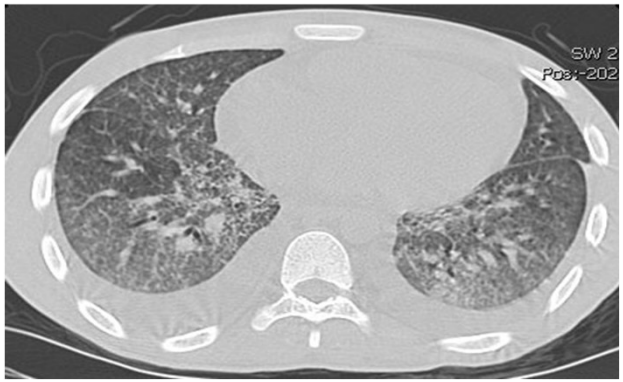
Question #3

- 35-year-old 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.

Question #3: Chest CT



Question #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

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Toxoplasmosis

- After SOT, acute toxoplasmosis can develop from
  - Reactivation,
  - Acquisition via blood transfusion,
  - Ingestion of contaminated food or water, or 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
- Most cases in SOT recipients occur in pts not on systemic PCP ppx

Question #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
  - Recently on camping trip with friends

Question #4

What is 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 transplant and 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.

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"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)
- Report potential unexpected donor derived transmissions into OPTN Safety Portal

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

SEE ENLARGED SLIDE FOLLOWING ENTIRE PRESENTATION

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
- Smallpox
- 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
- STId
- MDR-TB
- Blood supply (need for TRANSFUSIONS), etc.

AVOID LIVE VACCINES: Yellow Fever, Oral typhoid, etc.

DRUG INTERACTIONS →Transplant meds + travel related prophylactic agents

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Key Drug Toxicities / Syndromes

- Calcineurin inhibitors and TTP & PRES
- 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

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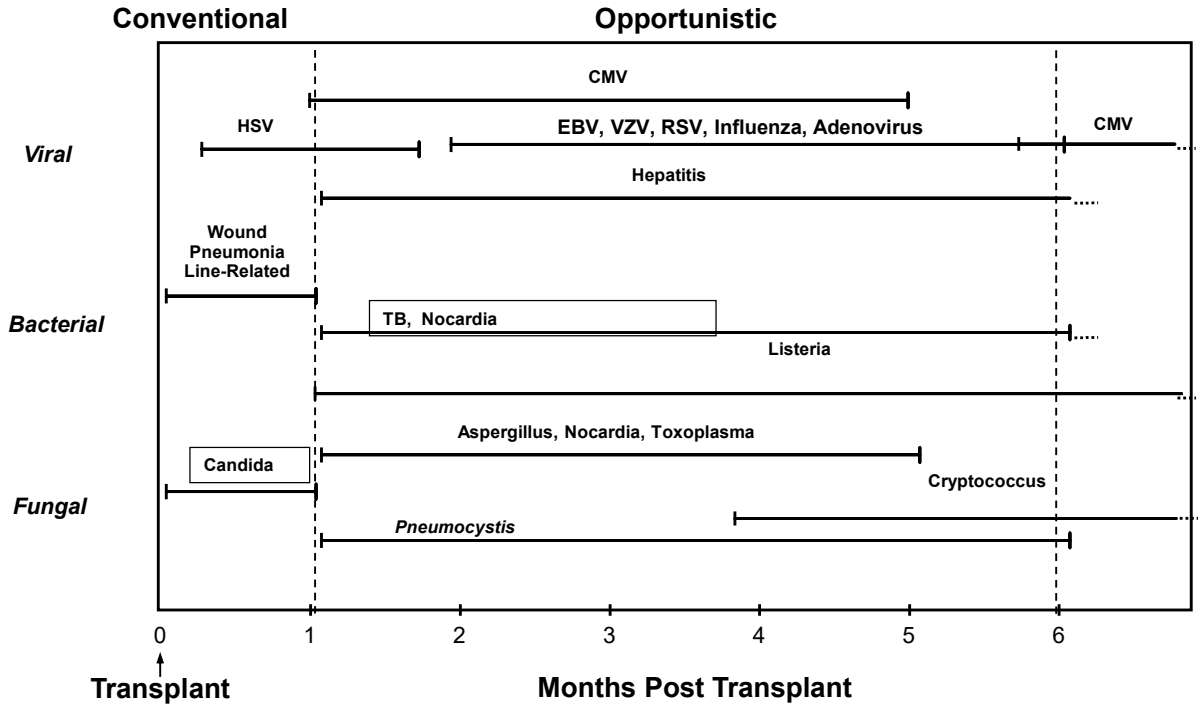
Classic Timing of Infections Following Solid Organ Transplantation

Timing altered by:

- Enhanced immunosuppression
- Prophylaxis regimen
- Unique exposures



SEE ENLARGED SLIDE FOLLOWING ENTIRE PRESENTATION

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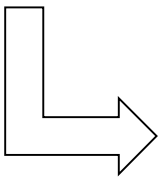
CMV Disease After SOT
Antiviral Resistance

Key mutations have been associated with resistance

- UL97 CMV Phosphotransferase gene mutations (most common)
- Imply ganciclovir resistance



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Atypical loci	F342S[e], K355M[e],V356G[e], V466G[e], C480R[e], C518Y, P521L[e]	L405P, I610T, A613V	M615V, Y617H, A619V, L634Q, E655K, A674T

[a] Moderate resistance (5-15×), low-grade resistance (2-5×), or insignificant resistance (<2×).
[b] del = in frame deletion of codon.
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[d] D605E is a baseline sequence polymorphism common in east Asia, unrelated to drug resistance.
[e] Maribavir cross-resistance documented; all except F342S are markedly growth-inhibited.

TRANSPLANTATION

- UL54 CMV DNA Polymerase gene mutations
  - May confer resistance to ganciclovir, foscarnet, & cidofovir

Lurain et al JID 2002; Limaye et al Lancet 2000; Limaye et al JID 2002; Kotton et al. Transplantation 2018;102(6):900-931. Torre-Cisneros at al Transplantation Reviews 2016.

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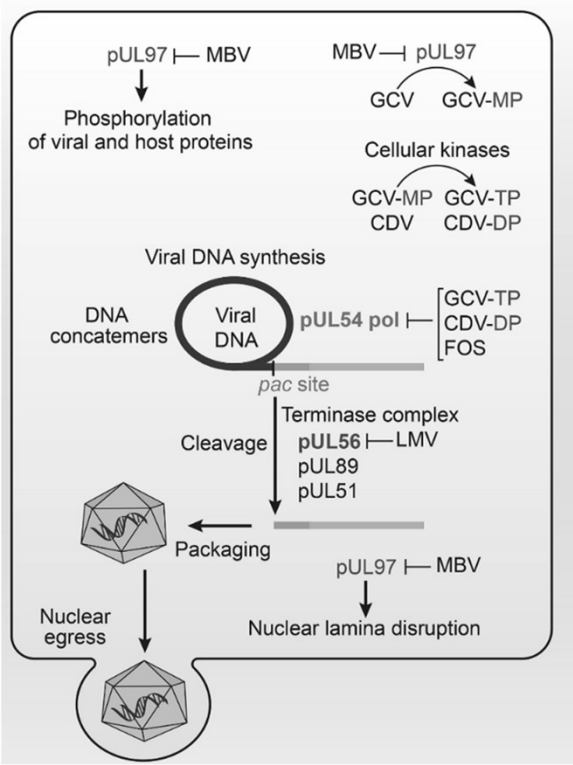
CMV Resistance: New Drug



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- Multi-modal CMV activity
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  - 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 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)
  - Add acyclovir

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Piret J, Boivin G. Antiviral Research 2019;163:91-105.
Avery RK, et al. Clin Infect Dis. 2021 Dec: Online ahead of print.

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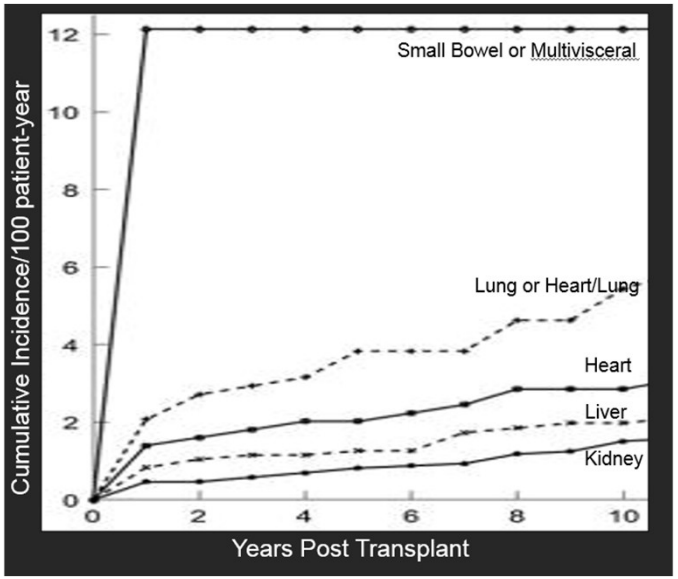
  - Lung / Heart / Liver: 3-12%
  - Kidney: 1-2%
- Biphasic pattern of disease after SOT:
  - First peak (20% cases) occurs 1st post-tx year
  - Second peak occurs 7-10 years post-tx



SEE ENLARGED SLIDE FOLLOWING ENTIRE PRESENTATION

Olagne, J, et al. Am J Transplant. 2011 Jun;11(6):1260-9.

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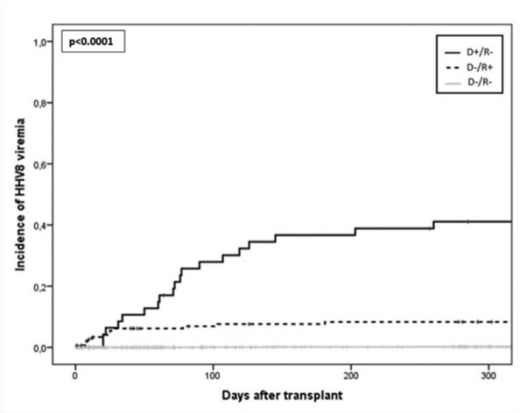
HHV-8 After Solid Organ Transplant

- Seroprevalence in U.S. considered low overall
- High seroprevalence among certain populations:
  - 68% among MSM w/ HIV ; 37% among MSM
  - 36% among women who inject drugs
- U.S. OPTN DTAC* 2018-2020 data:
  - 6 cases of HHV-8 transmission/KS from deceased organ donors
  - 6 donors -> 22 recipients -> 14 w/ post transplant HHV-8 infection
    - 6 developed KS; 4 died due to KS or associated complications
- Post-transplant KS Incidence: 12.4 per 100,000 person years



*OPTN DTAC – Organ Procurement Transplant Network, Disease Transmission Advisory Committee

Knights SM, et al. Open Forum Infect Dis. 2023 Mar 24;10(4):ofad160. Salyards M, et al. J Infect Dis. 2024 May 15;229(5):1387-1392. Cannon MJ, et al. N Engl J Med. 2001 Mar 1;344(9):637-43. Dollard, SC, et al. *American Journal of Transplantation.* 2021: *21*(2), 681–688. Cahoon EK et al.. Int J Cancer. 2018 Dec 1;143(11):2741-2748. Mularoni A, et al. American Journal of Transplantation. 2025; 25(5):10070-1085.

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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)
- Report potential unexpected donor derived transmissions into OPTN Safety Portal

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

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Saturday, August 22, 2026

07

Respiratory Viral Infections Including Influenza in Immunocompetent and Immunocompromised Persons

Andrew Pavia, MD

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Respiratory Viral Infections Including Influenza, Immunocompetent, and Immunocompromised Patients

Andrew T. Pavia, MD
University of Utah

8/1/2026

Disclosures of Financial Relationships with Relevant Commercial Interests

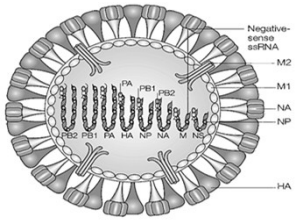
- Antimicrobial Therapy Inc,
- Haleon

What You Need to Know for the Boards

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

Influenza Virus

- Orthomyxovirus; 8 gene segments
- Flu A, B and C
- Flu A has 16 HA types, 9 N types
- High error rate leads to point mutations (drift); segment re-assortment leads to shift (pandemics)
- Huge reservoir in wild fowl. Causes disease in birds, poultry, and many mammals



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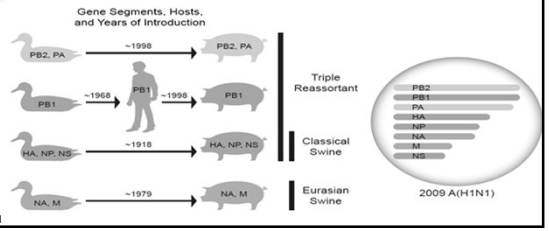
Reassortment of genes leads to pandemic shifts

e.g., A/California/7/2009 (H1N1)pdm09, the virus formerly known as swine flu



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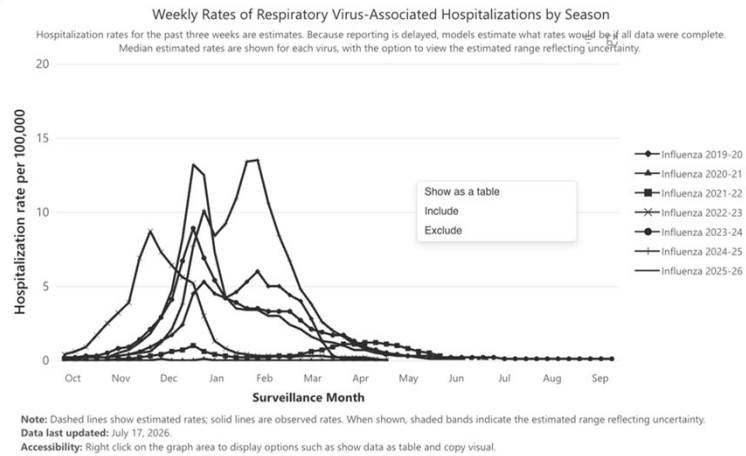

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Groups at Risk for Complications of Influenza

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

Clinical Findings of Influenza

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

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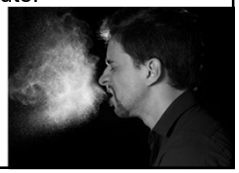
Influenza Transmission

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



https://www.cdc.gov/flu/hcp/infection-control/healthcare-settings.html?CDC_AAref_Val=https://www.cdc.gov/flu/professionals/infectioncontrol/healthcaresettings.htm

What Makes a "Human Influenza Strain?"

- Use of α2-6-linked receptors. PB2 adaptation
- Despite increasing study, anticipating changes difficult
- Many genes interacting in complex ways determine virulence species specificity and transmissibility (e.g., 1918 H1N1 virus)
- Influenza risk assessment tool (IRAT)
  - https://www.cdc.gov/flu/pandemic-resources/national-strategy/risk-assessment.htm

Influenza A Viruses Infecting Humans

- H1N1*: Emerged in 1918. Re-emerged in 1977
- H2N2: 1956-1977 but replaced by H3N2
- H3N2*: Emerged in 1968 (Hong Kong flu)
- H3N2v*: Assorted swine associated variants
- **H5N1*: Emerged 2003 in Hong Kong. Current strain causing severe outbreak in birds with recent spill over in mammals**
- H7N9: Caused >130 cases of severe disease 2013; >200 in second wave; now rare
- H7N3: Isolated cases in farm workers
- H7N7: H7 viruses associated with conjunctivitis
- H9N2: Sporadic cases associated with poultry
- H10N3: First human case 2021

* Currently causing human disease

H5N1 High Pathogenicity Avian Influenza

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HPAI H5N1 Influenza

- Initially identified in goose in Guangdong in 1996
- 18 human cases/6 deaths Hong Kong 1997
- Re-emerged in 2003 with large poultry outbreaks and sporadic human cases – high mortality
- In 2020, reassortment led to emergence of Eurasian clade of HPAI H5N1 Clade 2.3.4.4b
- Large outbreaks among commercial and backyard poultry and wild birds around the world
- ~ 150 million birds culled in US in since 2020

Photo: Mads Claus Rasmussen

Photo: NBC News

HPAI H5N1 Influenza

- 71 confirmed cases in US, 13 states
- 41 associated with dairy cows
- 24 commercial poultry
- 3 backyard poultry
- 3 unknown exposure

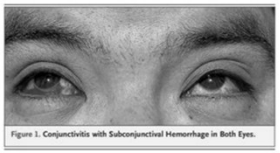
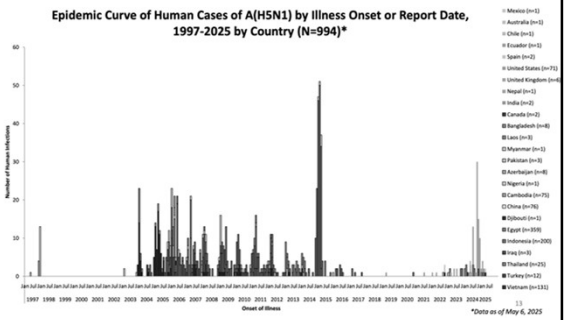


Figure 1. Conjunctivitis with Subconjunctival Hemorrhage in Both Eyes.

Uyeki NEJM 2024

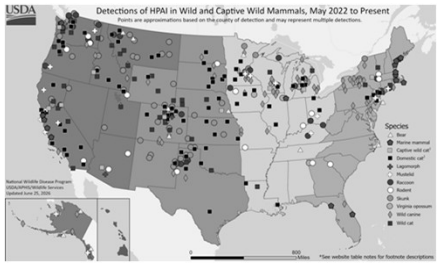


Source CDC

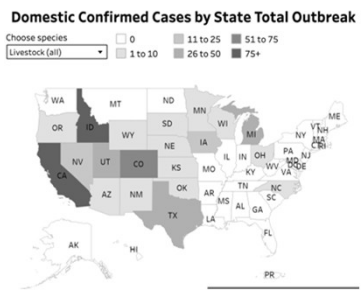
SEE ENLARGED SLIDE FOLLOWING ENTIRE PRESENTATION

Human and Other Mammalian Cases of H5N1

Other Mammals



Cattle Herds: 1168 cases in 20 states



SEE ENLARGED SLIDE FOLLOWING ENTIRE PRESENTATION

https://www.aphis.usda.gov/livestock-poultry-disease/avian/avian-influenza/hpai-detections/mammals

Question #1

An 18-year-old high school student develops chills, fever, cough, myalgia in January 2025. 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

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Question #1

What is the most likely cause of this influenza complication?

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

Mild Complications of Influenza

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

Severe Cardiopulmonary Complications of Influenza

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

Non-respiratory Complications of Influenza

Complication	Comment
Neurologic	
Seizures	
Encephalopathy/Encephalitis Acute necrotizing encephalitis	Viral particles and RNA are rarely found. More common in children but higher mortality in adults
Guillain Barre Syndrome	3- to 10-fold more common with infection than estimated association with vaccine
Other	Stroke, ADEM, Reyes Syndrome, cerebellar ataxia, transverse myelitis
Musculoskeletal	
Myositis, Rhabdomyolysis	Can be severe and lead to AKI
Cardiac	
Pericarditis	
Myocarditis	see also Uyeki Ann Intern Med 274:9 Nov 2021

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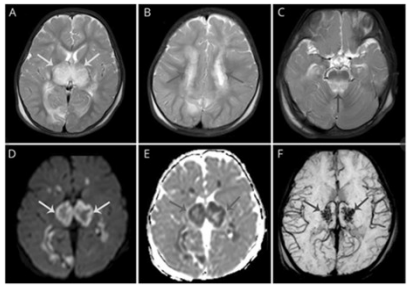
Acute Necrotizing Encephalitis May be Associated with Cytokine Storm and Genetic Predisposition

- No evidence of viral invasion
- Elevated IL-6 and other cytokines in serum and CSF thought to drive pathogenesis
- Strong association with RANBP2 mutations
- No proven therapy; antivirals, pulse steroids and IL-6 inhibitors have been used



Uyeki J Ped Infect Dis Soc 2022; 12:541

Question #2

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

Question #2

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

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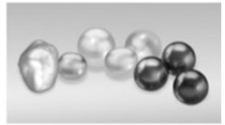
Diagnosis of Influenza

- Performance of all tests depends on prevalence of virus in community and specimen quality
- Clinical diagnosis: up to 80% PPV during peak (pre-Covid)
- Rapid influenza detection tests have low-moderate sensitivity 10-70%; reasonably specific
- Positive antigen test in peak season high PPV; negative test should not be used for decisions
- PCR/NAAT recommended by IDSA Guidelines, rapid platforms NAAT expanding. When flu is circulating, test for both SARS-COV-2 and flu
- Serology has no role

Influenza in Transplant Pearls

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



Question #3

- 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.

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. Baloxavir is the recommended therapy
E. Oseltamivir should be started as soon as possible

ACIP and IDSA Guidelines for Antiviral Use 2025

- Antiviral treatment is recommended for patients with confirmed or suspected influenza as soon as possible:
  - Who are hospitalized regardless of duration of symptoms
  - Have severe, complicated or progressive illness regardless of duration of symptoms
  - Outpatients with confirmed or suspected influenza who are at higher risk for influenza complications
  - Consider for otherwise healthy outpatients within 48 hrs of symptom onset

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

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ACIP Guidelines for Antiviral Use 2026

- Recommended medications for outpatients:
  - Oseltamivir, baloxavir, inhaled zanamivir
- Recommended medications for inpatients:
  - Oseltamivir. IV peramivir if unable to get any enteral therapy at all

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

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

Baloxavir

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

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

Antiviral Prophylaxis

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

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Vaccines

ACIP Recommendations for Influenza Vaccination 2024-25

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

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

Vaccine Pearls (Cont.)

- 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

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.

SEE ENLARGED SLIDE FOLLOWING ENTIRE PRESENTATION

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

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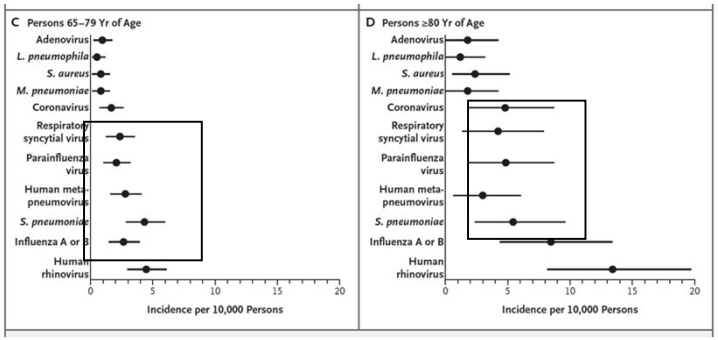
Other Important Respiratory Viruses Adenovirus, RSV, hMPV, Parainfluenza, Coronaviruses, Hantaviruses (and More)

What You May Be Tested On

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

Photo: ©Andrew Pavia

Incidence of Pathogens in Older Adults Hospitalized With CAP



SEE ENLARGED SLIDE FOLLOWING ENTIRE PRESENTATION

Jain NEJM 2015

Findings which may Suggest Viral vs. Bacterial CAP: Beware the Overlap!

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

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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
- Testing makes sense in hospitalized elderly

Question #4

- A 77-year-old man with COPD, history of MI is admitted in January with progressive dyspnea, cough, tachypnea, low grade fever. ROS is positive for rhinitis.
- He has been spending time with young grandchild who has bronchiolitis.
- Rapid Covid test negative. CXR shows bilateral perihilar infiltrates but no consolidation or effusion

Question #4

What should the recommended strategy be, pending more lab results, regarding isolation?

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

Question #5

Multiplex PCR of his nasal swab shows RSV

Which of the following is correct?

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

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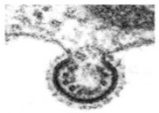
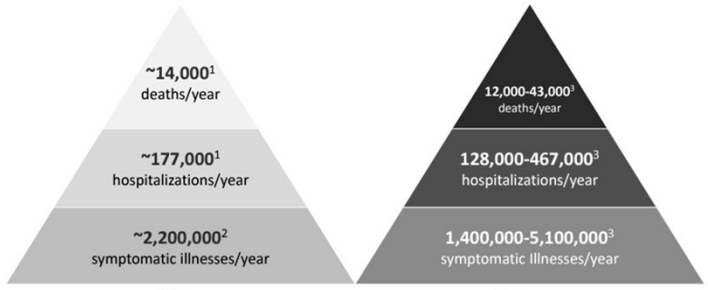
RSV



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

Falsey NEJM 2005, Widmer 2012
Brance Clin Infect Dis 2022

Among adults ≥65 years of age in the United States, RSV is associated with a similar burden of disease as influenza



[1]Falsey et al, NEJM (2005); [2]Adapted from Falsey et al, NEJM (2005); [3]Estimated Influenza Disease Burden 2015-2016 through 2019-2020, CDC (2022):

10

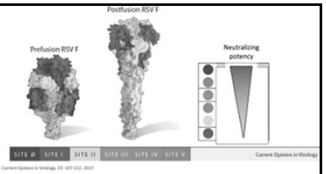
Havers F, ACIP meeting June 23, 2022

Risk Factors for RSV Hospitalization Among Adults

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

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

RSV Prevention!



- Three licensed vaccines for those
  - Protein >80% effective at preventing severe RSV
  - Target pre-fusion F protein
    - GSK adjuvanted single dose
    - Pfizer un-adjuvanted single dose
    - Moderna mRNA single dose
- Pfizer licensed for pregnant women to protect infant ~ 70% effective
- ACIP recommends adults ≥75 or ≥55 with risk factors

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RSV

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

Question #6

- A 35-year-old man is admitted to the ICU in July with fever, conjunctivitis, respiratory failure, hypotension.
- Symptoms have been present for 48 hours.
- History: He recently completed a 3-day adventure race with fresh water exposure.
- Has parakeet, dogs, cat had kittens recently, owns a hot tub. 2 kids in daycare have URI and conjunctivitis.

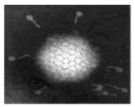
Question #6

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

What would you suspect?

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

Adenovirus



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

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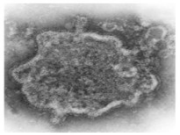
Adenovirus in Transplant Patients

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

Human Metapneumovirus



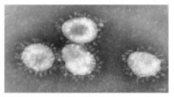
- "Discovered' in the last decades
- Non-segmented, single stranded, negative sense RNA virus: Paramyxoviridae family, Pneumovirinae subfamily
- Causes URI, bronchiolitis, pneumonia similar to RSV
- Winter/Spring in temperate climates
- In younger adults, URI common with sore throat, hoarseness, wheezing,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

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

Parainfluenza Virus

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

Other Human Coronaviruses



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

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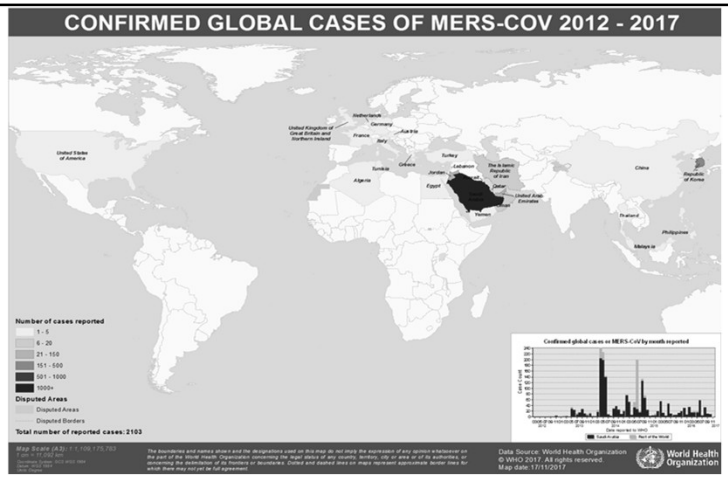
MERS Coronavirus

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



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Question #7

- A 25-year-old 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 abdominal pain.
- History: He works as a lineman in northern Arizona. He remembers electrical boxes with rodent infestations.
- Has parakeet, dogs, cat had kittens recently, owns a hot tub. No one in family is ill.

Question #7

- 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

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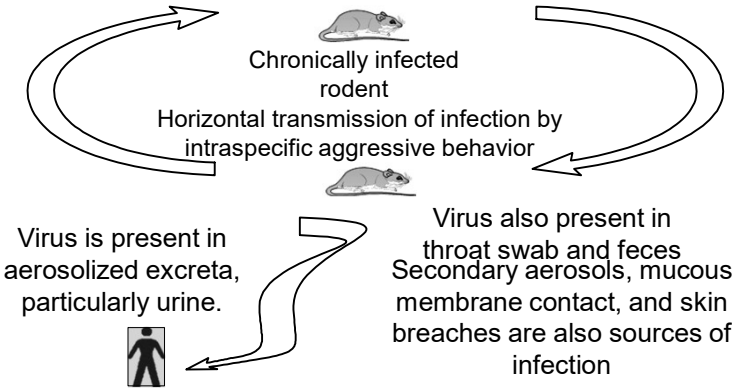
Question #7

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.
  - In North America, HPS caused by Sin Nombre virus, Black Creek Canal, New York virus and others
  - Several viruses in Chile and Argentina; Andes virus best known and only new world Hantavirus with documented human to human transmission



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

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HPS-Cardiopulmonary Phase

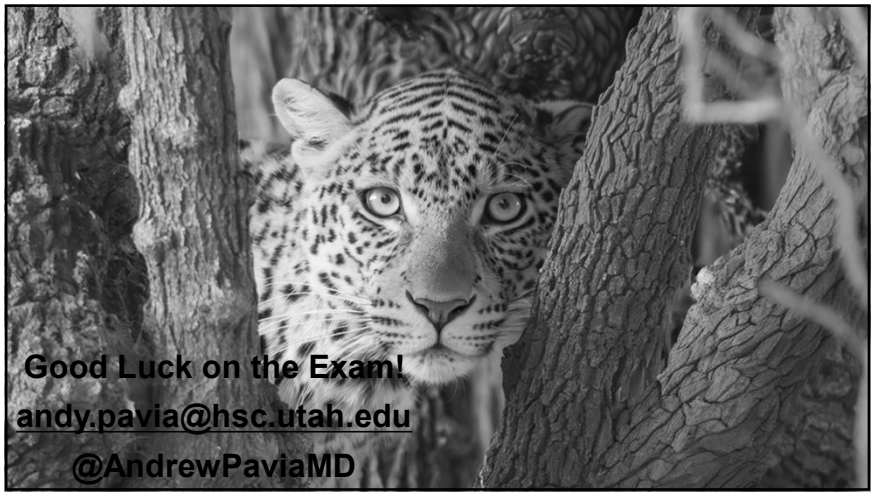
- Acute onset of cough and dyspnea
- Presentation and rapid progression of shock and pulmonary edema (4-24h non-productive cough and tachypnea (shortness of breath)
- Hypovolemia due to progressive leakage of high protein fluid from blood to lung interstitium and alveoli, decreased cardiac function

HPS-Cardiopulmonary Phase

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

Respiratory Viruses: Take Home

- RSV, hMPV, Parainfluenza viruses are common causes of CAP and exacerbation of underlying cardiopulmonary disease in elderly
- COPD and heart disease are risk factors
- Exposure to children probably a risk factor
- Nosocomial transmission has been documented in hospitals and ECF
- Testing and use of appropriate precautions
- HPS has distinct epidemiologic risks and recognizable lab abnormalities



7 Respiratory Viral Infections Including Influenza in Immunocompetent and Immunocompromised Persons
Speaker: Andrew Pavia, MD

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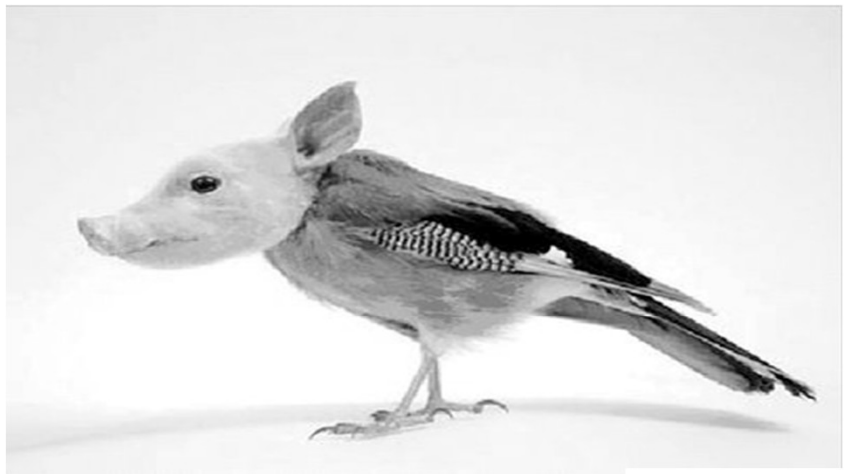
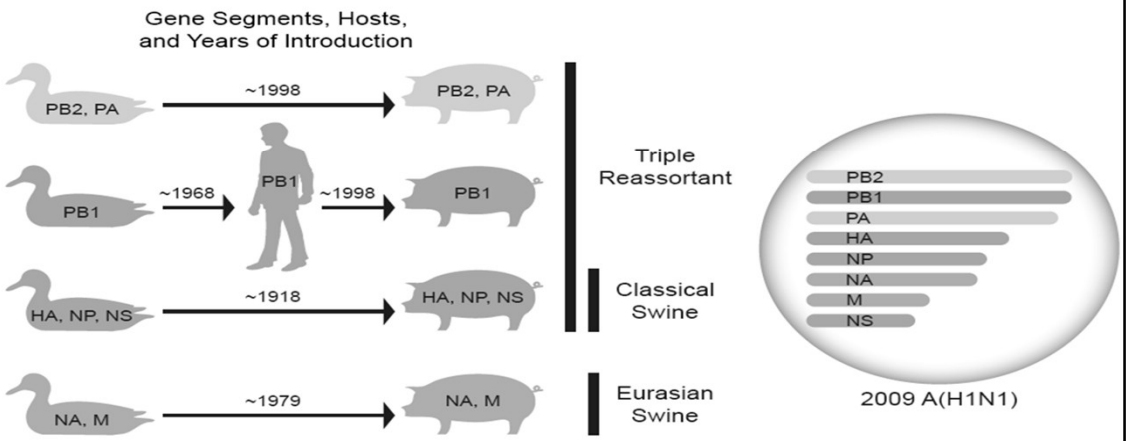


Reassortment of genes leads to pandemic shifts

e.g., A/California/7/2009 (H1N1)pdm09, the virus formerly known as swine flu



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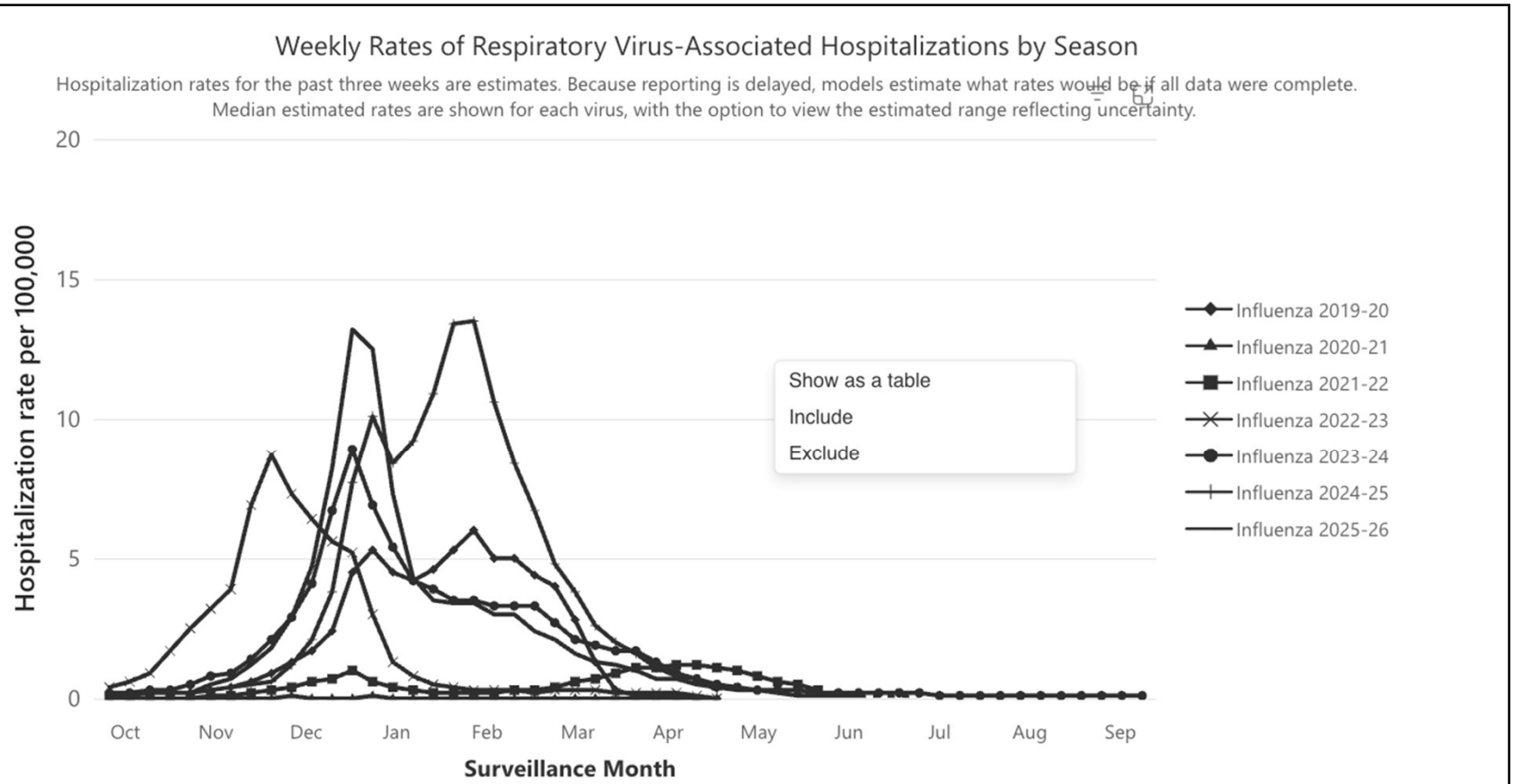

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HPAI H5N1 Influenza

- 71 confirmed cases in US, 13 states
- 41 associated with dairy cows
- 24 commercial poultry
- 3 backyard poultry
- 3 unknown exposure

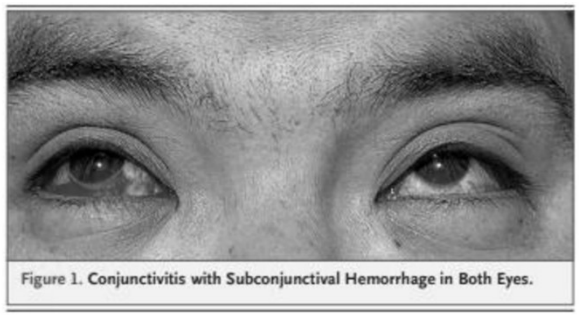
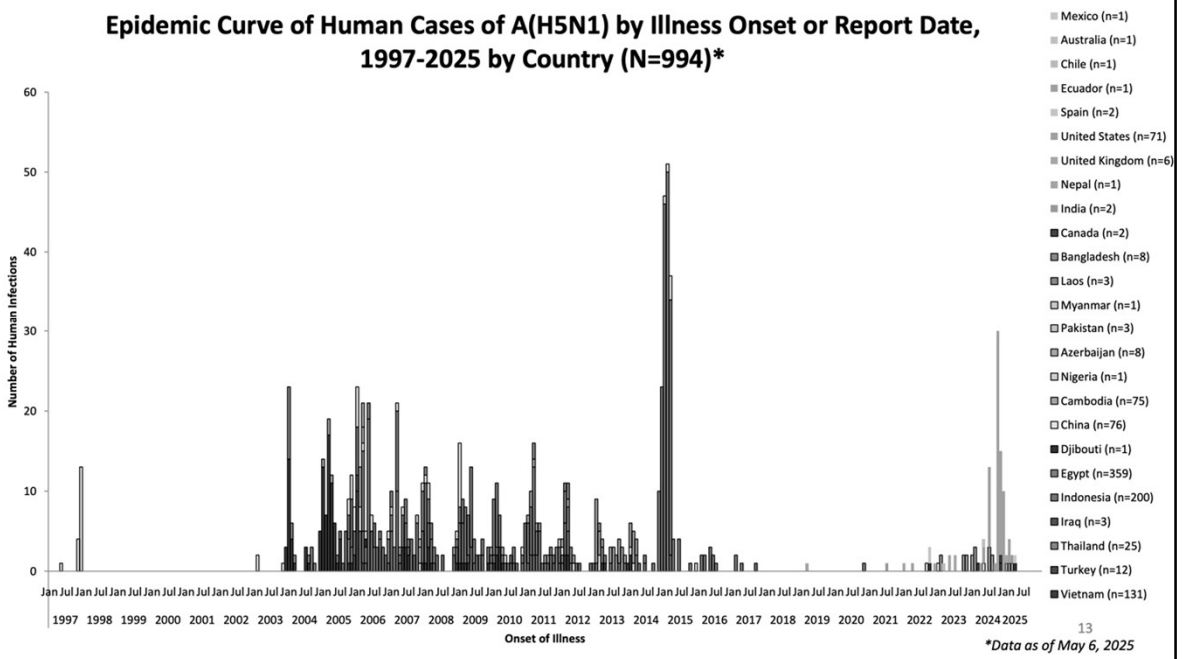


Figure 1. Conjunctivitis with Subconjunctival Hemorrhage in Both Eyes.

Uyeki NEJM 2024



Source CDC

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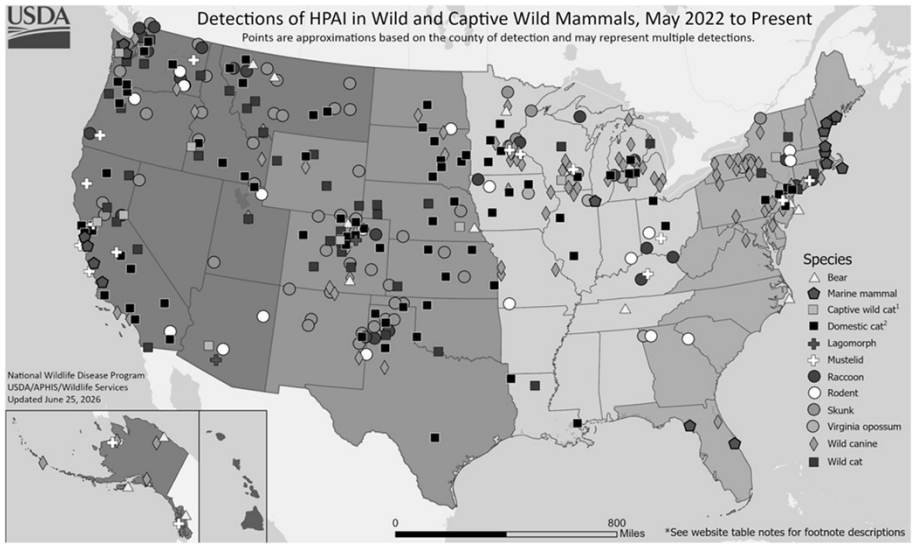
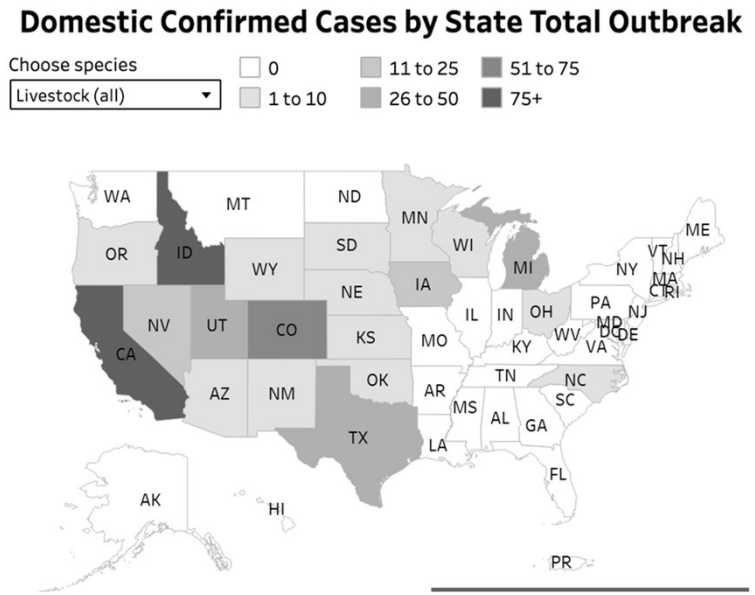
Human and Other Mammalian Cases of H5N1

Other Mammals



Cattle Herds: 1168 cases in 20 states



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https://www.aphis.usda.gov/livestock-poultry-disease/avian/avian-influenza/hpai-detections/mammals

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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.

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

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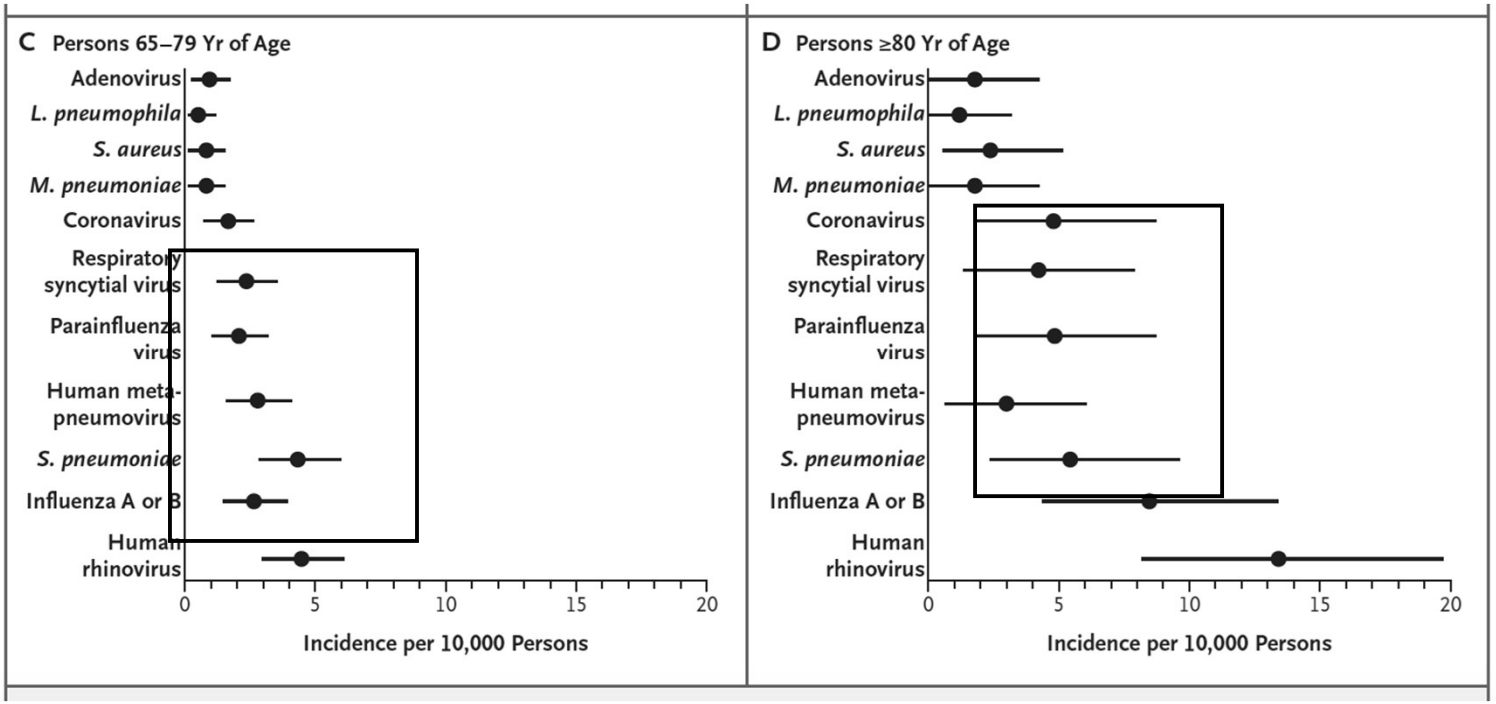
Incidence of Pathogens in Older Adults Hospitalized With CAP



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Jain NEJM 2015

7 Respiratory Viral Infections Including Influenza in Immunocompetent and Immunocompromised Persons

Speaker: Andrew Pavia, MD

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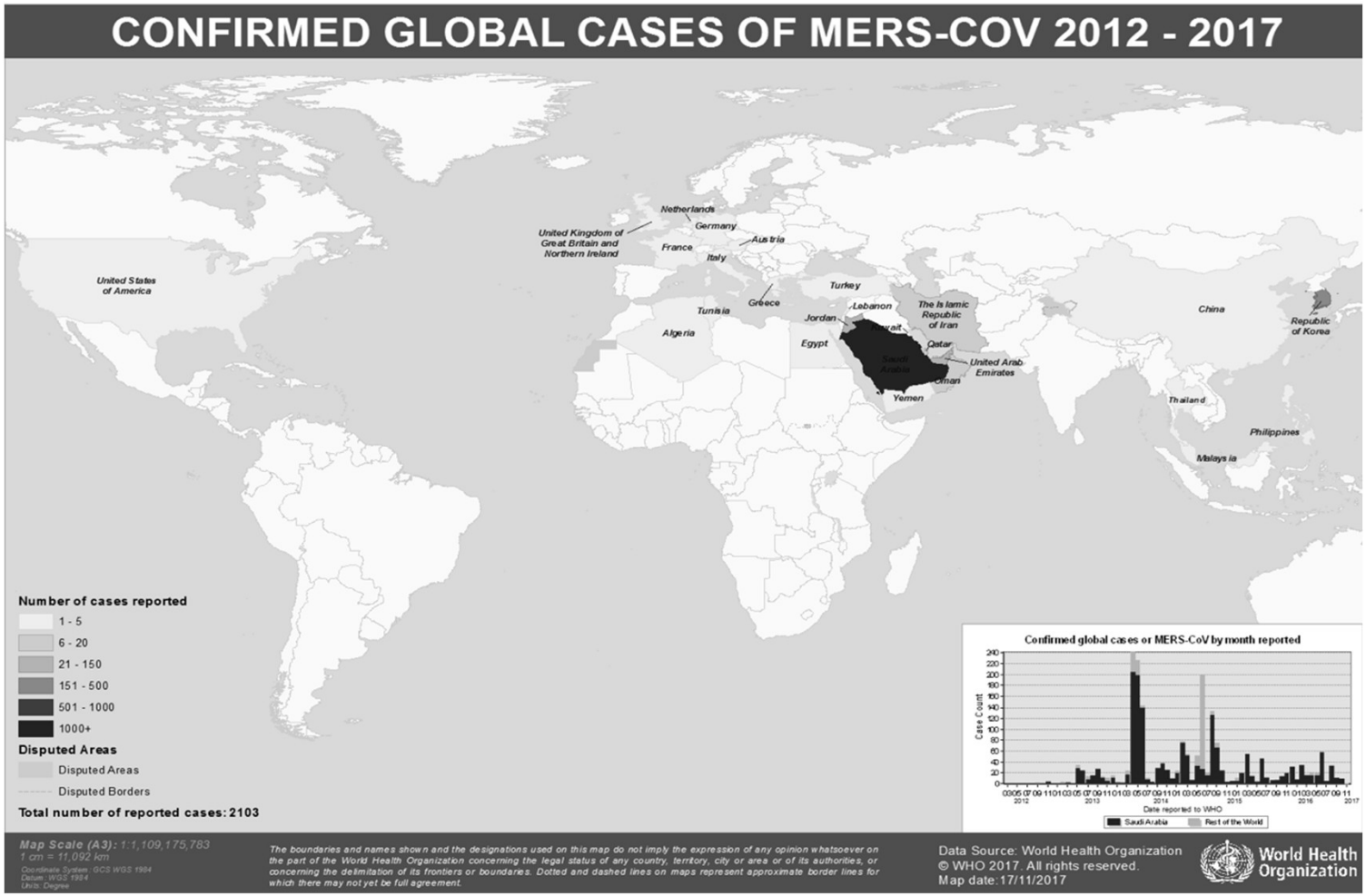

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Saturday, August 22, 2026

08

Infections in Cancer Patients

Jennifer Saullo, MD

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Infections in Cancer Patients

Jennifer Saullo, MD, PharmD, FIDSA
Associate Professor of Medicine
Transplant Infectious Diseases
Duke University Medical Center
Durham, NC

7/30/2026

Disclosures of Financial Relationships with Relevant Commercial Interests

- Royalties from UpToDate

Objectives

- Review testable complications in relevant immunocompromised hosts
- Broadly categorized, this includes
  - Risks of underlying diseases and applied chemo-, immunomodulatory and cellular therapies
  - Recognition of breakthrough infections
  - Recognition of specific clinical “syndromes”

Fundamental Concepts
Risk of Underlying Disease

- Important immune deficits associated with underlying disease
- Examples include
  - Acute myelogenous leukemia (AML) and myelodysplastic syndromes (MDS) – qualitative and quantitative neutropenia
  - Lymphomas – functional asplenia
  - Chronic lymphocytic leukemia (CLL) – hypogammaglobulinemia, complement deficiencies, neutrophil/monocyte defects
  - Multiple myeloma – hypogammaglobulinemia
  - Aplastic anemia – severe, prolonged neutropenia

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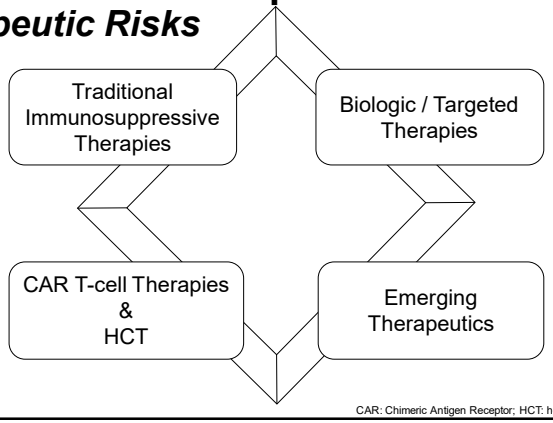
Fundamental Concepts
Therapeutic Risks



CAR: Chimeric Antigen Receptor; HCT: hematopoietic cell transplant

Fundamental Concepts
Therapeutic Risks

- Drugs that impact neutrophils
  - Cytotoxic chemotherapy (e.g., anthracycline, cyclophosphamide)
    - Infectious risks greatest when prolonged (> 7 days) and profound (< 500 cells/mm3) neutropenia
    - Severe bacterial and fungal infections

Fundamental Concepts
Therapeutic Risks

- Drugs that impact T cells
  - Purine analogs (fludaribine, cladribine, clofarabine) and temozolomide
    - Infections associated with
      - Herpesviruses (e.g., CMV, HSV, VZV)
      - Intracellular and other less common bacteria (e.g., Mycobacteria, Nocardia)
      - Fungi (e.g., PJP, Aspergillus)

CMV: Cytomegalovirus, HSV: herpes simplex virus; VZV: varicella zoster virus; PJP: *Pneumocystis jirovecii* pneumonia

Biologic / Targeted Therapies
****Online Lecture - Immunomodulatory Agents: What Can Be Tested****

Immunomodulatory Therapy	Examples	Board Buzz - Infection Risk
CD20 inhibitors	Rituximab, obintuzumab	Hepatitis B reactivation, impaired vaccine response, hypogammaglobulinemia, rare JCV PML
CD52 inhibitors	Alemtuzumab	PJP, CMV, HSV/VZV, other invasive fungal and opportunistic infections
TNF-alpha inhibitors	Infliximab, adalimumab	Tuberculosis, endemic fungi, other intracellular pathogens
Janus kinase inhibitors	Tofacitinib, ruxolitinib	Herpes zoster, TB/NTM, other opportunists
Interleukin-6 inhibitors	Tocilizumab, sarilumab	Severe infections, masked infectious signs/symptoms – normal CRP, GI perforation
Complement inhibitors	Eculizumab, ravulizumab	Severe/disseminated *Neisseria meningitis*, Gonococcal infections, other encapsulated bacteremia (e.g., Pneumococcus, *H. influenzae*)
Checkpoint inhibitors	Pembrolizumab, nivolumab, ipilimumab	PJP when treated for iRAEs and no prophylaxis, mimics from iRAEs (e.g.,pneumonitis, colitis)
Bruton's tyrosine kinase inhibitors	Ibrutinib, acalabrutinib	Invasive fungal infections (e.g., aspergillosis, cryptococcosis), including CNS involvement/dissemination

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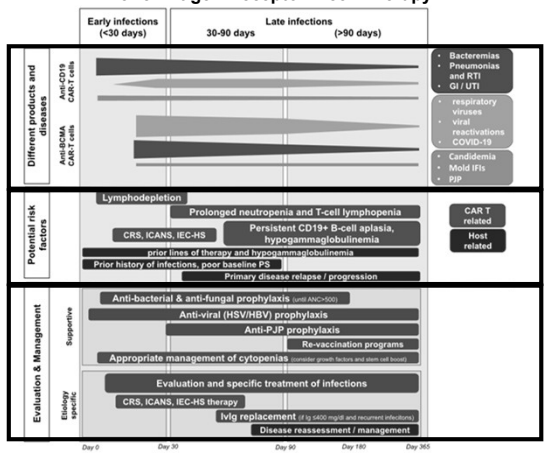
Question #1

- 61-year-old patient with relapsed/refractory diffuse large B-cell lymphoma (DLBCL) is now day +2 following CD-19-directed CAR T-cell therapy following Axicabtagene ciloleucel and received lymphodepleting chemotherapy with fludarabine and cyclophosphamide. Prophylaxis includes valacyclovir, levofloxacin, fluconazole, and SMX-TMP.
- He develops fever to 102, hypotension (90/60) requiring low-dose norepinephrine, tachycardia (HR 120s), and hypoxia (SaO2 90%). Blood cultures (peripheral and central line), urinalysis, and urine culture are sent. CXR and CT chest show mild bilateral ground-glass opacities and small pleural effusions.
- Labs: WBC 0.5 (ANC 0), CRP 4.0->10mg/dL, ferritin 200->2000 ng/mL. Remaining labs are stable.

Which of the following is the most appropriate management?

A. Modify antimicrobials: levofloxacin → IV cefepime and administer tocilizumab
B. Modify antimicrobials: levofloxacin → IV cefepime + vancomycin and administer tocilizumab
C. Modify antimicrobials: fluconazole → IV liposomal amphotericin B
D. Modify antimicrobials: valacyclovir→ IV ganciclovir
E. Administer tocilizumab x 1 dose

Chimeric Antigen Receptor T-cell Therapy



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From: Shahid Z, et al. Transplant Cell Ther. 2024 Oct;30(10):955.

Chimeric Antigen Receptor (CAR) T-cell Therapy

Variable	Cytokine Release Syndrome (CRS)	Immune Effector Cell-associated Neurotoxicity Syndrome (ICANS)
Definition	**Supraphysiologic response** after immune therapy with activation or engagement of endogenous or infused T cells and/or other immune effector cells	**Pathologic process involving the CNS** after immune therapy with activation or engagement of endogenous or infused T cells and/or other immune effector cells
Typical Onset	Early (2-3 days post-infusion)	Biphasic: early (4-10 days, overlaps with CRS), late (up to 1 month)
Incidence (range)	57-93%	20-70%
Typical Duration	7-8 days	Typically self-limited, most often 5-17 days
Typical signs/ Symptoms	**Fever (cardinal),** hypotension, hypoxia (capillary leak), may have end-organ dysfunction	Aphasia, altered consciousness, impaired cognitive skills, motor weakness, seizures, cerebral edema
First-Line Management	Supportive care (rule out infection, empiric antimicrobials + CRS directed therapies including **tocilizumab +/- corticosteroids** based on grading)	Supportive care + corticosteroids + seizures medications ***Tocilizumab does not resolve ICANS, may worsen it**

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Lee DW et al, Biol Blood Marrow Transplant. 2019;25(4):625.
Naidoo J et al. J Clin Oncol. 2021;39(35):3978. PMID: 34724386.

A Brief Primer On Consensus Grading, NOT for Memorization But For Context…

CRS Grading	Relevant Variables	Management
Grade 1	**Fever: temperature ≥ 38°C** Hypotension: none Hypoxia: none	Supportive care including consideration of broad-spectrum antibiotics, if persistent proceed to grade 2
Grade 2	**Fever: temperature ≥ 38°C** *plus* Hypotension: not requiring vasopressors *and/or* Hypoxia: requiring low-flow nasal cannula	Supportive care as above + tocilizumab +/- corticosteroids
Grade 3	**Fever: temperature ≥ 38°C** *plus* Hypotension: requiring vasopressors *and/or* Hypoxia: requiring high -flow nasal cannula, facemask, non-rebreather mask, or Venturi mask	Supportive care as above + tocilizumab +corticosteroids, admission to ICU
Grade 4	**Fever: temperature ≥ 38°C** *plus* Hypotension: requiring multiple vasopressors *and/or* Hypoxia: requiring positive pressure	Supportive care as above + tocilizumab + corticosteroids, admission to ICU +/- mechanical ventilation

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Naidoo J et al. J Clin Oncol. 2021;39(35):3978. PMID: 34724386.

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Interleukin-6 Inhibitors
Infection Risks

- **Black box warning (tocilizumab, sarilumab)** – bacterial, mycobacterial, fungal, protozoal / OIs
- **Bacterial infections** – severe pneumonia/bronchitis, UTI, cellulitis
- **Viral infections** – herpesviruses, HBV, HCV; HBsAg+ high risk, HBsAg-/HBcAb+ moderate risk
- **Fungal infections** – PJP, cryptococcus, aspergillosis, candidiasis, endemic fungi
- **Mycobacterial infections** – TB, pre-transplant screening
- **Additional considerations**
  - **May mask typical signs and symptoms of infection** (fever, elevated inflammatory markers – CRP)
  - Consider the possibility of disseminated infections
  - **GI perforation risk** – distinct risk with IL-6 inhibitors, particularly in patients with diverticulitis +/- concurrent corticosteroids

Question #2

- 40-year-old male with relapsed B-cell ALL is on day 15 of cycle 3 of **blinatumomab** via continuous infusion through a Hickman catheter. Prophylaxis includes valacyclovir, levofloxacin, fluconazole, and SMX-TMP.
- He develops fevers to 39.0, rigors, tachycardia (HR 120s), and hypotension (82/48), requiring vasopressors, and is transferred to the intensive care unit. He is lethargic but has a non-focal exam, including no tenderness, warmth, or drainage over the Hickman catheter. CXR is non-focal.
- Labs: WBC 1.3 (ANC 400), creatinine of 1.5 (baseline 1.0), normal hepatic panel, and elevated CRP. Blood cultures, urinalysis, and urine cultures are sent.

Which of the following is the most appropriate next step in management?

A. Modify antimicrobials: levofloxacin → IV cefepime + vancomycin and administer tocilizumab
B. Modify antimicrobials: levofloxacin → IV cefepime + vancomycin
C. Modify antimicrobials: fluconazole → IV liposomal amphotericin B
D. Modify antimicrobials: valacyclovir→ IV ganciclovir
E. Administer tocilizumab x 1 dose

Biologic/Targeted Therapies
Bispecific Therapeutics

- T-cell-engaging Bispecific Antibodies (BsAbs; aka BiTE)
- Simultaneously bind to antigens on tumor cells and CD3 subunits on T cells
- Recruit T cells to the tumor → T-cell activation and degranulation→ tumor cell elimination
- Have shown substantial activity in several hematological malignancies targeting
  - CD19 in acute lymphoblastic leukemia → Blinatumomab, first-in-class BiTE
  - CD20 in B-cell non-Hodgkin lymphoma
  - BCMA and GPRC5D in multiple myeloma

Biologic/Targeted Therapies
Blinatumomab – BiTE

- Mechanism/immune defect
  - Bridges CD3+ T cells to CD19+ B cells → forms cytolytic synapse → T-cell activation → release of perforin/granzymes → serial lysis of CD19+ cells (malignant and normal B cells)
  - B-cell aplasia and hypogammaglobulinemia
  - Neutropenia
- Use – B-cell precursor ALL
- Other important considerations
  - Short half-life (2.2 hours), requires continuous infusion x 28 days each cycle→ think about sepsis/CLABSIs**
  - CRS – median onset day 2 and risk greater with earlier than later cycles
  - ICANS
  - Hepatotoxicity, pancreatitis
  - Severe infections – including bacterial (bacteremia, PnA), viral (HSV/VZV, HBV reactivation, CMV PML/JCV rare) and OIs including PJP

Timing in the question stem was KEY – by C3D15, B cells are completely depleted, so there are no CD19+ target cells to trigger T-cell activation. CRS in later cycles quite uncommon → think infection > CRS… mimics are important!

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Biologic/Targeted Therapies
Bispecific Therapy in Multiple Myeloma

- **Agents:** 4 currently available; target tumor-associated antigens on myeloma cells
  - BCMA x CD3 – teclistamab, elranatamab, linvoseltamab (IV)
  - GPRC5D x CD3 – talquetamab
- **Mechanism/Immune defect**
  - B-cell, plasma cell aplasia and hypogammaglobulinemia (*particularly with BCMA-targeted therapies)
  - Neutropenia and T-cell exhaustion
  - Immune defects compounded with treatment for CRS/ICANS
- **Infectious risks**
  - Infections #1 cause of non-relapse mortality; BCMA > GPRC5D
  - **Bacterial** – respiratory tract infections, bacteremia
  - **Viral** – respiratory viruses, HSV/VZV, HBV, CMV, JCV-PML (rare)
  - **Fungal** – PJP and opportunistic molds and endemics
- **Prevention**
  - **Viral ppx** – e.g., (val)acyclovir, indefinitely on therapy
  - **PJP ppx** – duration of therapy + ≥ 6 months and CD4 ≥ 200 (whichever longest)
  - **Bacterial/fungal ppx** – for ANC < 500
  - Supplemental IVIG, update vaccinations PRIOR to start

SEE ENLARGED SLIDE FOLLOWING ENTIRE PRESENTATION

Neutropenic Fever and "Syndromes"

Question #3

- 70-year-old male with AML and recent initiation of azacitidine and venetoclax presenting with neutropenic fever (102F) and fatigue
- VS – 120/80, HR 100, RR 14, Sa02 96% on ambient air
- Exam – no significant OP lesions, lungs CTA, abd soft, nt/nd, no peri-rectal lesions/pain, no skin rash or lesions, no pain/redness/tenderness over central access site
- Cultures – blood/urine pending
- CXR – non-focal
- Current prophylaxis – levofloxacin and acyclovir
- Prior infection history – none

Which of the following is the most appropriate change in therapy?

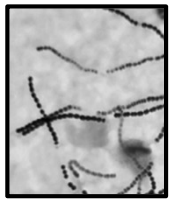
A. Levofloxacin → IV cefepime
B. Levofloxacin → IV cefepime + vancomycin
C. Levofloxacin → IV cefepime + metronidazole
D. Acyclovir → IV ganciclovir
E. Addition of antifungal therapy

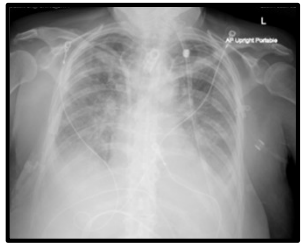
Question #4

- 35-year-old woman with AML, day 15 of induction therapy. Presentation - fever, chills, diffuse erythematous rash
- Exam – 100/62, HR 120, grade 2 oral mucositis, diffuse, blanching, erythematous rash
- Cultures - blood cultures with GPC in chains.
- CXR - bilateral diffuse infiltrates
- Prophylaxis - levofloxacin and acyclovir

Which organism is the most likely cause of this infection?

A. Streptococcus pneumoniae
B. Coagulase-negative Staphylococcus
C. Enterococcus faecalis
D. Streptococcus mitis
E. Stomatococcus mucilaginosus





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Viridans Group Streptococci (VGS)

- VGS include S. mitis, S. oralis, S. sanguinis
- Portal of entry: normal flora of the oral cavity, upper respiratory, and GI/GU tract
- Clinical presentation
  - Can include fevers, chills, flushing, stomatitis, pharyngitis
  - VGSS - **toxic shock-like syndrome**
    - Early vs late (2–3 days after presentation)
    - Hypotension→ respiratory failure→ **ARDS**
    - Maculopapular rash – centrifugal spread +/- palmar/sole desquamation
- Risk factors: profound neutropenia (AML, HCT), oral mucositis, high-dose cytarabine, fluoroquinolone prophylaxis, prior VGS
- Treatment: beta-lactams (increasing PCN resistance), **vancomycin (VGSS/ARDS)**

Shelburne et al. Clin Infect Dis. 2014;59(2):223.
Toonkel AR, Sepkowitz KA. Clin Infect Dis 2002;34(11):1524.

Board Testable Scenarios: Breakthrough BSIs

- Typical patient - neutropenic, progressive sepsis
- Recognize clinical presentation and holes in antimicrobial coverage
  - **ARDS, rash, quinolones, mucositis** → viridans Streptococci
  - **Sepsis with β-lactams** → Extended-spectrum (ESBL) and AmpC β-lactamase-Producing Enterobacterales +/- Stenotrophomonas
  - **Sepsis with carbapenems** → Carbapenem-resistant Enterobacterales/Acinetobacter baumannii, Stenotrophomonas (and other beta-lactams)
  - **Sepsis with broad-spectrum antibiotics** → Vancomycin-resistant Enterococcus (VRE)
  - **Lung and skin lesions** → P. aeruginosa (Ecthyma gangrenosum), fungi, Nocardia
  - **Mucositis (upper, lower tract)** → Fusobacterium spp., Clostridium spp including C. septicum, Rothia mucilaginosa

Question #5

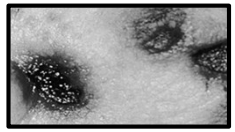
- 59-year-old woman with AML with neutropenia for 25 days and febrile for 6 days. She is receiving meropenem, vancomycin and acyclovir. Now with new skin lesions that are small, tender papules without central ulceration.

This is most consistent with infection with which of the following organisms?

A. Rhizopus spp.
B. Varicella zoster virus
C. Cryptococcus neoformans
D. Vancomycin resistant Enterococci
E. Candida tropicalis

Skin Lesions

- Candidiasis
  - Small, tender papules
- Herpes
  - Vesicular
- Aspergillus
  - Ulcerative, necrotic
- P. aeruginosa
  - Ecthyma gangrenosum
- Other filamentous fungi (Fusarium spp, Scedosporium spp)



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- 35-year-old woman with relapsed AML with dense neutropenia for over 30 days
- Ongoing fevers with rapidly progressing, painful papular and nodular lesions, varying stages, some with central necrosis.
- Receiving meropenem, vancomycin, micafungin and acyclovir.
- Micro lab update that blood cultures are growing a “mold”

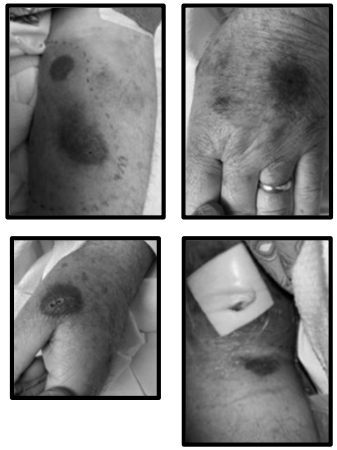
FUSARIOSIS

Question #6

- 70-year-old male with newly diagnosed AML developed erythematous, tender and edematous plaques over sites of trauma (blood draws, peripheral IV). He has been febrile to 38.7°C for the past several days.

What is the most likely etiology?

A. Candida albicans
B. Sweet’s syndrome
C. Aspergillus niger
D. Varicella Zoster virus
E. Pseudomonas aeruginosa



Sweet’s Syndrome

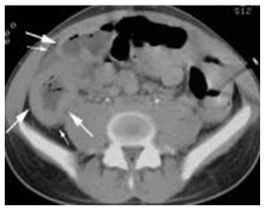
- Acute febrile neutrophilic dermatosis
- **Variants**
  - Classic (idiopathic)
  - Malignancy-associated (hematologic, most common – **AML**, MDS), often precedes or coincides with diagnosis
  - Drug-induced (e.g., G-CSF as trigger, bortezomib, others)
- **Clinical Presentation**
  - Skin (most common) - tender erythematous plaques and nodules (typical); also bullous, cellulitic, subcutaneous, and necrotizing lesions
  - Can demonstrate **pathergy** (lesions at site of trauma/injury)
  - Extracutaneous – can involve virtually any organ system (e.g., eyes, lungs, joints, kidney, CNS)
- **Classic Stem** – neutropenia→ **G-CSF initiated**→ neutropenia resolving→ fever + tender skin lesions→ cultures negative and biopsy shows dense dermal neutrophilic infiltrate
- **Treatment** – steroids (first-line); in cases of malignancy, treatment targeted at underlying disease

Question #7

- 70-year-old woman with AML receiving induction chemotherapy and neutropenic for 15 days. Develops fever, diarrhea and abdominal pain. Exam with decreased bowel sounds and tenderness with deep palpation in her RLQ. CT shows inflammation in cecum. Receiving levofloxacin and fluconazole prophylaxis. Four days prior to her admission for chemotherapy she ate out at a Chinese restaurant and had fried rice.

Which is the most likely etiology?

A. Norovirus
B. Clostridioides (Clostridium) difficile
C. Mixed anaerobic and aerobic bacteria
D. Candida albicans
E. Bacillus cereus



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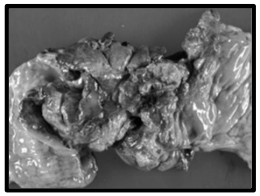
Neutropenic Enterocolitis

- AKA typhlitis, ileocecal syndrome (Greek: typhlon = cecum)
- **Mechanism:** chemotherapy-induced mucosal injury → secondary bacterial/fungal invasion of bowel wall during neutropenia → transmural necrosis
- **Risks**
  - Cytotoxic chemotherapy (e.g., high-dose cytarabine) +/- steroids
  - Dense neutropenia
- **Clinical Presentation**
  - Fever + abdominal pain + neutropenia
  - Can be accompanied by bacteremia (hint: mixed, anaerobic with C. septicum, C. tertium, Bacteroides spp)
- **Microbiology:** polymicrobial with gram-negative, gram-positive, anaerobic bacteria and fungi
- **Diagnostics:** CT imaging (mural thickening, fat stranding, pneumatosis)
- **Management:** medical (supportive care, IV antimicrobials +/- G-CSF), less often surgical management
- **Relevant DdX:** C difficile, viral colitis (CMV, adenovirus), GVHD, acute appendicitis



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From: Xia R, Zhang X. World J Gastrointest Pathophysiol 2019;10(3):36.

Hepatosplenic Candidiasis

- Form of chronic disseminated candidiasis, primarily involves liver & spleen, occasionally other organs – kidney
- **Clinical Clues**
  - Hematologic malignancy, prolonged neutropenia, not improving on broad-spectrum antibiotics
  - Fever, abdominal/flank pain, hepatosplenomegaly, nausea/vomiting
  - Neutrophil recovery/engraftment (typically occurs within 2 weeks)
  - Labs: abnormal hepatic panel (↑alk phos)
- **Microbiology** – C. albicans most common, C. tropicalis, alt Candida spp
- **Diagnostics**
  - **Blood cultures often negative**, role of BDG, biopsy
  - Imaging: more sensitive AFTER neutrophil recovery – US, CT, MRI
- **Differential** – other fungi, bacteria/mycobacteria, underlying cancer
- **Treatment** – echinocandin or lipid formulation of amphotericin B, step-down course with oral azole (+/- steroids)

SEE ENLARGED SLIDE FOLLOWING ENTIRE PRESENTATION

Pappas PG. Clin Infect Dis. 2016;62(4):e1.

Infections in Neutropenic Cancer Patients Summary of Key Points

- Recognize typical infections associated with neutropenia and/or immunomodulatory therapies
- Predict breakthrough pathogens based on applied therapies
- Know specific syndromes
  - VGS sepsis
  - Differential of skin lesions
  - Invasive fungal infections in neutropenic patients
    - Sinopulmonary
    - Bloodstream
    - Hepatosplenic candidiasis
  - Neutropenic enterocolitis

Thank You

Questions/Comments:
jennifer.horan@duke.edu

Special Thanks to Kieren Marr, MD

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Biologic / Targeted Therapies

Online Lecture - Immunomodulatory Agents: What Can Be Tested

Immunomodulatory Therapy	Examples	Board Buzz - Infection Risk
CD20 inhibitors	Rituximab, obintuzumab	Hepatitis B reactivation, impaired vaccine response, hypogammaglobulinemia, rare JCV PML
CD52 inhibitors	Alemtuzumab	PJP, CMV, HSV/VZV, other invasive fungal and opportunistic infections
TNF-alpha inhibitors	Infliximab, adalimumab	Tuberculosis, endemic fungi, other intracellular pathogens
Janus kinase inhibitors	Tofacitinib, ruxolitinib	Herpes zoster, TB/NTM, other opportunists
Interleukin-6 inhibitors	Tocilizumab, sarilumab	Severe infections, masked infectious signs/symptoms – normal CRP, GI perforation
Complement inhibitors	Eculizumab, ravulizumab	Severe/disseminated *Neisseria meningitis*, Gonococcal infections, other encapsulated bacteremia (e.g., Pneumococcus, *H. influenzae*)
Checkpoint inhibitors	Pembrolizumab, nivolumab, ipilimumab	PJP when treated for iRAEs and no prophylaxis, mimics from iRAEs (e.g.,pneumonitis, colitis)
Bruton's tyrosine kinase inhibitors	Ibrutinib, acalabrutinib	Invasive fungal infections (e.g., aspergillosis, cryptococcosis), including CNS involvement/dissemination

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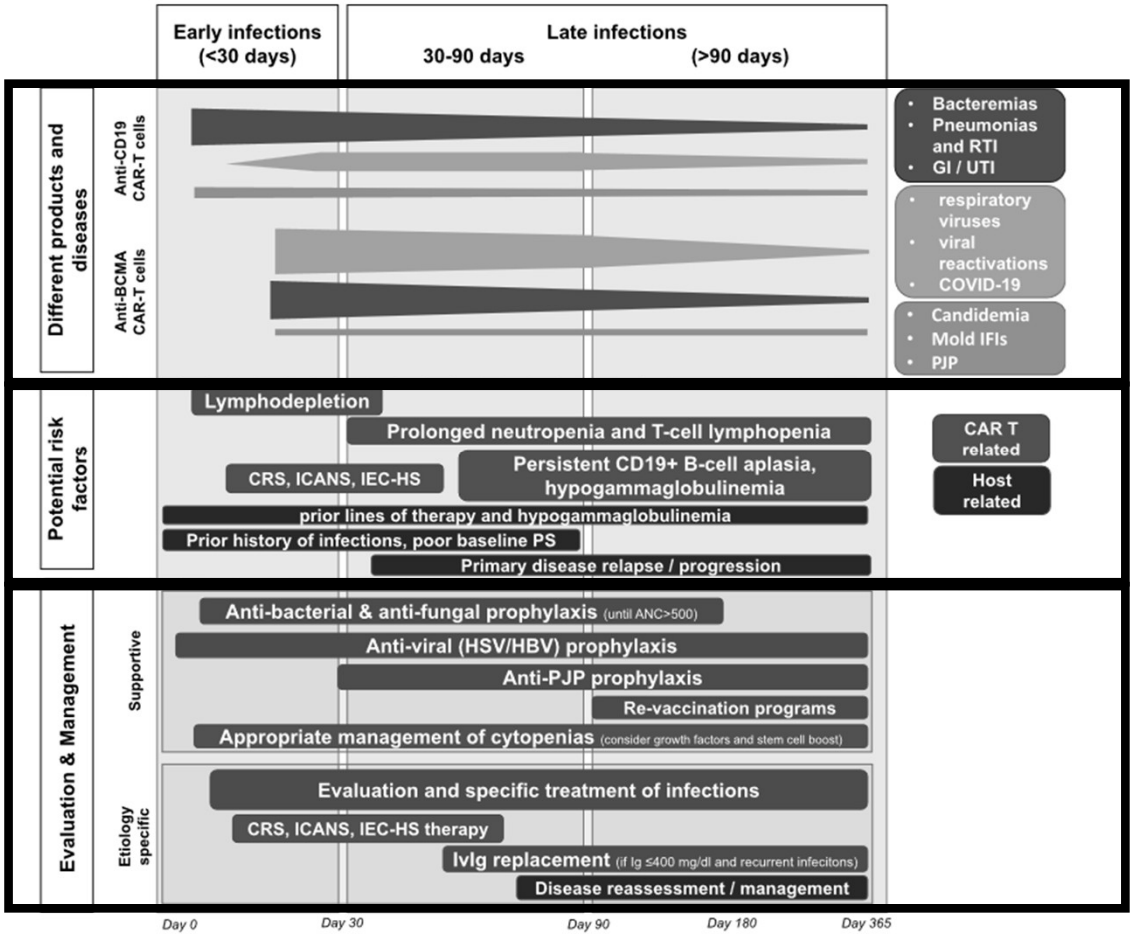
Chimeric Antigen Receptor T-cell Therapy



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From: Shahid Z, et al. Transplant Cell Ther. 2024 Oct;30(10):955.

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Chimeric Antigen Receptor (CAR) T-cell Therapy

Variable	**Cytokine Release Syndrome (CRS)**	**Immune Effector Cell-associated Neurotoxicity Syndrome (ICANS)**
Definition	**Supraphysiologic response** after immune therapy with activation or engagement of endogenous or infused T cells and/or other immune effector cells	**Pathologic process involving the CNS** after immune therapy with activation or engagement of endogenous or infused T cells and/or other immune effector cells
Typical Onset	Early (2-3 days post-infusion)	Biphasic: early (4-10 days, overlaps with CRS), late (up to 1 month)
Incidence (range)	57-93%	20-70%
Typical Duration	7-8 days	Typically self-limited, most often 5-17 days
Typical signs/ Symptoms	**Fever (cardinal),** hypotension, hypoxia (capillary leak), may have end-organ dysfunction	Aphasia, altered consciousness, impaired cognitive skills, motor weakness, seizures, cerebral edema
First-Line Management	Supportive care (rule out infection, empiric antimicrobials + CRS directed therapies including **tocilizumab +/- corticosteroids** based on grading)	Supportive care + corticosteroids + seizures medications ***Tocilizumab does not resolve ICANS, may worsen it**

SEE ENLARGED SLIDE FOLLOWING ENTIRE PRESENTATION

Lee DW et al, Biol Blood Marrow Transplant. 2019;25(4):625.
Naidoo J et al. J Clin Oncol. 2021;39(35):3978. PMID: 34724386.

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A Brief Primer On Consensus Grading, NOT for Memorization But For Context…

CRS Grading	Relevant Variables	Management
Grade 1	**Fever: temperature ≥ 38°C** Hypotension: none Hypoxia: none	Supportive care including consideration of broad-spectrum antibiotics, if persistent proceed to grade 2
Grade 2	**Fever: temperature ≥ 38°C** *plus* Hypotension: not requiring vasopressors *and/or* Hypoxia: requiring low-flow nasal cannula	Supportive care as above + tocilizumab +/- corticosteroids
Grade 3	**Fever: temperature ≥ 38°C** *plus* Hypotension: requiring vasopressors *and/or* Hypoxia: requiring high -flow nasal cannula, facemask, non-rebreather mask, or Venturi mask	Supportive care as above + tocilizumab +corticosteroids, admission to ICU
Grade 4	**Fever: temperature ≥ 38°C** *plus* Hypotension: requiring multiple vasopressors *and/or* Hypoxia: requiring positive pressure	Supportive care as above + tocilizumab + corticosteroids, admission to ICU +/- mechanical ventilation

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Naidoo J et al. J Clin Oncol. 2021;39(35):3978. PMID: 34724386.

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Biologic/Targeted Therapies
Bispecific Therapy in Multiple Myeloma

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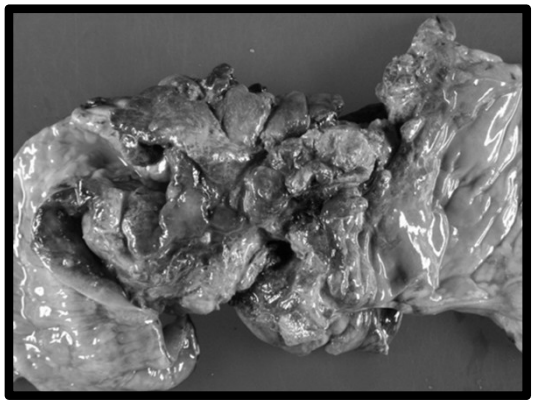

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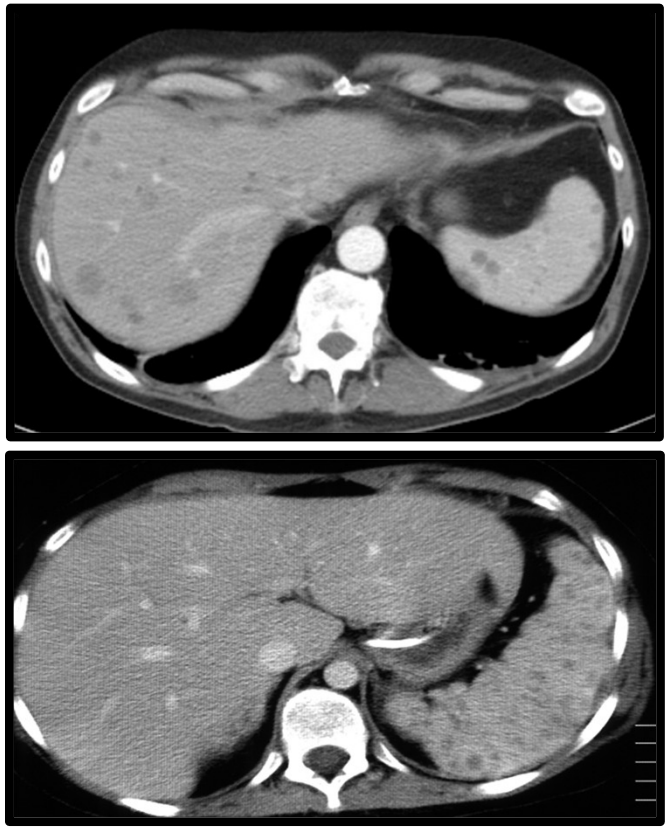

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Pappas PG. Clin Infect Dis. 2016;62(4):e1.

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Saturday, August 22, 2026

09

SARS-CoV-2 and COVID-19

Andrew Pavia, MD

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SARS-CoV-2 and Covid 19

Andrew T. Pavia, MD
University of Utah

8/1/2026

Disclosures of Financial Relationships with Relevant Commercial Interests

- Antimicrobial Therapy Inc,
- Haleon

What Seems Testable

- Disease course
  - High risk groups
- Diagnosis
  - NAAT, antigen, serology
- Treatment recommendations
- Vaccine complications
  - Myocarditis
- MIS-C/A
- Probably not vaccine recommendations (currently too political), variants (too changeable), long covid (no proven therapy

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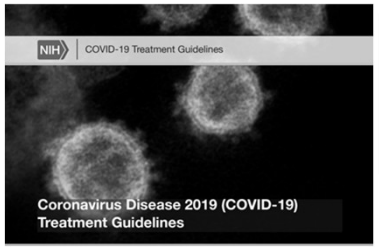

Roy M Gulick 1, Alice K Pau 2, Eric Daar 3, Laura Evans 4, **Rajesh T Gandhi 5**, Pablo Tebas 6, Renée Ridzon 2, **Henry Masur 2**, H Clifford Lane 2; NIH COVID-19 Treatment Guidelines Panel; Adaora A Adimora, Jason Baker, Lisa Baumann Kreuziger, Roger Bedimo, Pamela Belperio, Anoopindar Bhalla, Timothy Burgess, Danielle Campbell, Stephen Cantrill, Kara Chew, Kathleen Chiotos, Craig Coopersmith, Richard Davey, Amy Dzierba, Derek Eisnor, Gregory Eschenauer, Joseph Francis, John Gallagher, David Glidden, Neil Goldenberg, Birgit Grund, Alison Han, Erica Hardy, Carly Harrison, Lauren Henderson, Elizabeth Higgs, Carl Hinkson, Brenna Hughes, Steven Johnson, Marla Keller, Arthur Kim, Richard Knight, Safia Kuriakose, Jeffrey Lennox, Andrea Lerner, Mitchell Levy, Jonathan Li, Christine MacBrayne, Greg Martin, Nandita Nadig, Martha Nason, Pragna Patel, **Andrew Pavia**, Michael Proschan, Grant Schulert, Nitin Seam, Virginia Sheikh, Steven Simpson, Kanal Singh, Susan Swindells, Phyllis Tien, Timothy Uyeki, Alpana Waghmare, Cameron Wolfe, Jinoos Yazdany, Judith Aberg

Ann Intern Med. 2024 Nov;177(11):1547
https://wayback.archive-it.org/4887/20240626155208/https://www.covid19treatmentguidelines.nih.gov/

IDSA PRACTICE GUIDELINES ● CURRENT

IDSA Guidelines on the Treatment and Management of Patients with COVID-19

Published August 12, 2024 **Last Updated** January 23, 2023

(as of spring 2024) Adarsh Bhimraj, Yngve Falck-Ytter, Arthur Y. Kim, Jonathan Li, Lindsey R. Baden, Steven Johnson, Robert W. Shafer, Shmuel Shoham, Pablo Tebas, Roger Bedimo, Vincent Chi-Chung Cheng, Kara Chew, Kathleen Chiotos, Eric Daar, Amy L. Dzierba, David V. Glidden, Erica J. Hardy, Greg S. Martin, Christine MacBrayne, Nandita Nadig, Mari M. Nakamura, Amy Hirsch Shumaker, Phyllis Tien, Jennifer Loveless, Rebecca L. Morgan, Rajesh T. Gandhi

(prior to spring 2024) Adarsh Bhimraj,* Rebecca L. Morgan,** Amy Hirsch Shumaker, Lindsey Baden, Vincent Chi-Chung Cheng, Kathryn M. Edwards, Jason C. Gallagher, Rajesh T. Gandhi, William J. Muller, Mari M. Nakamura, John C. O'Horo, Robert W. Shafer, Shmuel Shoham, M. Hassan Murad,** Reem A. Mustafa, ** Shahnaz Sultan,** Yngve Falck-Ytter**

https://www.idsociety.org/practice-guideline/covid-19-guideline-treatment-and-management/

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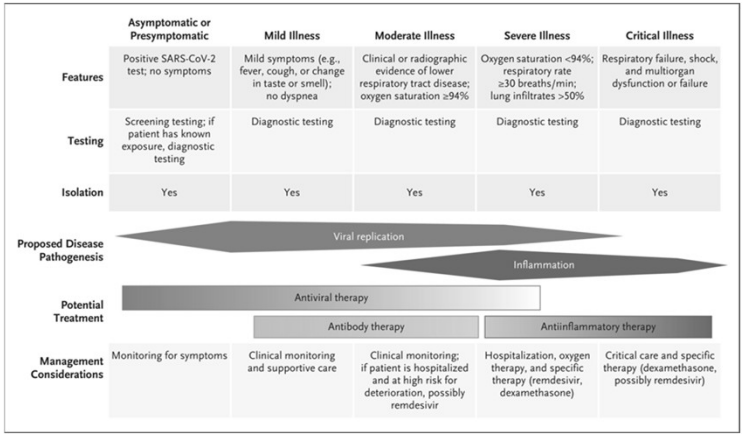

SEE ENLARGED SLIDE FOLLOWING ENTIRE PRESENTATION

Gandhi. N Engl J Med 2020;383:1757-1766

Diagnostics

- NAAT most sensitive and specific.
  - May remain positive for weeks
- Antigen detection. Highly specific but lower sensitivity, especially early. Beware false negative
- Serology. IDSA recommends against for diagnosis of acute disease
  - Antibody to spike detects vaccination and infection
  - Persists. No correlate of protection for binding antibody
  - Antibody to nucleocapsid reflects infection
- Antibody testing may be helpful in MIS-C/A

Question #1

- A 35-year-old woman presents to your ED because she tested positive for Covid-19 at home. She is coughing, fatigued and has a low-grade fever
- She is 30 weeks pregnant. She has familial hypercholesterolemia and her BMI is 36
- You find out she had Covid vaccine in the summer of 2020 (5 years ago) but has not had a booster nor a known infection since
- She is febrile and uncomfortable. Her exam is otherwise unremarkable
- O2 saturation 92% on room air

Question #1

What is the most appropriate therapy?

A. Molnupiravir for 5 days
B. Monoclonal antibody against SARS-CoV-2
C. Hospitalize her for 5 days of IV remdesivir and dexamethasone
D. Nirmatrelvir-ritonavir (Paxlovid) as outpatient but instruct her to hold her statin for 7 days
E. Prednisone or dexamethasone alone

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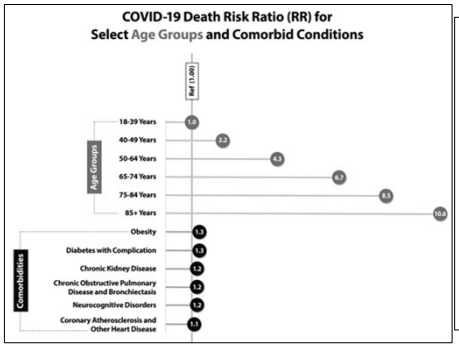
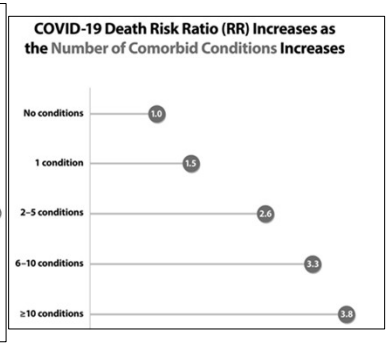
Risk Factors for Severe Disease





- Immunocompromise
- Pregnancy
- Social determinants of health

SEE ENLARGED SLIDE FOLLOWING ENTIRE PRESENTATION

Kompaniyets. Prev Chronic Dis 2021;18:2101230

Covid-19: Therapeutic Management of Outpatients

Management of Nonhospitalized Patients

Patient Disposition	Panel's Recommendations
All Patients	• Symptom management should be initiated for all patients (AIII). • The Panel recommends against the use of dexamethasone or other systemic corticosteroids (AIIb), unless these agents are being used to treat an underlying condition (AIII).
Patients Who Are at High Risk for Progressing to Severe COVID-19	*Preferred therapies. Listed in order of preference:* • Ritonavir-boosted nirmatrelvir (Paxlovid) (AIIa). Start as soon as possible and within 5 days of symptom onset. See footnote on drug-drug interactions. • Remdesivir (BIIa). Start as soon as possible and within 7 days of symptom onset. *Alternative therapy. For use when the preferred therapies are not available, feasible to use, or clinically appropriate:* • Molnupiravir (CIIa). Start as soon as possible and within 5 days of symptom onset. There is insufficient evidence for the Panel to recommend either for or against initiating these antiviral agents after the timeframes listed above.
Each recommendation in the Guidelines receives a rating for the strength of the recommendation (A, B, or C) and a rating for the evidence that supports it (I, IIa, IIb, or III).	

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Antiviral Agents for Sars-CoV-2 Infection

- Paxlovid (nirmatrelvir/ritonavir)
  - Decreased hospitalization or death by 86% in unvaccinated patients with increased risk. Recent study in highly immune patients with modestly increased risk did not show reduced hospitalization
  - Considered safe in pregnancy
  - Many DDI's via CYP3A. Many are manageable. https://www.covid19-druginteractions.org/
- IV Remdesivir
  - 3 days effective for high-risk outpatients in PineTree
  - 5 days for hospitalized patients
- Molnupiravir
  - Inhibits viral replication by inducing RNA mutagenesis
  - Less effective than N/R or remdesivir
  - Contraindicated in pregnancy, patients < 18 years
- Convalescent plasma (?)

Covid-19: Therapeutic Management of Hospitalized Patients - 1

Disease Severity	Recommendations for Antiviral or Immunomodulator Therapy		Recommendations for Anticoagulant Therapy
	Clinical Scenario	Recommendation	
Hospitalized for Reasons Other Than COVID-19	Patients with mild to moderate COVID-19 who are at high risk for progressing to severe COVID-19	Recommendations for these patients are the same as those for nonhospitalized adults with COVID-19. See the Management of Nonhospitalized Patients figure.	For patients without an indication for therapeutic anticoagulation: • Prophylactic dose of heparin, unless contraindicated (AI); (BIII) for pregnant patients
Hospitalized but Does Not Require Supplemental Oxygen	All patients	The Panel recommends against the use of dexamethasone (AIIa) or other systemic corticosteroids (AIII) for the treatment of COVID-19.	
	Patients who are at high risk for progressing to severe COVID-19	Remdesivir (BIIb) for patients who are immunocompromised; (BIII) for other high-risk patients.	
Hospitalized and Requires Conventional Oxygen	Patients who require minimal conventional oxygen	Remdesivir (BIIa).	For nonpregnant patients with D-dimer levels above the ULN who do not have an increased bleeding risk: • Therapeutic dose of heparin (CIIa) For other patients: • Prophylactic dose of heparin, unless contraindicated (AI); (BIII) for pregnant patients
	Most patients	Use dexamethasone plus remdesivir (BIIa). If remdesivir cannot be obtained, use dexamethasone (BI).	
	Patients who are receiving dexamethasone and who have rapidly increasing oxygen needs and systemic inflammation	Add 1 of the following immunomodulators: *Preferred* • PO baricitinib (BIIa) • IV tocilizumab (BIIa) *Alternatives (Listed in Alphabetical Order)* • IV abatacept (CIIa) • IV infliximab (CIIa)	

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Covid-19: Therapeutic Management of Hospitalized Patients - 2

Disease Severity	Recommendations for Antiviral or Immunomodulator Therapy		Recommendations for Anticoagulant Therapy
	Clinical Scenario	Recommendation	
Hospitalized and Requires HFNC Oxygen or NIV	All patients	Dexamethasone should be administered to all patients (AI). If not already initiated, promptly add 1 of the following immunomodulators: *Preferred* • PO baricitinib (AI) *Preferred Alternative* • IV tocilizumab (BIIa) *Additional Alternatives (Listed in Alphabetical Order)* • IV abatacept (CIIa) • IV infliximab (CIIa) Add remdesivir to 1 of the options above in certain patients.	For patients without an indication for therapeutic anticoagulation: • Prophylactic dose of heparin, unless contraindicated (AI); (BII) for pregnant patients For patients who start on a therapeutic dose of heparin in a non-ICU setting and then transfer to the ICU, the Panel recommends switching to a prophylactic dose of heparin, unless there is another indication for therapeutic anticoagulation (BIII).
Hospitalized and Requires MV or ECMO	All patients	Dexamethasone should be administered to all patients (AI). If the patient has not already received a second immunomodulator, promptly add 1 of the following (listed in alphabetical order): • PO baricitinib (BIIa) • IV tocilizumab (BIIa)	

SEE ENLARGED SLIDE FOLLOWING ENTIRE PRESENTATION

Question #2

- 23-year-old man presents with 3 days of fever, abdominal pain, diarrhea; one day of chest pain and shortness of breath
- He and his housemates had cough, fever, sore throat 4 weeks ago. One of them developed anosmia and tested positive for SARS-CoV-2
- On exam he is tachypneic, tachycardic and febrile to 38.4 with mild conjunctivitis, rales at both lung bases and abdominal tenderness
- WBC 10K, ANC 1000; Platelets 140K, Creatine 1.9, CRP 22, transaminases in 90s, Ferritin 1020;
- CXR shows pulmonary edema, no consolidation. EKG non-specific T wave inversion
- Covid antigen negative in ED but PCR positive

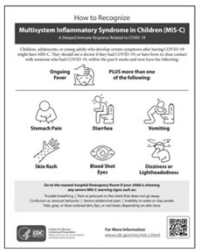
Question #2

What is the most likely to be helpful?

A. Send him to the cath lab for angioplasty and stent
B. Begin cefepime and vancomycin for presumed sepsis
C. Start remdesivir and dexamethasone
D. Start IVIG and Methylprednisolone
E. Obtain chest CT angiogram and start TPA

CDC Case Definition of MIS-C

- An individual aged <21 years presenting with fever*, laboratory evidence of inflammation**, and evidence of clinically severe illness requiring hospitalization, with multisystem (>2) organ involvement (cardiac, renal, respiratory, hematologic, gastrointestinal, dermatologic or neurological); AND
- No alternative plausible diagnoses; AND
- Positive for current or recent SARS-CoV-2 infection by RT-PCR, serology, or antigen test; or exposure to a suspected or confirmed COVID-19 case within the 4 weeks prior to the onset of symptoms.
- **Including, but not limited to, one or more of the following: an elevated C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), fibrinogen, procalcitonin, d-dimer, ferritin, lactic acid dehydrogenase (LDH), or interleukin 6 (IL-6), elevated neutrophils, reduced lymphocytes and low albumin



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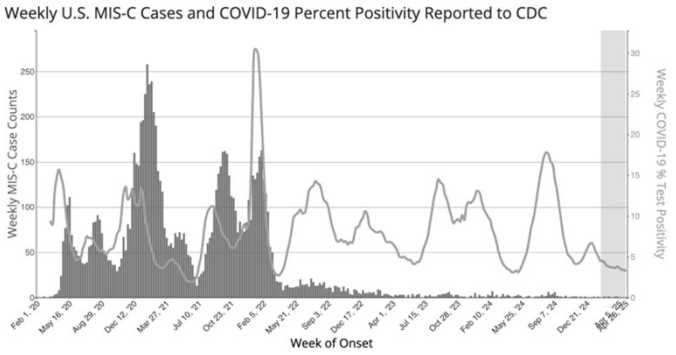
MIS-C Case Peaks Follows Peaks in Covid Cases by about 4 Weeks



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https://covid.cdc.gov/covid-data-tracker/#mis-national-surveillance

MIS-A vs Acute Covid-19

- MIS-A from 6 academic centers. Matched to pts with acute Covid
- MIS-A more likely to be black
- Less likely to be obese (OR 0.45), have underlying conditions (OR 0.36)
- 87% with cardiac dysfunction, 81%elevated troponin

Signs and symptoms up to and including the day of hospital admission	MIS-A (N-53)	Covid-19 (N=106)	
Rash	8 (15)	1 (1)	16.38 (2.82–420.80)[f]
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Altered mental status	4 (8)	1 (1)	7.69 (1.03–213.80)[h]
Conjunctival injection	3 (6)	1 (1)	5.73 (.65–167.21)[h]
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Fever[i]	47 (89)	86 (81)	1.73 (.60–4.94)
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Dyspnea	33 (62)	92 (87)	.25 (.11–.58)
Cough	19 (36)	91 (86)	.02 (.00–.15)
Neck pain	3 (6)	0 (0)	$P = .04$[g]
Cervical lymphadenopathy	1 (2)	0 (0)	$P = .33$[g]

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Melgar CID 2023:77;1395

Take Homes

- Recognize risk factors for severe Covid-19, including pregnancy
- Recognize windows for antiviral therapy and immunomodulator therapy
- Remember thrombotic complications of Covid
- Prepare for questions about treating moderate and severe disease
  - Don't memorize all of the DDI's
- Be alert for MIS-A case
- Myocarditis in an adolescent or young male after mRNA vaccine is a possible question

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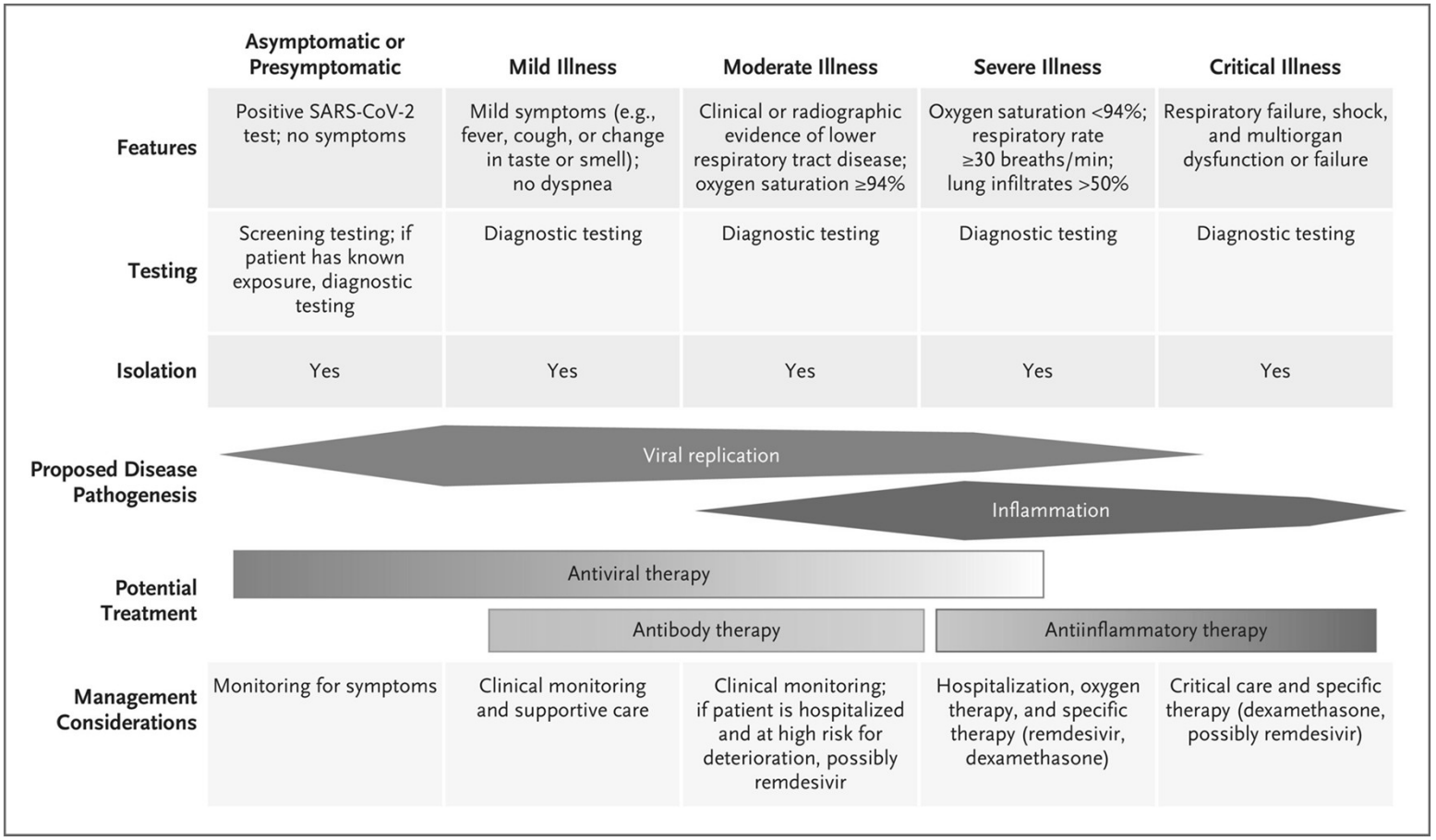

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Gandhi. N Engl J Med 2020;383:1757-1766

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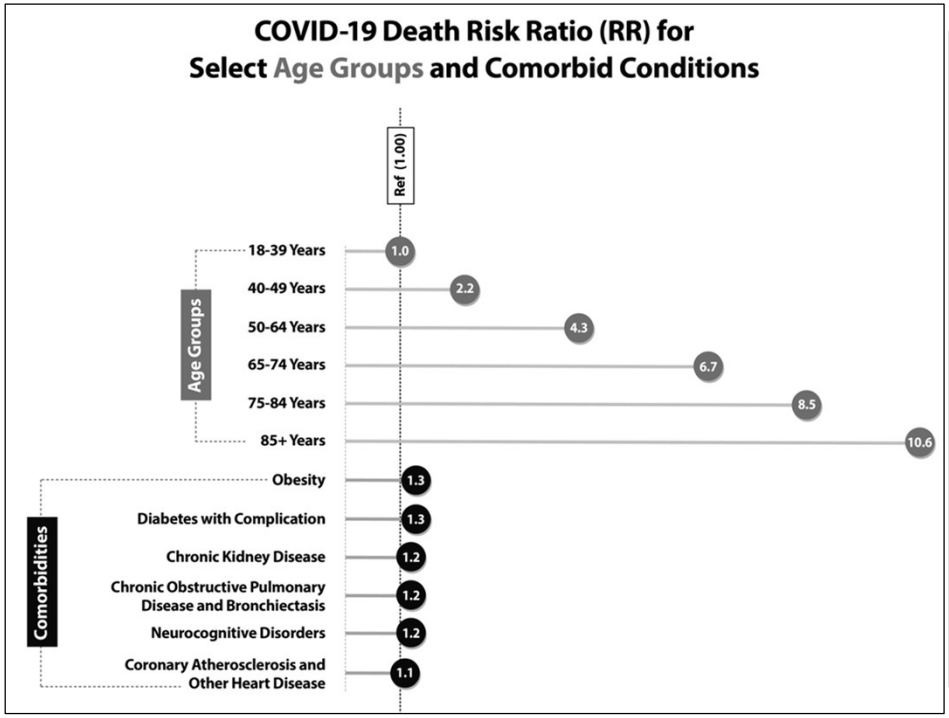
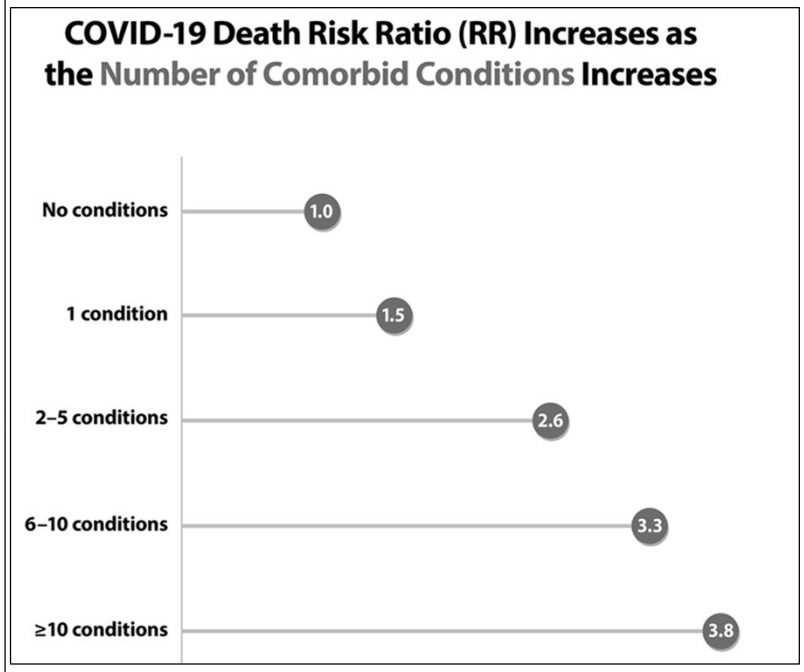
Risk Factors for Severe Disease





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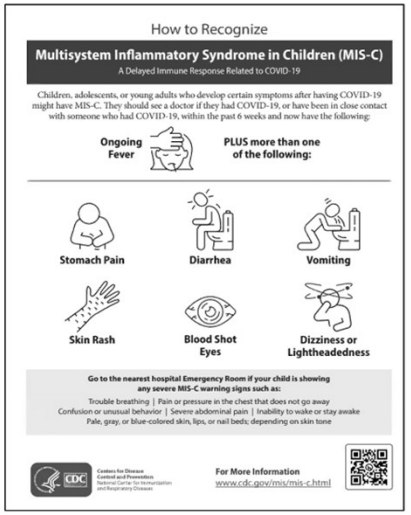

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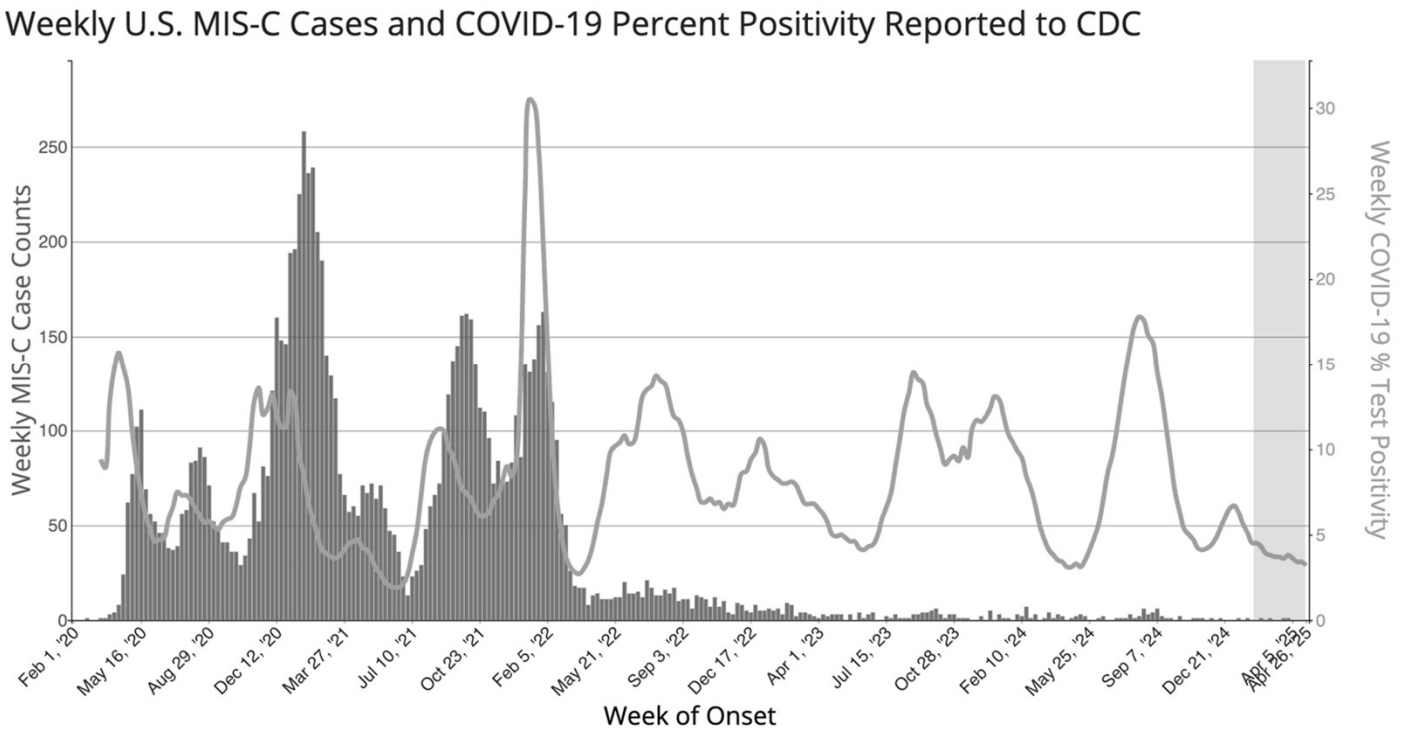

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Melgar CID 2023:77;1395

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AGENDA DAY 2: Sunday, August 23, 2026

AM Moderator: Henry Masur, MD

#	Start		End	Presentation	Faculty
10	8:00 AM	-	9:00 AM	Clinical Immunology and Host Defense	Steve Holland, MD
11	9:00 AM	-	10:00 AM	Protozoa That Could Be Tested	Edward Mitre, MD
	10:00 AM	-	10:15 AM	Morning Break	
12	10:15 AM	-	11:00 AM	Brain Abscess, Cavernous Sinus Thrombosis, and Subdural and Epidural Empyema	Allan Tunkel, MD
13	11:00 AM		11:45 AM	Worms You Should Know	Edward Mitre, MD
	11:45 AM	-	12:00 PM	Lunch Break	

PM Moderator: Paul Auwaerter, MD

BR2	12:00 PM	-	12:45 PM	Board Review Day 2	Drs. Auwaerter (Moderator), Bell, Bennett, Mitre, Platts-Mills, and Tunkel
14	12:45 PM	-	1:30 PM	Encephalitis including West Nile and Rabies	Allan Tunkel, MD
15	1:30 PM	-	2:15 PM	Syndromes in the ICU that ID Physicians Should Know	Taison Bell, MD
16	2:15 PM	-	3:00 PM	Ticks, Mites, Lice, and the Diseases They Transmit	Paul Auwaerter, MD
17	3:00 PM	-	3:30 PM	GI Infections Part I	James Platts-Mills, MD
	3:30 PM	-	3:45 PM	Afternoon Break	
18	3:45 PM	-	4:15 PM	GI Infections Part 2	James Platts-Mills, MD
19	4:15 PM	-	4:45 PM	Lyme Disease	Paul Auwaerter, MD
	4:45 PM	-	5:00 PM	Afternoon Break	
20	5:00 PM	-	5:45 PM	Fungal Diseases in Immunocompetent and Immunosuppressed Hosts	John Bennett, MD
21	5:45 PM	-	6:15 PM	Pneumonia	Paul Auwaerter, MD

Sunday, August 23, 2026

10

Clinical Immunology and Host Defense

Steven Holland, MD

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Host Defense: Where the Rubber of Immunology Hits the Road of Life

Steven M. Holland, MD
Laboratory of Clinical Immunology and Microbiology
National Institute of Allergy and Infectious Diseases
National Institutes of Health
smh@nih.gov

7/31/2026

Disclosures of Financial Relationships with Relevant Commercial Interests

- List of disclosures or “None”

Concepts of Hell

Host Immune Defense

Humoral
- Complement
- Mannose binding lectin
- Antibody

Cellular
- Neutrophils
- Monocytes
- Eosinophils
- Lymphocytes (NK, T, B)
- Other (erythrocytes, platelets)

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Basic Principles

Patients with impaired inflammation:

- May be unable to tell you they are sick (feel fine)
- Are often sicker than they look
- Often have more extensive disease than is apparent
- May require longer treatment than normals
- May have unusual infections

In vitro testing is tricky and variable, genetics is not

Who's Got a Problem?

Abnormal frequency of infections

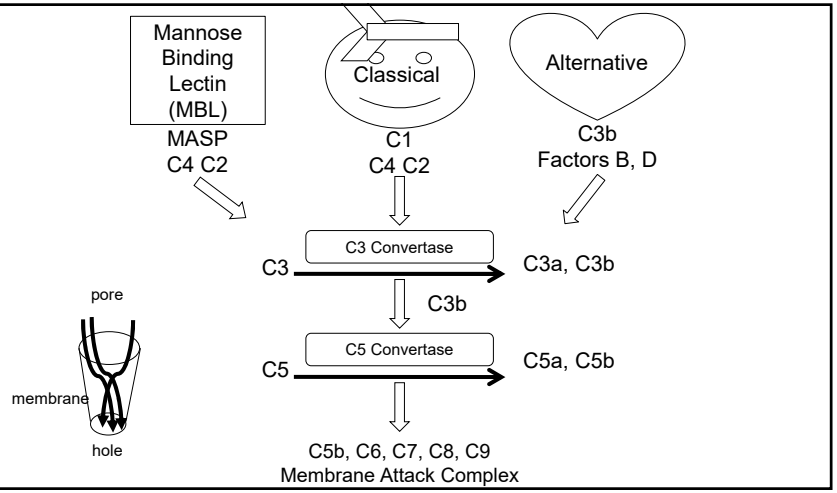
- *Recurrent Neisseria* bacteremia, pneumonia

Abnormal presentation of infections

- Necrotic cutaneous ulcers (not anthrax)
- *Aspergillus* pneumonia

Unusual infections

- *Pneumocystis jirovecii*
- *Burkholderia cepacia complex*
- *Nontuberculous mycobacteria*



Complement Deficiencies

Classical Pathway (C1-C9) (Recessive)

- Antibody *de*pendent bacterial lysis
- Deficiency leads to recurrent bacteremia and meningitis

Alternative Pathway (Factors I, H, Properdin, C3)
(Properdin X-linked, others AR)

- Antibody *in*dependent bacterial lysis
- More severe than classical defects

Mannose Binding Lectin (MBL) Pathway

- Very modest IF ANY defect, mild effect in infancy

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Complement Defects

C5-C9 Defects
- Recurrent Neisseria bacteremia and meningitis
- Average age of onset 17 y, milder CNS sequelae
- High rates of relapse and reinfection

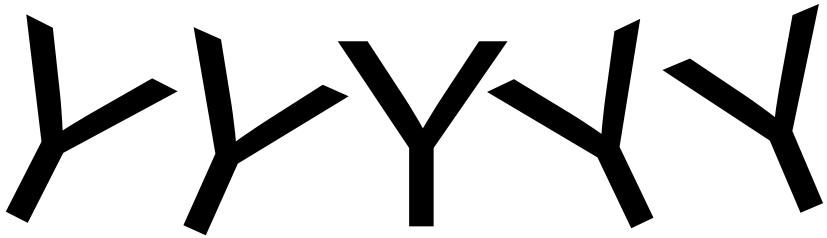
C1-C4 Defects
- Autoimmune disease (SLE, DLE) more common

Dx - CH_{50} (Classical), AH50 (Alternative)

Rx - treat infections, prophylaxis if needed, hypervaccination?

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

Let's Talk About Antibodies!!! Five Flavors



IgD IgM **IgG** IgA IgE

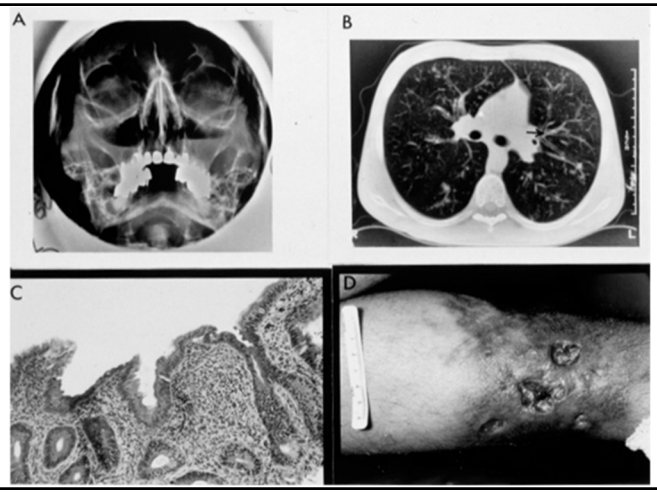
Antibody Deficiencies

IgA Deficiency (AR)
- Common (1/700 adults)
- Probably not a pathologic condition per se
- Frequently associated with other deficits, such as common variable immunodeficiency (CVID), Ig subclass deficiencies, allergies, etc.

Dx - Low IgA

Rx - None

J Transl Autoimmun 2019 Nov 23:2:100025



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Common Variable Immunodeficiency (CVID)

Recurrent sino-pulmonary bacterial infections

Chronic enteric *Giardia, Campy, Salmonella, Shigella*

Severe enteroviral meningitis/encephalitis/myositis

Nodular regenerative hyperplasia of liver

Dx - IgG (total and subclasses 1,3 or 2,4),
IgA, IgM, isohemagglutinins, DTH,
Impaired response to new or recall immunization
Autoimmunity and cancer

Rx - Treat infections, Ig replacement

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

Question #1

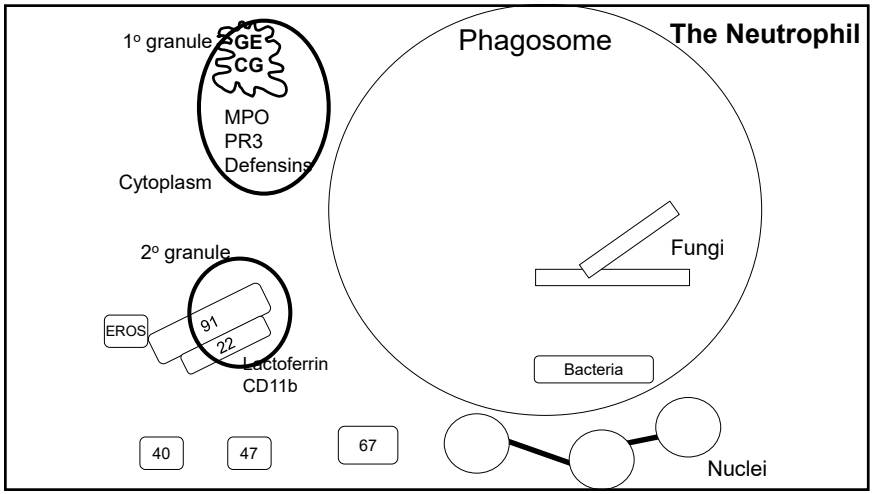
47-year-old woman

- Recurrent episodes of bronchitis, recently more exacerbations; tired
- One episode of documented bacterial pneumonia and sinusitis
- Immunoglobulin levels:
  - IgG 500 (normal 523-1482)
  - IgA <10 (normal 51-375)
  - IgM 165 (normal 37-200)

Question #1

What is the next step?

A. IgG subclasses and titers against tetanus and pneumococcus. If low, consider IVIG.
B. Repeat IgG levels. If low, consider IVIG.
C. Skin tests for DTH. If anergic, consider IVIG.
D. Titers against tetanus and pneumococcus, immunize, and repeat. If low, consider IVIG.
E. Check MBL levels. If low, consider IVIG.



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Question #2

Neutrophils: Nobody cares until they are not around.

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

So, how many do you make a day?

Question #2

How many neutrophils do you make a day?

A. 10e8; the half-life is 10 days
B. 10e9; the half-life is 5 days
C. 10e10; the half-life is 1 day
D. 10e11; the half-life is 7 hours
E. 10e6; they live until you use them up

Neutrophils: Always Fresh, Always Ready!

D. 10e11; the half-life is 7 hours*

- Make around 1011/day
- Most are in bone marrow
- Can go up 10-fold in emergency
- Circulating half life 7 hours
- About 50% marginated

Cyclic and Severe Chronic Neutropenias

Cyclic and SCN: *ELANE* mutations (AD)

Kostmann SCN: *HAX1* mutations (AR)

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

Dx - Molecular; periodicity, family history, genetics

Rx - G-CSF, BMT

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

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Other Causes of Neutropenia

X-linked
WAS
GATA1
TAZ

Dominant
GFI1
ELA2
GATA2
DNM2
SRP54
CXCR4

Recessive
G6PC3
HAX1
JAGN
USB1
CSF3R
VPS45
GSD1B
SBDS

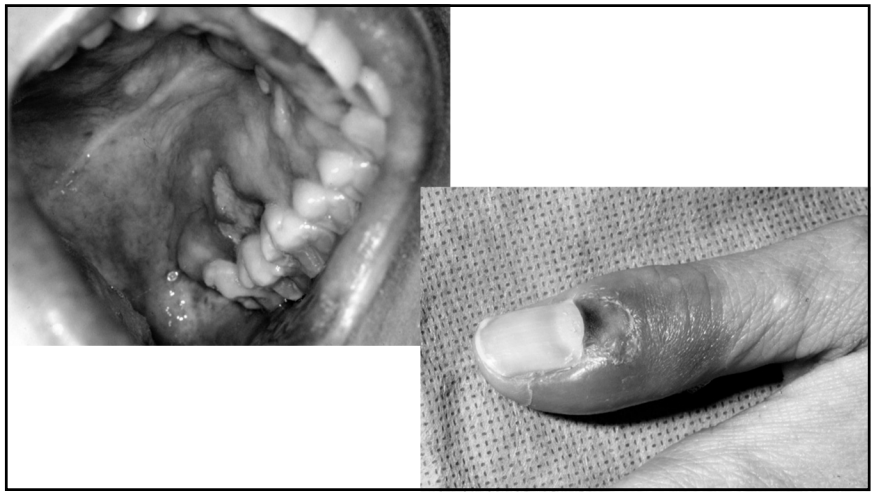
Big Causes
Drugs

Splenomegaly/ sequestration

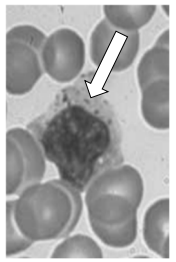
Autoimmunity

Case Study

52-year-old man
- Referred from his Family Practitioner
- Recurrent digital and oral ulcers occurring every month or so for the last 4 months
- One CBC showed an ANC of 100, but on repeat several days later was normal
- Previous health good
- Took “some antibiotic for a cold a few months ago”
- Spleen tip felt



Acquired Neutropenia in Adults



- Drugs, lupus, etc.
- Acquired cyclic neutropenia
  (Large Granular Lymphocytosis, LGL)
  Splenomegaly, often associated with
  Rheumatoid arthritis (Felty Syndrome)
- **Dx -** Clonal CD3+/8+/57+ lymphs (LGL)
  (Gain of Function mutations in STAT3)
- **Rx -** Treatment of the abnormal clone can be curative
  (Cyclosporine, MTX, steroids, alemtuzumab)
  G-CSF may lift both nadir and baseline

Hematol Malig Rep. 2020 Apr;15(2):103-112.

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Myeloperoxidase (MPO) Deficiency (AR)

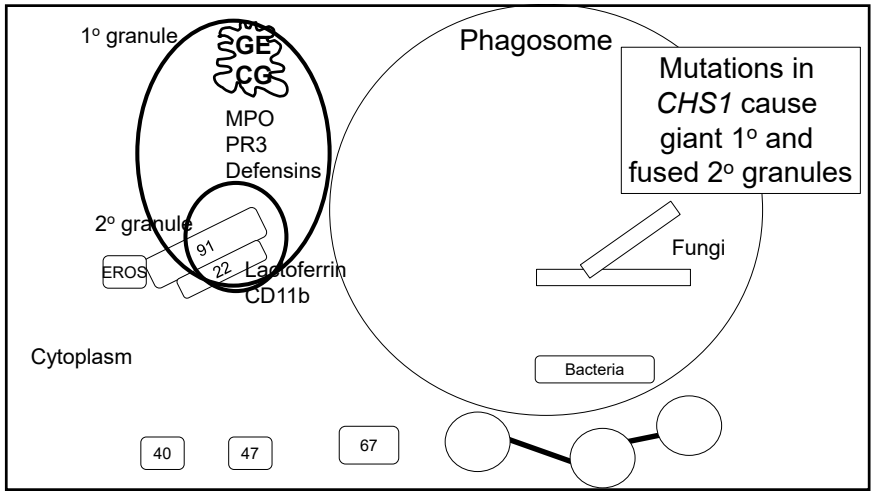
Most common neutrophil disorder (1/2000)

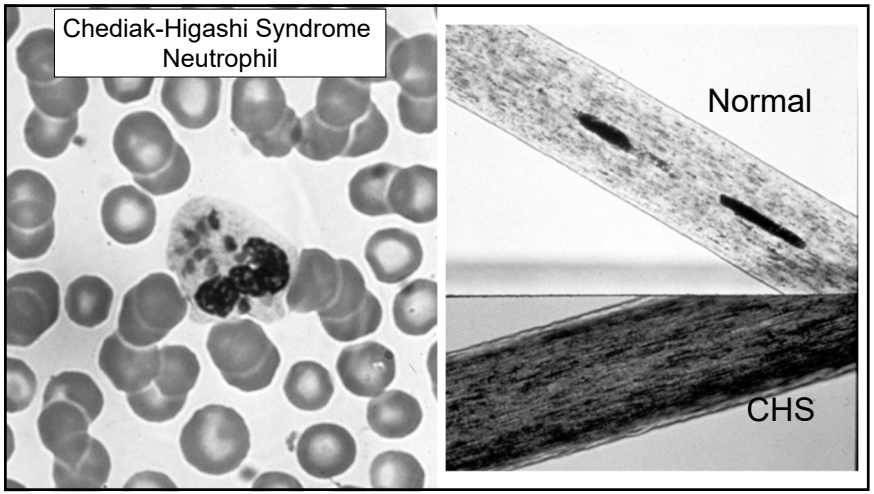
- Not a pathologic condition per se
- Failure of H_2O_2 -----MPO-----> HOCl
- Compensated by increased H_2O_2 production
- Appears to need another condition to potentiate, such as diabetes

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

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

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





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Chediak-Higashi Syndrome (Recessive)

Recurrent cutaneous, sino-pulmonary infections
- GNR, staph, strep, no fungi
- Mild neutropenia (intramedullary destruction)

Partial oculocutaneous albinism,

Mental retardation, neuropathy (late)

Lymphoma or HLH-like “accelerated phase” (late)

Dx - Giant blue PMN granules or chaotic hair granules due to mutations in CHS1, encodes LYST

Rx - Prophylaxis, treatment of infections, BMT

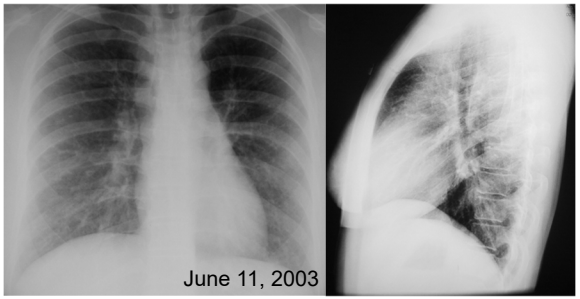
Drug Discov Today Dis Models. 2020;31:31-36

Silvery Sheen **Peripheral Neuropathy**

Case Study

23-year-old woman; athletic coach

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



ER Presentation

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

PMH
- Respiratory infections in infancy
- Cat scratch disease 8-year-old: resolved with antibiotics

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

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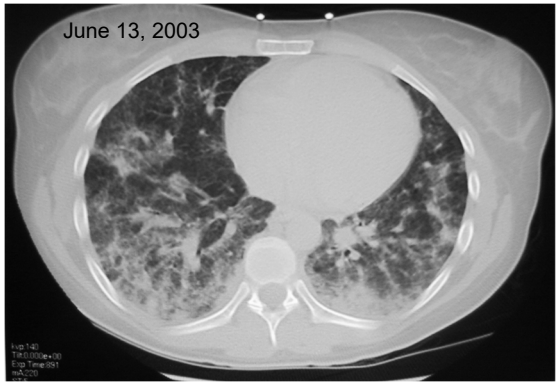
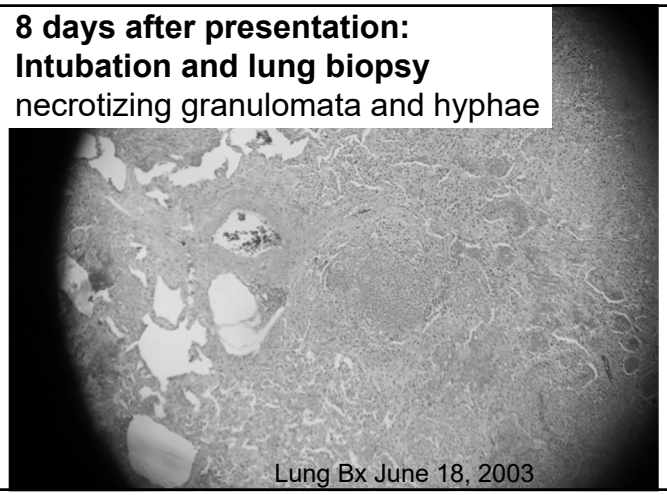
2 Days Later, Hypoxia And Fever



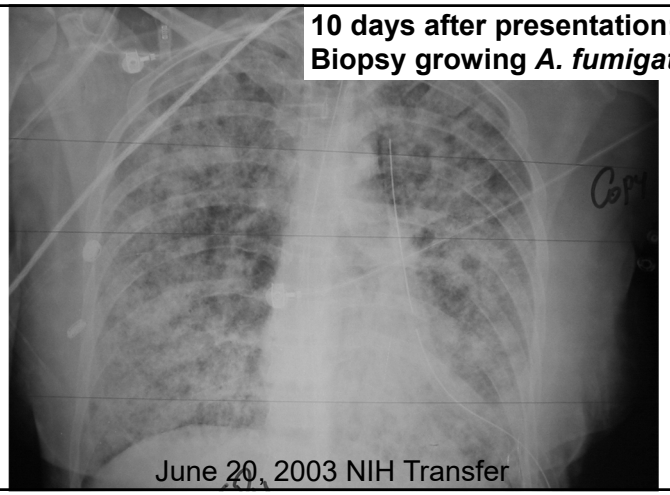
Hospital Course

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

8 days after presentation:
Intubation and lung biopsy
necrotizing granulomata and hyphae



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



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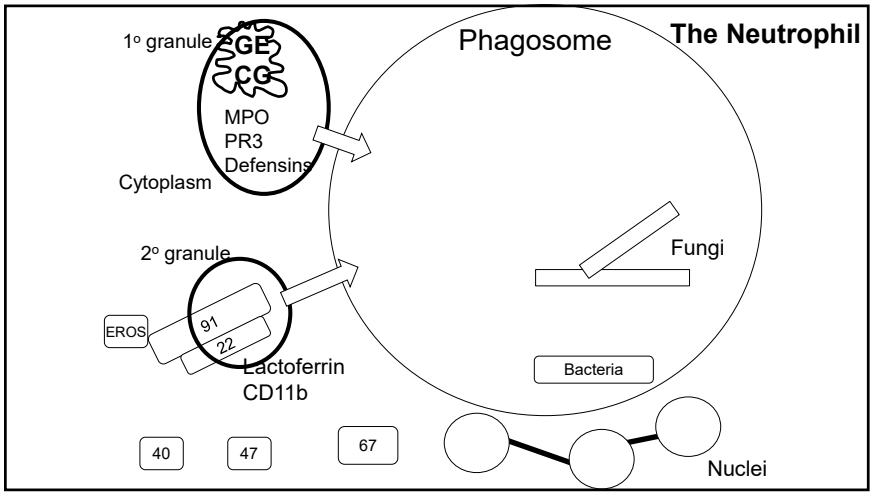
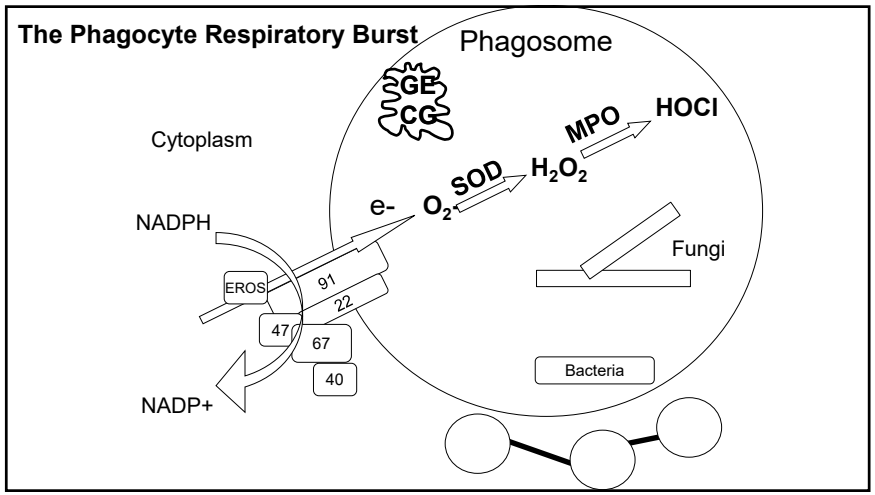
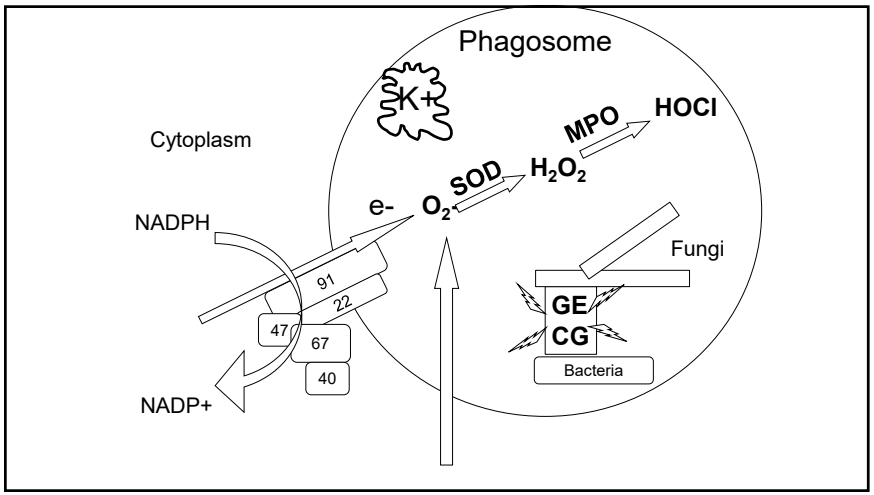
Question #3

Which of the following is a cause of invasive aspergillosis in an otherwise normal host?

A. Allergic bronchopulmonary aspergillosis
B. Cystic fibrosis
C. Lymphocyte dysfunction (SCID)
D. Phagocyte defect
E. Acute HIV







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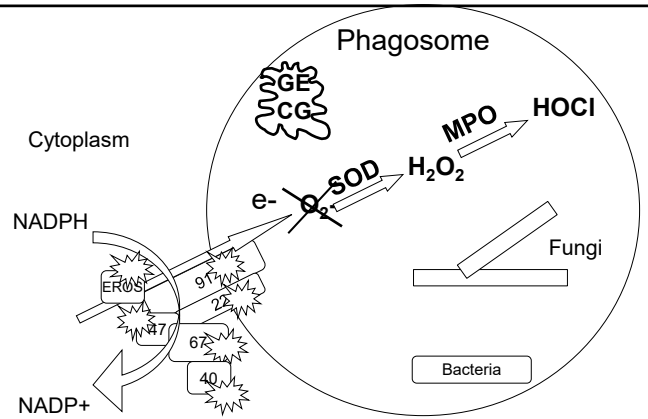


Chronic Granulomatous Disease (X, AR)

Failure to make the phagocyte respiratory burst

Frequency 1/100,000 - 1/200,000 live births

- Presentation usually in childhood; more adults recognized

Recurrent life-threatening infections

- Catalase-positive bacteria, fungi (this is nuanced)
- Tissue granuloma formation

Infections: Lung, liver, lymph nodes, skin, bone

Bacteremia: Uncommon but bad

Infections in CGD

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

Chromobacterium violaceum (warm brackish water, soil, e.g., Disney World)

Francisella philomiragia (brackish water, Chesapeake Bay, Sounds)

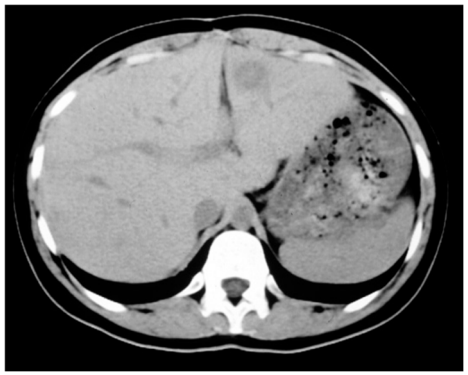
Burkholderia gladioli (causes onion rot)

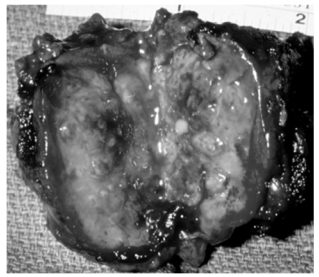
Granulibacter bethesdensis (necrotizing LN, hard to grow, likes CYE)

Paecilomyces spp.

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

Staphylococcal Liver Abscess in CGD





CID 2018;66:1427-1434

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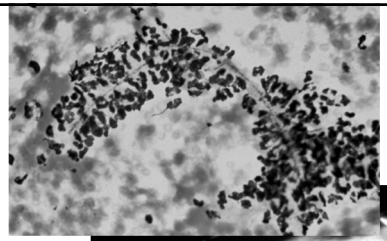
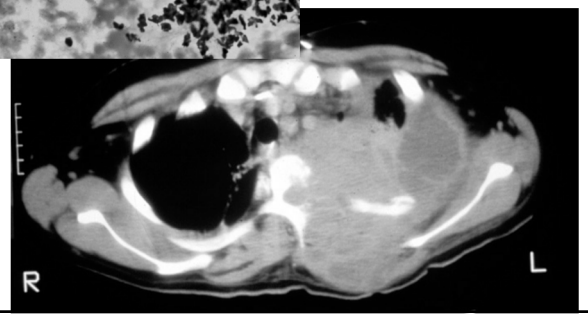
Staph aureus Osteomyelitis in CGD

Burkholderia cepacia Complex Bacteremia in CGD



CGD
Aspergillus nidulans
Pneumonia



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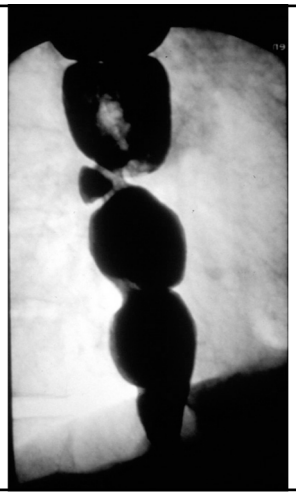
Thoracotomy 10 Days Postop

CGD Granulomatous Wound Dehiscence

CGD Granulomatous Esophageal Obstruction



CGD Inflammatory Bowel Disease

Chronic Granulomatous Disease

- X-linked, chr. Xp21 (70% of US cases)
  - Carrier females are mosaic (Lyonization)
  - 1/2 of offspring of carrier Mom will receive the gene
    - ~1/3 of carriers are sporadic, from sperm
  - X-linked male: all daughters carriers, no sons affected
- Autosomal recessive (30% of cases)

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

BE CAREFUL ABOUT THE LAB AND HOW YOU DISCUSS IT!

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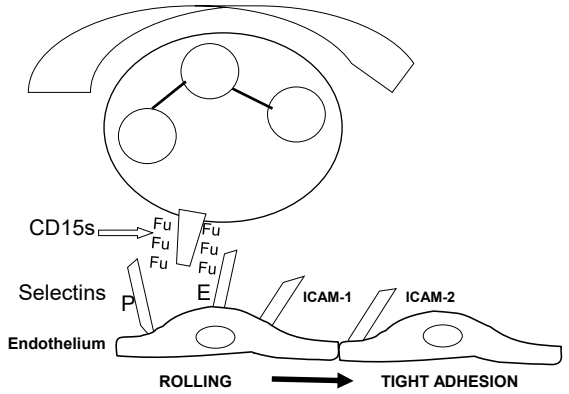
CGD Management and Treatment

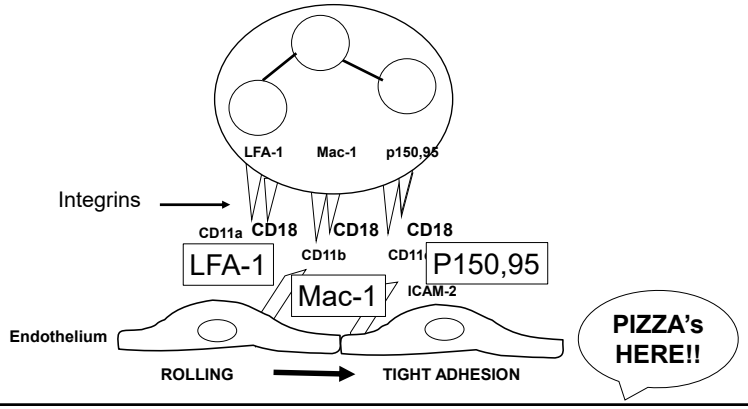
- 90% overall long-term survival
- Follow CRP, radiographs
- Prophylactic antibiotics and antifungals
  - TMP/SMX, itraconazole
- Prophylactic interferon gamma
  - 50 µg/m2 subcutaneously three times weekly
- Aggressive search for and treatment of infections
- BMT (gene therapy)

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

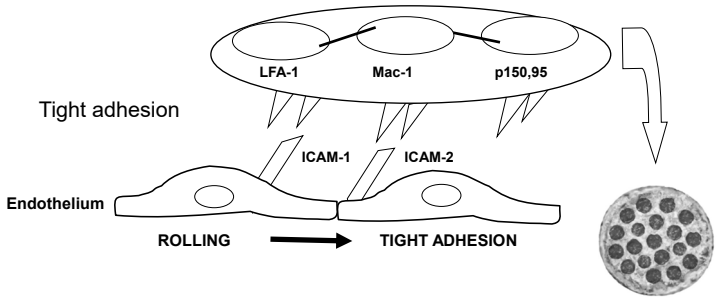
Neutrophil Rolling



Neutrophil Adhesion



Neutrophil Tissue Entry (Diapedesis)



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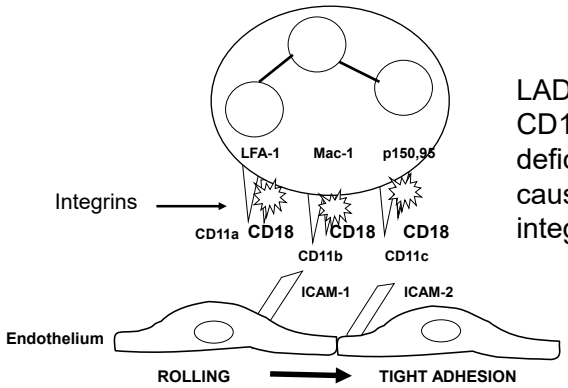
Leukocyte Adhesion Deficiency Type 1



LAD1 is due to CD18 deficiency, causing loss of integrins

Leukocyte Adhesion Deficiency Type 1 (AR)

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

Dx - FACS for CD18, genetics

Rx - Treatment of infections, BMT

Leukocyte Adhesion Deficiency I

- Delayed umbilical stump separation
- Dystrophic, “cigarette paper” scars
- Gingivitis with tooth loss, alveolar ridge resorption
- Biopsies show no neutrophils at sites of infection, rare monocytes and eosinophils
- Severe and moderate forms of disease

Almost Universal Tooth Loss in LAD1 By Adulthood

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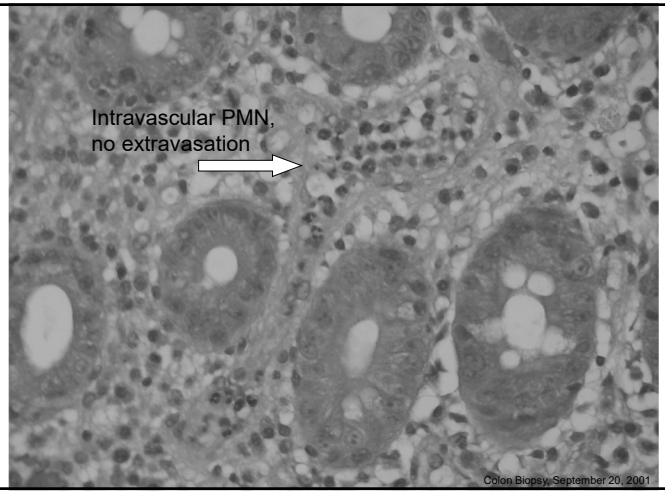
Impaired Wound Healing in LAD1

Cigarette Paper Scarring



Question #4

19-year-old boy with Pneumonia

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

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Question #4

Which of the following would rule <u>against</u> LAD1?

A. Gingivitis, tooth loss, and alveolar ridge resorption
B. FACS showing 5% of normal expression of CD18 and CD11a-c on granulocytes
C. He is the product of a first cousin union
D. Extensive neutrophil infiltration in the left shin ulcer
E. Multiple dystrophic scars over the legs from previous ulcers

27-year-old Woman with Boils

Referred for recurrent boils with *S. aureus*

- IgE of 12,376 IU
- "Bronchitis and sinusitis at least once a year"
- Persistent eczema requiring topical steroids
- Never hospitalized but having "more trouble" lately

Job's Syndrome

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

HIE (Job's) Syndrome History and Exam

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

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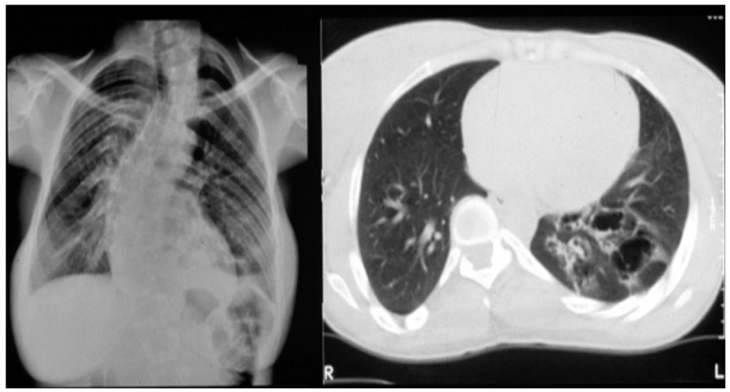

Pulmonary Pathogens in HIE

Primary Pathogens:
- *Staphylococcus aureus*
- *Streptococcus pneumoniae*
- *Hemophilus influenzae*

Secondary Pathogens:
- *Pseudomonas aeruginosa*
- *Aspergillus fumigatus*

Others:
- *Pneumocystis jirovecii, M. avium* complex

Candida

Group A Strep

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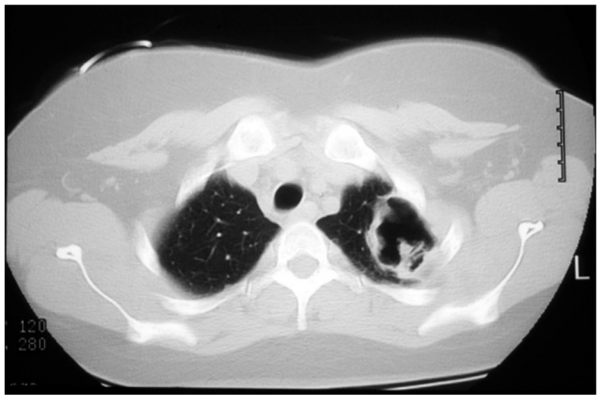
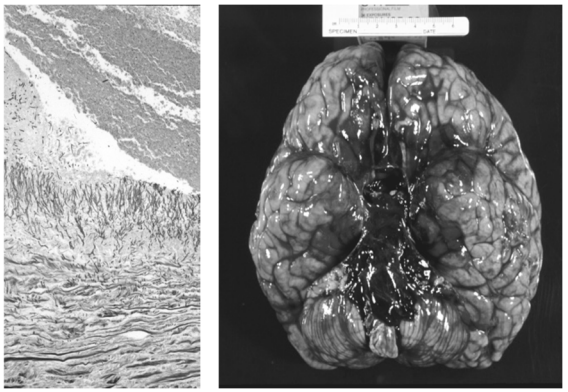
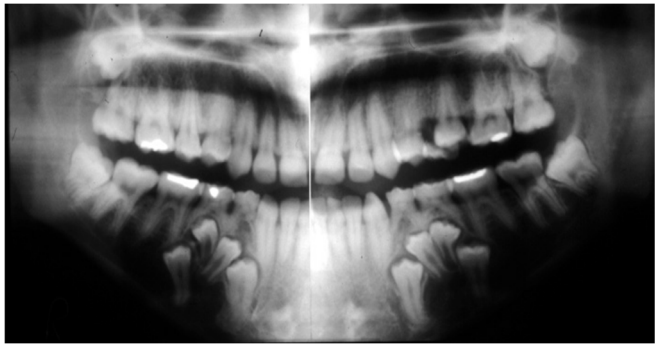
Aspergillus Lung Infection



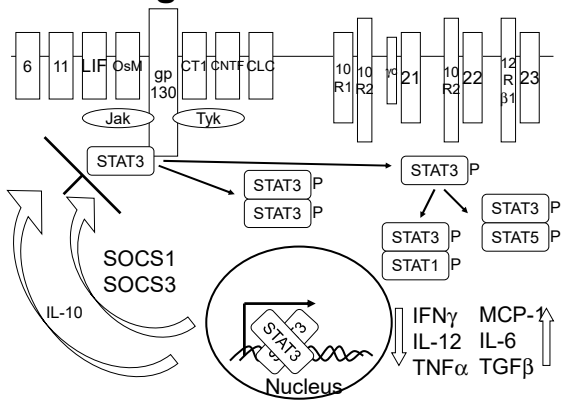
Metastatic *Aspergillus* Brain Infection



Failure Of Primary Dental Deciduation



Dominant Negative Mutant STAT3



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Hyper IgE Recurrent Infection (Job's)

- Recurrent sinopulmonary *S. aureus, S. pneumo, H. flu*
- Post-infectious pulmonary cyst formation
- Recurrent S. aureus skin abscesses
- Characteristic facies, eczema, scoliosis, fractures
- Very elevated IgE (>2000 IU), modest eosinophilia

DDx - Atopic dermatitis is a close mimic
Job's: pneumonia, lung cysts, skeletal, mutations in STAT3

Rx - Treatment of infections, prophylactic antibiotics, antifungals increasingly BMT

J Clin Immunol. 2021;41:864-880

Close Mimic: DOCK8 Deficiency

Autosomal Recessive hyper IgE syndrome
Eczema, allergies, asthma, high IgE
Staph, Strep, H. flu, Acinetobacter, Pseudomonas
Candida, Cryptococcus, Histoplasma
HPV, HSV, molluscum
Squamous cell carcinomas, lymphoma

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

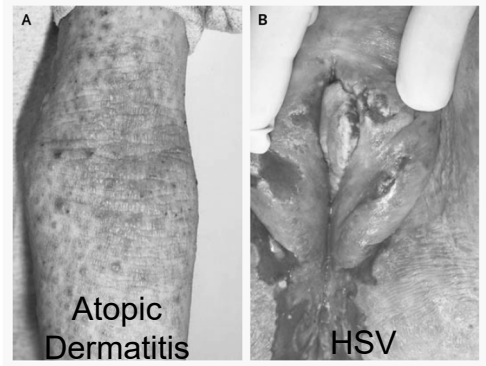
DOCK8 Deficiency

HPV

Molluscum contagiosum

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

DOCK8 Deficiency



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DOCK8 vs. STAT3 Hyper IgEs

	DOCK8 (Recessive)	STAT3 (Dominant)
Pneumonia	+	+++
Pneumatoceles	-	+++
Retained teeth	-	+++
Fractures	-	+++
Viral infections	+++	-
Fungal infections	+	++
Allergies	+++	-
IgM	Low	Normal
Eosinophils	+ to ++	+

Question #5

15-year-old girl with recurrent infections

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

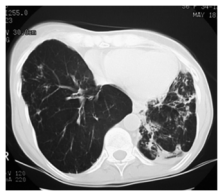
Going over the allotted 15 minutes, you elicit points trying to establish whether she has hyper-IgE recurrent infection syndrome (Job's).

Question #5

Which one of the following is not supportive of the diagnosis of Job's (STAT3DN)?

A. Pneumatoceles
B. Scoliosis
C. Severe warts
D. Retained baby teeth
E. Recurrent fractures

Clinical Spectrum of NTM Infections

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

Lancet Infect Dis. 2015;15:968-80

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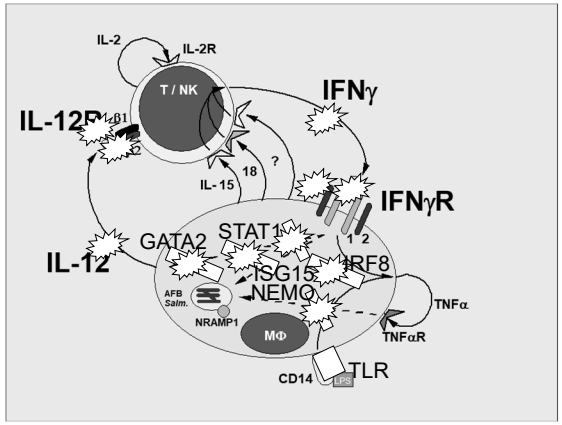
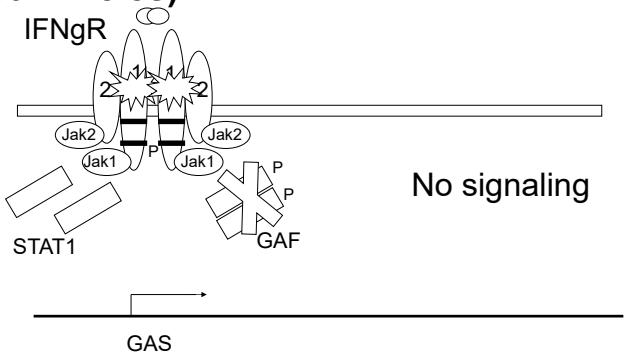
Disseminated NTM Only

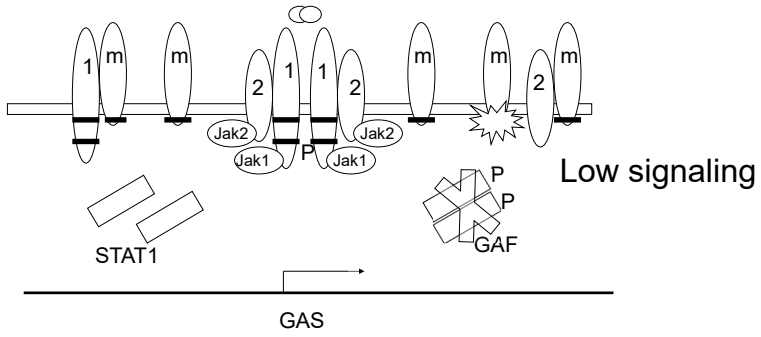


Autosomal Recessive IFNGR1 (Both Alleles)



BCG Vaccinated
Local and Disseminated BCGosis

Autosomal Dominant IFNGR1 (One Allele)



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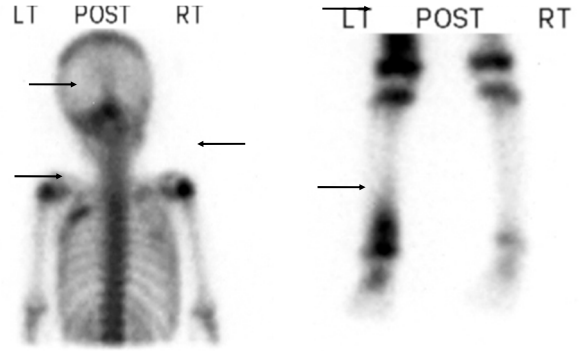
Mycobacterial Osteomyelitis in Dominant IFNγR1 Deficiency



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

Pathogens in Human IFNγR Deficiencies

M. avium	Salmonella
M. intracellulare	Listeria
M. chelonae	
M. abscessus	CMV
M. smegmatis	HSV
M. fortuitum	VZV
M. tuberculosis	RSV
Bacille Calmette Guerin	HHV-8
Coccidioides	
Histoplasma	

NOT JUST MYCOBACTERIA!!

IFNGR1: Dominant vs. Recessive

Characteristic	AD	AR
IFNγR1 display	High	None
IFNγR1 responsiveness	Low	None
Clinical presentation	Local	Disseminated
Granulomata	Present	Absent
Osteomyelitis	100%	Rare
Survival	Excellent	Most die

Lancet. 2004;364:2113-21

Interferon γ Receptor Deficiencies

Absent or defective IFNγR1

- MAC and other NTM, *Salmonella*, TB, viruses
- Complete defects present in childhood
- Partial defects present later in life
- May be misdiagnosed as malignancy!
- NOT a cause of isolated lung disease in adults

- **Dx -** genetics, flow cytometry for IFNγR1
- **Rx -** antimycobacterials, BMT

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

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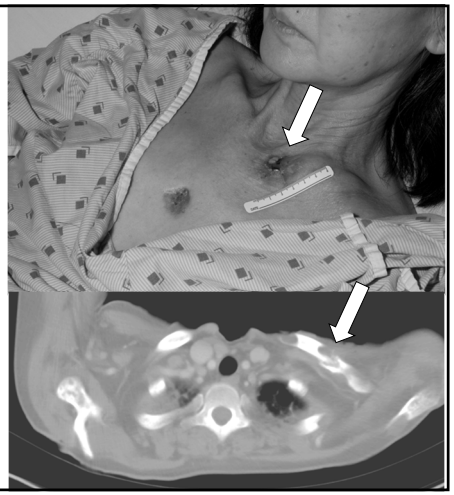
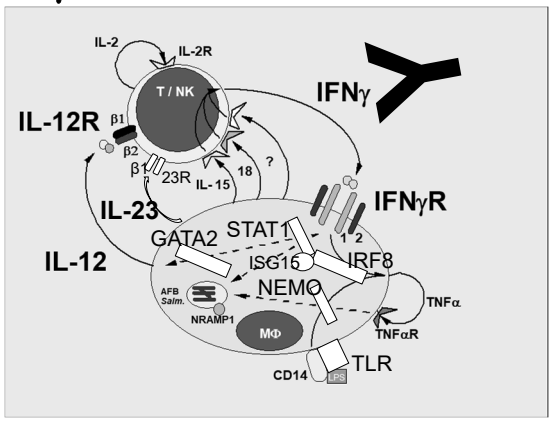
60-year-old Vietnamese Woman

- USA 1970s
- 1 year recurring disseminated *M. avium* complex
- Numerous fistulae



Anti-IFNγ Autoantibodies

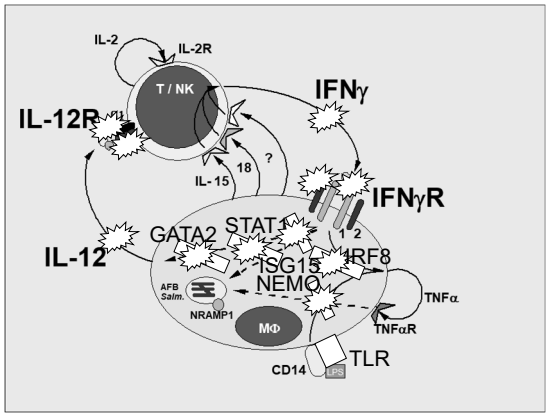


Anti-IFNγ Autoantibody Syndrome

- *Disseminated* NTM later in life also TB, *Talaromyces*, *Burkholderia*, VZV
- Predominantly female, mostly East Asian
- **Dx -** anti-IFNγ autoantibody detection Quantiferon is often INDETERMINATE
- **Rx -** antimycobacterials, possibly rituximab

NEJM 2012;367:725

NOT the Pathway for Lung Disease



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Question #6

30-year-old Thai Woman with Back Pain

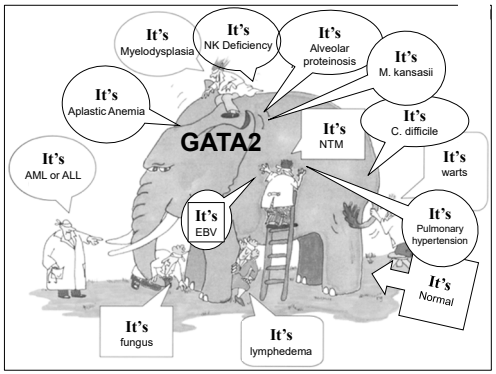
- 2 months pain and weight loss
- HIV-, normal CBC and chemistries, normal CD4
- Biopsy: osteomyelitis, MAC growing
- Quantiferon indeterminate
- You suspect that she has the anti-interferon gamma autoantibody syndrome

Question #6

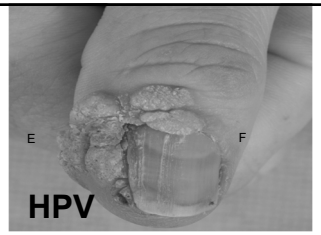
Supporting this diagnosis, what should you do?

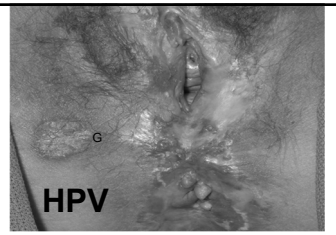
A. Check complements and total IgG
B. Determine anti-IFNγ antibody levels
C. Determine anti-GM-CSF autoantibody levels
D. Determine anti-IFNα autoantibody levels
E. Determine her cellular response to IFNγ

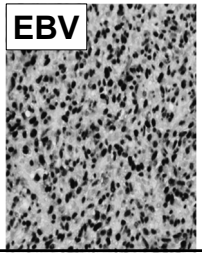
The Blind



The Elephant







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GATA2 Deficiency

- Mutations in GATA2, a critical hematopoietic gene
- Adolescent to adult onset
  - HPV (hands, genitals, cervical, vulvar)
  - Disseminated NTM (mediastinal *M. kansasii*)
  - Pancytopenia
- Labs: profound monocytopenia, low B, low NK
- CT: subpleural blebs
- Autosomal dominant
- Dx: genetics, hypocellular marrow, abnormal megakaryocytes
- Rx: antibiotics, BMT

Blood 2014; 123:809-21

Idiopathic CD4+ T-lymphocytopenia

- Idiopathic CD4+ T-lymphocytopenia (ICL)
  - ≤ 300 CD4+/µl
  - Associated with AIDS-like infections (crypto, PCP, MAC)
    - Exclude HIV infection (PCR, bDNA, p24, culture)
    - Often older onset than HIV associated OI
    - Surprisingly stable, consider incident cancers
- **Dx -** Determination of CD4 and CD8 number
  Often due to an underlying defect, so LOOK
- **Rx -** Treat infections (follow CD4+, ?cytokines)

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

Screening Laboratories

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

Screening Laboratories

- Phagocytes
  - DHR for CGD
  - Genetics for everything else
- Complement
  - CH_{50} (classical pathway)
  - AH_{50} (alternative pathway)
  - Think about the gene involved!
  - Use Pubmed OMIM
  - Sequence is faster and cheaper than you think

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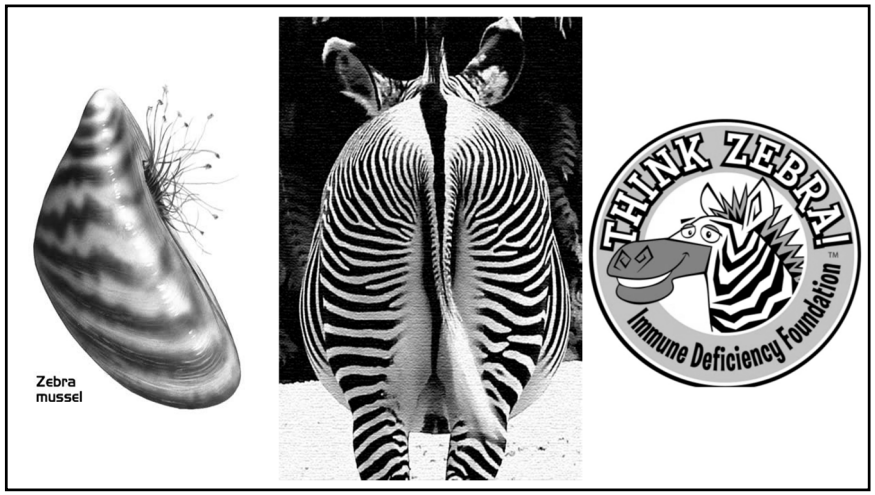

10 Clinical Immunology and Host Defense

Speaker: Steven Holland, MD

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Protozoa That Could Be Tested

Edward Mitre, MD

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Protozoa that Could be Tested

Edward Mitre, MD
Rockville, MD

Disclaimer: Dr. Mitre is giving this presentation in a personal capacity. The views expressed in this presentation are the sole responsibility of the presenter and do not necessarily reflect the views, opinions, or policies of the Uniformed Services University of the Health Sciences, the Department of Defense, or the United States Government.

8/8/2026

Disclosures of Financial Relationships with Relevant Commercial Interests

- None

Protozoa*

Extraintestinal	Intestinal
Apicomplexa (SAR)	**Apicomplexa (SAR)**
Plasmodia	Cryptosporidium (no apicoplast)
(Babesia)	Cyclospora
(Toxoplasma)	Cystoisospora
Flagellates (Excavata)	**Flagellates (Excavata)**
Leishmania (kinetoplast)	Giardia (metamonad)
Trypanosomes (kinetoplast)	Dientamoeba (metamonad)
(Trichomonas) (metamonad/no mitochondria)	**Amoebae (Amoebozoa)**
Amoebae (Amoebozoa)	Entamoeba
Acanthamoeba	**Ciliates (SAR)**
Balamuthia	Balantidium
Amoeboflagellate (Excavata)	**Non-motile (SAR)**
Naegleria	Blastocystis

*Note: There has been a shift from categorizing organisms that used to be known as Protozoa into the SAR (Stramenopiles/Alveolata/Rhizaria), Excavata, and Amoebozoa Supergroups. These are levels of taxonomic organization which are below the domain level of Eukaryota and above the traditional kingdom level. This recategorization occurred b/c taxonomists learned that many organisms in the prior Kingdom Protista were more closely related to animals, plants, or fungi than they were to each other. In terms of motility, Apicomplexans move via gliding motility via a glideosome apparatus which contains actin and myosin whereas Amoebae move via pseudopodia. Naegleria in humans exists in its trophozoite (amoeboid) form but under certain environmental conditions can develop into a flagellate form. Naegleria also has a cyst stage.

Kingdom Fungi Microsporidiosis agents

Protozoa*

Extraintestinal	Intestinal
Apicomplexa (SAR)	**Apicomplexa (SAR)**
Plasmodia	Cryptosporidium (no apicoplast)
(Babesia)	Cyclospora
(Toxoplasma)	Cystoisospora
Flagellates (Excavata)	**Flagellates (Excavata)**
Leishmania (kinetoplast)	Giardia (metamonad)
Trypanosomes (kinetoplast)	Dientamoeba (metamonad)
(Trichomonas) (metamonad/no mitochondria)	**Amoebae (Amoebozoa)**
Amoebae (Amoebozoa)	Entamoeba
Acanthamoeba	**Ciliates (SAR)**
Balamuthia	Balantidium
Amoeboflagellate (Excavata)	**Non-motile (SAR)**
Naegleria	Blastocystis

Kingdom Fungi Microsporidiosis agents

11 Protozoa That Could Be Tested
Speaker: Edward Mitre, MD

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Question #1

A 54-year-old 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.

Which is the most likely infectious agent causing the patient's illness?

A. Plasmodium malariae
B. Plasmodium knowlesi
C. Plasmodium vivax
D. Plasmodium falciparum
E. Babesia microti

P. knowlesi

*M*orphologically similar to *P. malariae*

Usually a parasite of long-tailed macaques

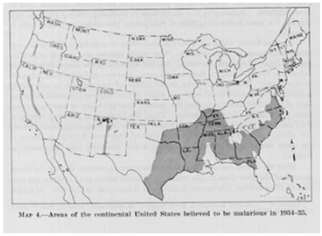
Increasingly recognized in Myanmar, Philippines, Indonesia, and Thailand

Causes high parasitemia

Highly morbid and can be lethal

Malaria

One Of The Most Important Pathogens In The History Of The World



Map 4.—Areas of the continental United States believed to be malarious in 1934-35.

National Malaria Elimination Program: 1947- 1951

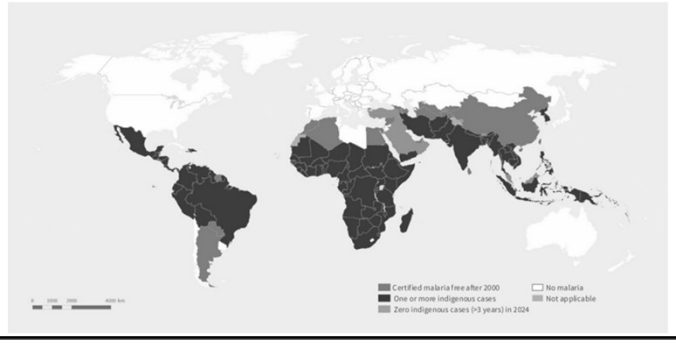
→ DDT spraying, drainage of wetlands

→ Atlanta was chosen for the Office of Malaria Control in War Areas (the predecessor agency of the CDC) in part because of its location in a malaria-endemic region

In 1775 the Continental Congress purchased quinine for George Washington's troops

Disease Burden - WHO 2025 World

282 million cases
610,000 deaths
U.S. ~ 2000 cases reported each year



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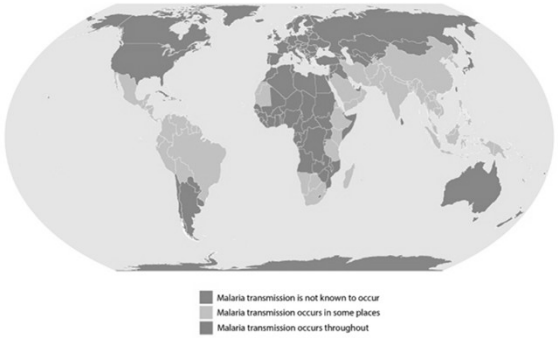
Malaria Epidemiology – CDC Map From a Few Years Ago…What's Missing?

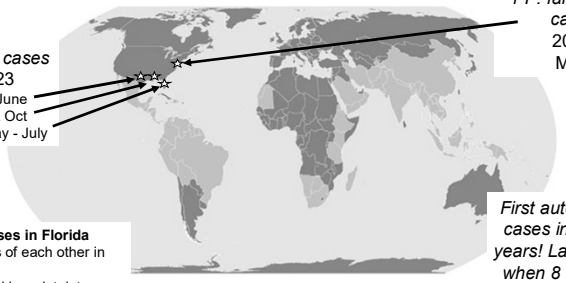


https://www.cdc.gov/malaria/about/distribution.html

2023 U.S. Malaria Cases

9 P. vivax cases 2023
1- TX June
1 – AR Oct
7 – FL May - July

1 P. falciparum case 2023 MD



2023 7 P. vivax cases in Florida
- All within 4 miles of each other in Sarasota county
- All with fever and low platelets
- 3 individuals were homeless
- April 20th there had been an imported P. vivax case
- CDC testing of 407 Anopheles mosquitoes → 3 A. crucians were PCR+

First autochthonous cases in U.S. in 20 years! Last was 2003 when 8 cases of P. vivax *were reported in Palm Beach County, FL.*

https://www.cdc.gov/mmwr/volumes/72/wr/mm7236a1.htm
https://www.cdc.gov/malaria/about/distribution.html

In Non-immune Patients, Falciparum Malaria Is A Medical Emergency!!

One of the most common causes of fever in a returned traveler

Infected individuals can rapidly progress from appearing well to being critically ill

Some Helpful Heuristics

If Patient Has	Make Sure Patient Doesn't Have
Fever and freshwater contact →	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 dysuria →	Malaria
Fever and cough →	Malaria

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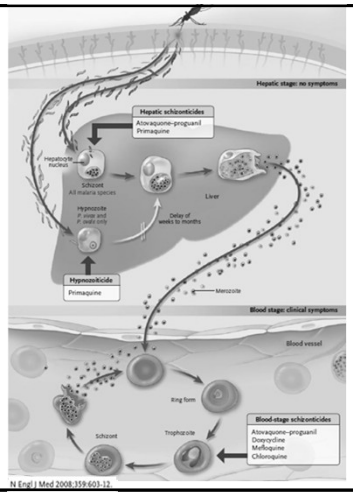

Sporozoites
- **Infective stage**
- Come from mosquito

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

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Complicated (Severe) Malaria

- Cerebral malaria (altered mental status, seizures)
- Respiratory distress/pulmonary edema
- Severe anemia (hct <15% in children, <20% in adults)

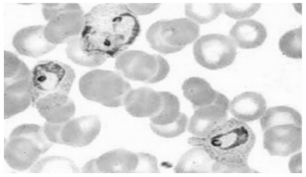
} Often seen in children of endemic countries. Adults more often get multiorgan failure.

- Renal failure
- Hypoglycemia
- Shock (SBP < 80 mm Hg or capillary refill > 3 seconds)
- Acidosis (often lactic acidosis)
- Jaundice (total bilirubin > 3 mg/dL)
- Bleeding disorder (spontaneous bleeding or evidence of DIC)

These complications primarily occur with *Plasmodium falciparum*, usually when parasitemia ≥ 2%

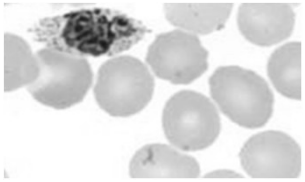
NOTE: in the absence of end organ damage, parasitemia ≥ 5% is often used as the cut-off to treat for severe malaria in the U.S.

P. vivax or ovale



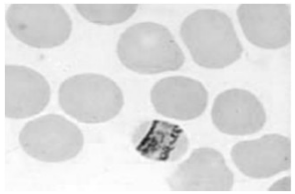
- Intracellular schüffner's dots
- Enlarged infected cells

P. ovale



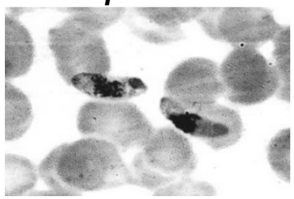
- Elongated or oval
- 6-12 merozoites (vs 12-24 for vivax)

P. malariae



- Band form (also seen in *P. Knowlesi*)

P. falciparum



- Banana shaped gametocyte

Malaria: Diagnosis

Rapid diagnostic antigen tests

→ sensitivity > 90% for P. falciparum
(about 85% for P. vivax, lower for P. knowlesi and P. ovale)

Binax Now® ICT assay for the detection of *Plasmodium falciparum* malaria according to the level of parasitemia

Parasitemia (no. of parasites/μL of whole blood)	Microscopy (no. positive)	NOW ICT (no. positive)	Sensitivity (%)
1–100	4	3	75.0
101–1,000	26	25	96.2
1,001–10,000	37	36	97.3
>10,000	34	33	97.1

Am. J. Trop. Med. Hyg., 69(6), 2003, pp. 589–592

for P. falciparum (T1) → tests for histidine-rich protein 2
for all species (T2) → tests for aldolase

*Most false-negative antigen tests are due to low parasite burden
→ Retest suspected patients that initially test negative

*Increasing false negative cases occurring worldwide due to mutations in HRP2

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Question #2

A 33-year-old woman is traveling to Uganda to do field studies in anthropology. She is two months pregnant.

Which of the following do you prescribe for malaria prophylaxis?

A. Doxycycline
B. Chloroquine
C. Mefloquine
D. Atovaquone/progruanil
E. No prophylaxis

Malaria Chemoprophylaxis

(Note: No Malaria Vaccine Approved For U.S. Travelers)

Some Regions In Central America and the 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	1 Tab/wk x 2-3 wks	1 Tab/wk	4 Weeks

**** Tafenoquine can precipitate severe hemolytic anemia in individuals that are G6PD deficient***

***** FDA black box warning mefloquine can cause neurologic symptoms, hallucinations, and feelings of anxiety, mistrust, and depression. Can also cause QT prolongation. Thus, many U.S. practitioners now reserve mefloquine for pregnant travelers to areas with chloroquine resistance.***

SEE ENLARGED SLIDE FOLLOWING ENTIRE PRESENTATION

P. falciparum Treatment

Excellent Review → 2022 JAMA, 328(5):460-47, PMID: 3591684

Uncomplicated P. falciparum malaria (no organ dysfunction, low parasitemia, able take PO)

- If chloroquine sensitive area → Chloroquine or hydroxychloroquine
- If not chloroquine sensitive area (most cases) → **Artemether/lumefantrine (Coartem)**
  ACTs are treatment of choice, WHO 2022 guidelines

Alternatives if artemether/lumefrantrine not available:
- Atovaquone/proguanil (Malarone), quinine + doxycycline, mefloquine

Severe Malaria
→ **IV artesunate** (CDC Malaria Hotline: 770-488-7788)

NOTES

1. Treatment failures can occur with artemether/lumefrantrine, especially when > 65 kg
   Abanyie F. et al, *Clinical Infectious Diseases* 2022 PMID: 36052468
2. Artemisinin resistance reported in SE Asia (Cambodia, Laos, Myanmar, Thailand, Vietnam), parts of Africa (Uganda, Rwanda), and in S. America (Guyuna)
3. Delayed-onset anemia in 2.7% of U.S. patients after treatment with artesunate
   Sonden K. et al, *Clinical Infectious Diseases* 2017 PMID: 27986683
4. Hypoglycemia and ARDS are complications that can occur during treatment of malaria. ARDS sometimes develops even as pt improving from malaria.

SEE ENLARGED SLIDE FOLLOWING ENTIRE PRESENTATION

P. vivax/P. ovale Treatment

Chloroquine x 3 days, or ACT (artemether/lumefrantrine in U.S.)
Note: PNG, Indonesia, Oceania have CLQ R P. vivax → use ACT

Then ANTIRELAPSE THERAPY with primaquine or tafenoquine

→ Need to check G6PD status before administering primaquine OR tafenoquine
(as both can cause severe hemolysis in patients with G6PD deficiency)

→ Both primaquine and tafenoquine contraindicated during pregnancy

- **Primaquine – weigh- based dosing and duration as determined by G6PD activity**

*****ALWAYS LOOK UP DOSING BEFORE ADMINISTERING*****

-> Usually 30 mg primaquine base per day x 14 days if normal G6PD activity
-> Do not exceed 30 mg primaquine base per day
-> If over 70 kg, can calculate total dose 6 mg/kg and then extend duration of 30 mg daily doses until total goal met
-> If G6PD deficient consider weekly chloroquine x 1 year

- **Tafenoquine (two 150 mg tabs once, given on 1st or 2nd day of chloroquine therapy)**
  (Tafenoquine was approved for radical cure of *P. vivax* in 2018, *P. ovale* treatment is off-label)

2020 : Company (GSK) reported some failures when tafenoquine was used after ACT treatment of P. vivax.
NEW FDA LABELING: **Tafenoquine now only approved and recommended after chloroquine treatment**

SEE ENLARGED SLIDE FOLLOWING ENTIRE PRESENTATION
https://www.cdc.gov/malaria/hcp/clinical-guidance/treatment-uncomplicated.html

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* Suggestions For All ID Practitioners *

1. Make sure the facility where one works has the means to rapidly test for malaria
2. Ensure that hospital pharmacy has access to appropriate medications for treatment of malaria

Babesia

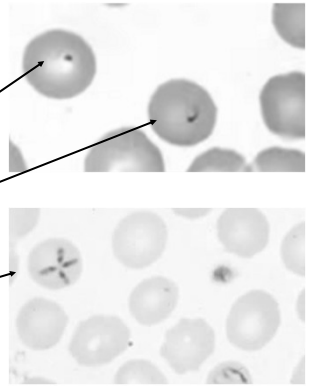
Transmission
- Ixodes ticks in Northeast and upper Midwest
  - Co-infection with Lyme and Anaplasma
- Transfusion
  (Ab and NAT screening tests approved by FDA 2018)

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*

Extraintestinal

Apicomplexa (SAR)
- Plasmodia
- (Babesia)
- (Toxoplasma)

Flagellates (Excavata)
- Leishmania (kinetoplast)
- Trypanosomes (kinetoplast)
- (Trichomonas) (metamonad/no mitochondria)

Amoebae (Amoebozoa)
- Acanthamoeba
- Balamuthia

Amoeboflagellate (Excavata)
- Naegleria

Intestinal

Apicomplexa (SAR)
- Cryptosporidium (no apicoplast)
- Cyclospora
- Cystoisospora

Flagellates (Excavata)
- Giardia (metamonad)
- Dientamoeba (metamonad)

Amoebae (Amoebozoa)
- Entamoeba

Ciliates (SAR)
- Balantidium

Non-motile (SAR)
- Blastocystis

Kingdom Fungi Microsporidiosis agents

Leishmaniasis

Obligate intracellular protozoan infection
Transmitted by sand flies (noiseless, active in evenings)

Lutzomyia
- New world leishmaniasis

Leishmaniasis
- Old world leishmaniasis

11 Protozoa That Could Be Tested
Speaker: Edward Mitre, MD

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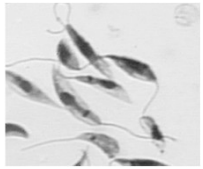
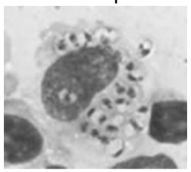
Leishmania Life Cycle – Two Stages

Promastigote
- Extracellular, in sand fly
- 2 µm wide x 20 µm long
  - Flagella
  - Large central nucleus
  - Band shaped kinetoplast



Amastigote
- Intracellular (macrophages)
- Round or oval
- Wright-Giemsa:
  - Dark-purple nucleus
  - Small rod shaped kinetoplast



CDC DpDx

Question #3

A 42-year-old man from Bolivia presents with nasal stuffiness and is found to have nasal septal perforation. Biopsy demonstrates intracellular amastigotes consistent with Leishmania.

Which is the most likely species?

A. L. mexicana
B. L. braziliensis
C. L. peruviana
D. L. infantum chagasi
E. L. major

Leishmania Taxonomy and Disease Simplified

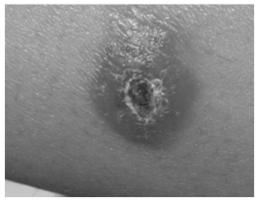
	Cutaneous	Mucosal	Visceral
NEW WORLD			
L. mexicana complex	X		
L. braziliensis	X	X	
L. infantum chagasi			X
OLD WORLD			
L. tropica	X		
L. major	X		
L. donovani			X
L. infantum chagasi			X

***Note: *L. braziliensis* is in the Viannia subgenus. *L. V. guyanensis* and *L. V. panamensis* also cause mucosal disease. *L. peruviana* DOES NOT**

Cutaneous Leishmaniasis
Clinical Presentation

Papule → Nodule → Ulcerative lesion → Atrophic scar

Ulcerative lesion may have:
- Induration
- Scaliness
- Central depression
- Raised border



- Takes weeks to months to develop
- Usually painless, unless superinfected
- Most lesions will eventually resolve on their own

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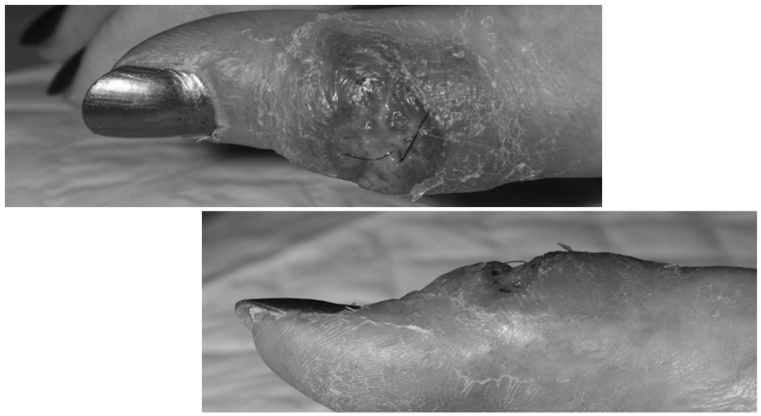

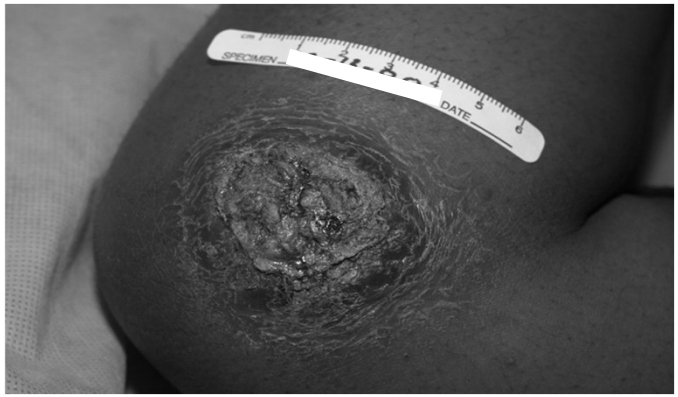

11 Protozoa That Could Be Tested

Speaker: Edward Mitre, MD

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Cutaneous Leishmaniasis – Diagnosis

Definitive diagnosis is very helpful because

1. Allows you to rule out other possibilities
2. May help in deciding whether and how to treat

Diagnostic Tools (edge of ulcer skin: scraping, aspirate, punch)

Touch prep with examination under oil looking for amastigotes

Culture on triple N media (may take weeks to grow)

(Nicolle's modification of Novy and MacNeal's medium-biphasic)

Histology

PCR

Cutaneous Leishmaniasis Treatment Recommendations

- Treat systemically if L. (V.) braziliensis, guyanensis, panamensis
- If not, ok to observe if there are:
  - Few lesions, they are < 5 cm, not on face/fingers/toes/genitals, normal host, no subcutaneous nodules

Treatment Options

- Local: heat with radiotherapy (FDA approved), cryotherapy, intralesional therapy systemic
  - Oral: miltefosine for certain species, especially New World CL species ketoconazole, fluconazole (off-label)
  - IV: Liposomal amphotericin B (off-label)

    Pentavalent antimony (meglumine antimoniate, ASTMH website has instructions for obtaining on IND from Sanofi)

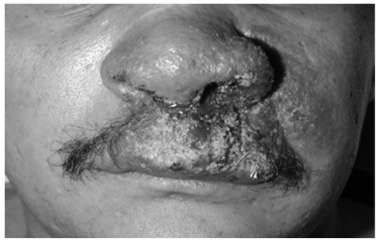
2016 IDSA GUIDELINES FOR TREATMENT OF LEISHMANIA

http://www.idsociety.org/Guidelines/Patient_Care/IDSA_Practice_Guidelines/Infections_by_Organism/Parasites/Leishmaniasis/

Mucosal Leishmaniasis

Leishmania (Viannia) braziliensis, guyanensis, panemensis

- Dissemination to nasal mucosa
- Slow, progressive, destructive
- Can occur months or years after cutaneous ulcer



Treatment

- Oral miltefosine (FDA approved for *L. braziliensis*)
- IV lip. amphotericin (off-label)
- IV antimony (no longer commercially available)

Miltefosine Notes
side effects: nausea, vomiting, diarrhea, increased AST/ALT
contraindicated in pregnancy, use contraception for 5 months after treatment ($t_{1/2}$ = 30 d)

Visceral Leishmaniasis

L. donovani *(South Asia, East Africa)*

L. infantum chagasi *(Middle East, Central Asia, Mediterranean, Central and S. America)*

Amastigotes in macrophages go to local LNs then hematogenously to liver, spleen, bone marrow

A persistent disease that can reactivate

TNF blockade, HIV CD4 < 200

- Weeks/months of fevers, chills, hepatosplenomegaly
- Pancytopenia & hypergammaglobulinemia

Diagnosis: PCR, culture, or histopathology for intracellular amastigotes
→ Bone marrow aspirate preferred, can also check LN, spleen, or buffy coat antibody to rK39 recombinant Ag

Treatment: Liposomal ampho B (FDA approved)
Miltefosine (oral) FDA approved for *L. donovani*

(Combination treatment for L. donovani in people living with HIV in SE Asia)

SEE ENLARGED SLIDE FOLLOWING ENTIRE PRESENTATION

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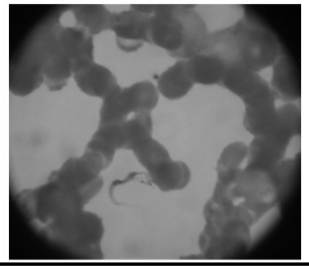
Question #4

A 41-year-old woman presented to a local emergency department with a one-day history of fever associated with swelling and redness in her groin four days after returning from safari in Tanzania. Peripheral blood smear is obtained.

What is the most likely diagnosis?

A. Leishmania donovani
B. Plasmodium vivax
C. Trypanosoma brucei
D. Wuchereria bancrofti
E. Leptospira interrogans



African Trypanosomiasis
Sleeping Sickness

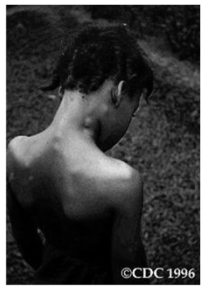
Vector = Tsetse fly (Glossina sp)

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 Tsetse fly bite
Regional lymphadenopathy
For weeks: Fever, hepatosplenomegaly, lymphadenopathy, faint rash, headache
Late: Mental status changes, terminal somnolent state



African Trypanosomiasis
Lab Findings

Non-specific Lab Findings

- Anemia
- Thrombocytopenia
- Elevated IgM
- Hypergammaglobulinemia

Diagnostic Lab Findings

- Detection of parasite in lymph node, circulating blood, or CSF
  - Do FNA of lymph node while massaging node, then push out the aspirate onto a slide and immediately inspect under 400x power. Trypanosomes can be seen moving for 15-20minutes, usually at edge of the coverslip
- A card agglutination test that detects *T.b.gambiense* sp. antibodies.
  - V. sensitive (94-98%), but poor specificity
  - Can get false +s in pts with Schisto, filaria, toxo, malaria

African Trypanosomiasis – Life Cycle

Why are Trypanosoma brucei infections associated with persistently elevated IgM levels?

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

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African Trypanosomiasis
The Lady Gaga of the Microbial World

African Trypanosomiasis – Treatment

July 16, 2021: Oral fexinidazole FDA approved for *T. gambiense*

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 > 6 yo and > 20kg: 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*)

If < 6 yo or < 20 kg: lumbar puncture

CSF < 5 WBC/ul → suramin

CSF > 5 WBC/ul → melarsoprol

If > 6 yo and > 20kg → oral fexinidazole (IV melarsoprol or suramin depending on CSF counts if unable to take PO)

Notes: *1. Melarsoprol associated with ~5% death rate due to reactive encephalopathy*

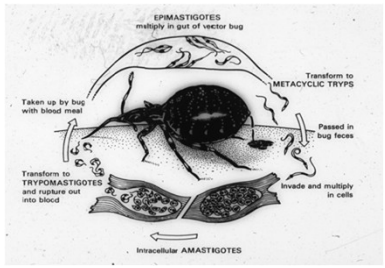
2. This is reduced by co-administration of corticosteroids

SEE ENLARGED SLIDE FOLLOWING ENTIRE PRESENTATION

Chagas Disease

- Caused by Trypanosoma cruzi
  (Also blood transfusion and congenitally)
- Vector: reduviid (triatomine) bugs
- Reservoirs: opossums, rats, armadillos, raccoons, dogs, cats
- Autochthonous cases in the U.S.
  - Texas
  - Louisiana
  - Mississippi
  - Missouri
  - California

Oral ingestion of food and drinks contaminated with reduviid bugs or the feces of those bugs is a major route of infection (acai and sugar cane juice)

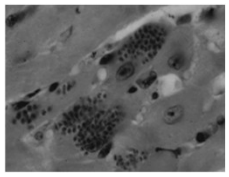


Chagas – Clinical Disease

Acute (starts 1 week after infection, can persist for 8 weeks)
- Fever
- Local lymphadenopathy
- Unilateral, painless periorbital edema

Indeterminate stage
- Serology positive, no evidence of disease

Chronic



Dilated cardiomyopathy, R>L
(CHF, syncope, arrythmia)

Megaesophagus

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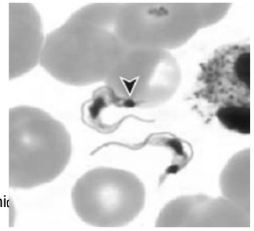
Chagas Diagnosis & Rx



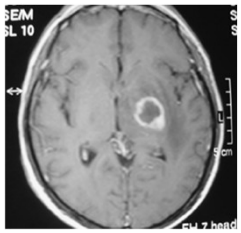
Acute Disease
- Identification of parasites in blood

Chronic Disease
- *T. cruzi* specific IgG antibodies in serum
- Two antibody tests using different antigens and different techni
  (research: xenodiagnosis, hemoculture, PCR)

NOTE: U.S. blood supply screened for 1st time donors

Treatment
- Benznidazole for 30-60 d, alternative: Nifurtimox (both FDA approved)
- **Benznidazole AEs**: peripheral neuropathy, granulocytopenia, rash
- **Nifurtimox AEs**: abdominal pain/vomiting, tremors, peripheral neuropathy
- **Always offer**: acute infection, congenital, < 18 yo, reactivation disease
- **Usually offer**: 19-50 years old and no advanced cardiac disease
- **Individual decision**: > 50 years old and no advanced cardiac disease

Chagas in Immunosuppressed Patients



2008 Int J Infectious Diseases

***T. cruzi* and AIDS**

Primarily reactivation neurologic disease
- Acute, diffuse, necrotic, meningoencephalitis
- Focal CNS lesions (similar to Toxo)**

***T. cruzi* and solid organ transplant**
- Recipient of infected organ: fevers, hepatosplenomegaly, myocarditis
- Disease often does not occur until months after transplant

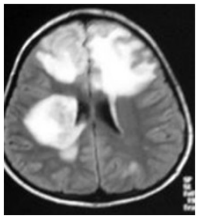
ALSO…Reactivation myocarditis occurs in ~40% of patients that receive heart transplant because of Chagas cardiomyopathy

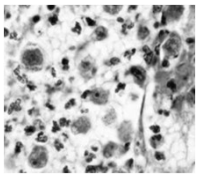
Protozoa*

Extraintestinal	Intestinal
Apicomplexa (SAR)	**Apicomplexa (SAR)**
Plasmodia	Cryptosporidium (no apicoplast)
(Babesia)	Cyclospora
(Toxoplasma)	Cystoisospora
Flagellates (Excavata)	**Flagellates (Excavata)**
Leishmania (kinetoplast)	Giardia (metamonad)
Trypanosomes (kinetoplast)	Dientamoeba (metamonad)
(Trichomonas) (metamonad/no mitochondria)	**Amoebae (Amoebozoa)**
Amoebae (Amoebozoa)	Entamoeba
Acanthamoeba	**Ciliates (SAR)**
Balamuthia	Balantidium
Amoeboflagellate (Excavata)	**Non-motile (SAR)**
Naegleria	Blastocystis

Kingdom Fungi Microsporidiosis agents

Free-living Amoebae





Naegleria fowleri (amoeboflagellate!)
- Warm freshwater exposure
- Enters through olfactory neuroepithelium
- Fulminant meningoencephalitis
- Immunocompetent children/young adults

Acanthamoeba
- Found in soil and water
- Enter through lower respiratory tract or broken skin
- Subacute granulomatous encephalitis
- Immunocompromised hosts
- Chronic granulomatous keratitis (contact lens, LASIK)

Balamuthia mandrillaris
- Likely enters through lower respiratory tract or broken skin
- Transmission by solid organ transplantation has been reported
- Subacute granulomatous encephalitis
- Normal and immunocompromised hosts

Outcome → often fatal (amphotericin B, azoles, pentamidine, others tried)

SEE ENLARGED SLIDE FOLLOWING ENTIRE PRESENTATION

11 Protozoa That Could Be Tested

Speaker: Edward Mitre, MD

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Protozoa*

Extraintestinal	Intestinal
Apicomplexa (SAR)	**Apicomplexa (SAR)**
Plasmodia	Cryptosporidium (no apicoplast)
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(Trichomonas) (metamonad/no mitochondria)	**Amoebae (Amoebozoa)**
Amoebae (Amoebozoa)	Entamoeba
Acanthamoeba	**Ciliates (SAR)**
Balamuthia	Balantidium
Amoeboflagellate (Excavata)	**Non-motile (SAR)**
Naegleria	Blastocystis

Kingdom Fungi Microsporidiosis agents

When to Suspect an Intestinal Protozoan Infection

Patient has:

- Protracted watery diarrhea (weeks to months)

AND/OR:

- History of travel [domestic (esp. Camping) or foreign]
- Recreational water activities
- Altered immunity (HIV infection)
- Exposure to group care (daycare)

Note: Discussion will focus on intestinal protozoa as they occur in patients seen in the U.S. These are leading causes of diarrhea, morbidity, and mortality worldwide, especially in young children.

Intestinal Apicomplexa Parasites

Cryptosporidium

- C. parvum: cows
- C. hominis: humans

Cyclospora cayetanensis

Cystoisospora belli

Cryptosporidium in enterocyte. CDC DpDx

- All have worldwide distribution
- All transmitted by water or food contaminated with oocysts
- Organisms invade enterocytes
- All cause watery diarrhea that can be prolonged & severe in immunocompromised

Intestinal Apicomplexa: Clinical Clues

Cryptosporidium

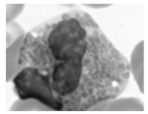
- Watery diarrhea of several weeks
- Cattle workers and daycare outbreaks
- Cysts are resistant to chlorine (water supply outbreaks)
- #1 cause of water park/swimming pool outbreaks

Cyclospora cayetanensis

- Self-limited immunocompetent BUT can last up to 10 weeks!
- Abrupt onset with nausea, vomiting, and fever early
- Anorexia, weight loss, fatigue late in course
- Food associated outbreaks: raspberries, lettuce, herbs
- Esp. Nepal, Peru, Guatemala

Cystoisospora belli

- No animal reservoirs known
- Watery diarrhea
- May be associated with a peripheral eosinophilia!



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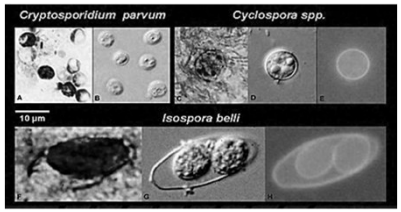
Intestinal Apicomplexa Characteristics

Pathogen	Size	Stain	Treatment
Cryptosporidium	4 µm	M acid-fast	(None) nitazoxanide or paromomycin
Cyclospora	10 µm	M acid-fast	TMP/SMX
Cystoisospora	20 µm	M acid-fast	TMP/SMX



CDC

Molecular Tests

Most stool multiplex PCR assays detect cryptosporidium AND cyclospora
But NOT cystoisospora

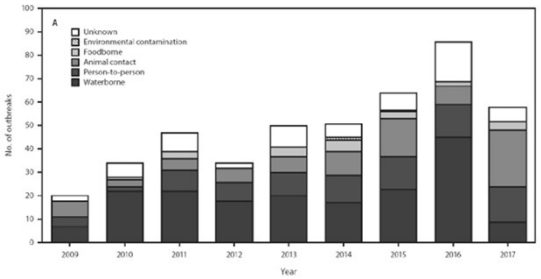
Stool Ag tests are commercially available for cryptosporidium

SEE ENLARGED SLIDE FOLLOWING ENTIRE PRESENTATION

Morbidity and Mortality Weekly Report

Cryptosporidiosis Outbreaks – United States, 2009 – 2017

MMWR / June 28, 2019 / Vol. 68 / No. 25



"The number of reported outbreaks has increased an average of approximately 13% per year."

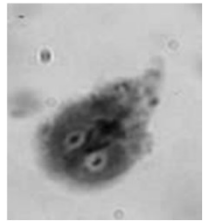
Giardia duodenalis

→ described by Antony van Leeuwenhoek in 1681!

Flagellated Protozoan
- Fecal/oral via ingestion of cyst form in food/water
- Cyst is chlorine resistant
- Cysts from humans (beavers, muskrats)

Disease in U.S.
- Most common parasitic infection in the U.S.
- (20k cases reported/year, likely 2m)
  - U.S-acquired cases peak in the late summer/early fall
  - A leading cause of traveler's diarrhea

Symptoms
- Intermittent watery diarrhea weeks to months
- Foul smelling stools, flatulence, "sulfur burps"



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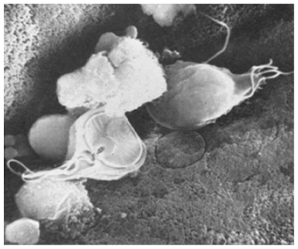
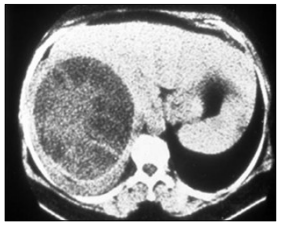
Giardia duodenalis

- **At Risk Populations**
  - International travelers
  - Swimming in lakes/streams, outdoor survival/camping
  - Infants in daycare
  - Childcare workers
  - Immunoglobulin deficiencies (esp CVID)
  - HIV when CD4 < 100
- **Diagnosis**
  - Stool antigen test
  - Stool multiplex PCR
- **Treatment**
  - Tinidazole (FDA approved)
  - Metronidazole (off-label), nitazoxanide (FDA-approved), and albendazole (off label)



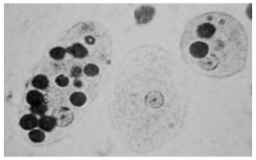
Entamoeba histolytica

- **Strictly Human Pathogen**
  - Fecal/oral (contaminated food/water)
  - Cysts = infective stage
  - Trophozoites = active form, tissue-destructive
- **Clinical Presentations**
  - Asymptomatic
  - Traveler's diarrhea
  - Colitis
    - Sharp abdominal pain
    - Bloody diarrhea
    - Fever
    - Flask-shaped ulcerations
    - Onset can occur weeks to months after travel



- Ameboma
- Liver and brain abscesses, esp in young men, usually 2-5 months after travel

Entamoeba histolytica



E. histolytica trophozoites with ingested RBCs.

Diagnosis

Stool PCR (multiplex or single)
- Close to 100% sensitivity and specificity

Stool O/P
- Only 50% sensitive for colitis and abscess
- Poor specificity b/c unable to differentiate *E.Histolytica* from non-pathogenic *E. Dispar* and the diarrhea-only causing *E. Moshkovskii*
  (Note: ingested RBCs suggestive of *eh*, but not 100%)

Stool antigen testing > 85% sensitive for intestinal disease

Serology 95% sensitive for liver abscess, 85% sensitive for intestinal infection

Treatment
- Asymptomatic: luminal agents such as paromomycin
- Symptomatic: tissue agents such as metronidazole or tinidazole THEN luminal agent
- Liver abscess: medical therapy (tissue agent then luminal agent) usually sufficient!
- Drainage if no response to medical therapy or dx unclear or v large abscess

Question #5

A 28-year-old woman returns after studying mosquito breeding habits in Honduras for one year. She reports intermittent abdominal pain and diarrhea for several months. Stool ova and parasite exam is positive for the presence of a ciliated single cell organism.

What is the most likely diagnosis?

A. Balantidium coli
B. Entamoeba histolytica
C. Giardia lamblia
D. Dientamoeba fragilis
E. Endolimax nana

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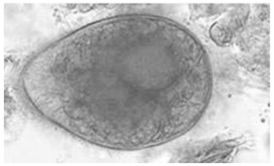
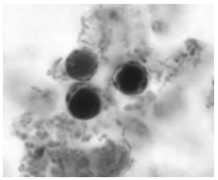
Balantidium coli



CDC DpDx

- The only ciliated pathogen of humans!
- Largest protozoan pathogen of humans!
  - (About 70 µm wide and up to 200 µm long)
- Found worldwide, especially central and S. America, S.E. Asia, and Papua New Guinea
- Associated with eating food/water contaminated with pig feces
- Symptoms: most people asymptomatic
  - Can cause colitis with abdominal pain, weight loss, +/- diarrhea
  - (Especially in malnourished and immunocompromised)
- Treatment: tetracycline (!) or metronidazole

Blastocystis



Blastocystis cyst-like forms ,trichrome (CDC DpDx)

What is it?

- Currently classified as a protozoa
- Forms are 5-40 microns wide
- Anaerobic, Eukaryotic
  cystic, ameboid, granular, and vacuolar forms

Often the most common eukaryotic organism found in human stool samples

Does it cause disease?

- Maybe
- Associated with watery diarrhea, abdominal discomfort, nausea, and flatulence

Diagnosis

- Light microscopy of stool samples

Treatment?

- Metronidazole, tinidazole, TMP/SMX, or nitazoxanide (none FDA-approved)

Other Intestinal Protozoa

Non-pathogens

Amoebae	Flagellates
Entamoeba dispar	Chilomastix mesnili
Entamoeba hartmanni	Trichomonas hominis
Entamoeba coli	
Endolimax nana	
Iodamoeba bütschlii	

Treat if symptomatic: Dientamoeba fragilis (implicated in IBS)

Protozoa*

Extraintestinal	Intestinal
Apicomplexa (SAR)	**Apicomplexa (SAR)**
Plasmodia	Cryptosporidium (no apicoplast)
(Babesia)	Cyclospora
(Toxoplasma)	Cystoisospora
Flagellates (Excavata)	**Flagellates (Excavata)**
Leishmania (kinetoplast)	Giardia (metamonad)
Trypanosomes (kinetoplast)	Dientamoeba (metamonad)
(Trichomonas) (metamonad/no mitochondria)	**Amoebae (Amoebozoa)**
Amoebae (Amoebozoa)	Entamoeba
Acanthamoeba	**Ciliates (SAR)**
Balamuthia	Balantidium
Amoeboflagellate (Excavata)	**Non-motile (SAR)**
Naegleria	Blastocystis

Kingdom Fungi Microsporidiosis agents

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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

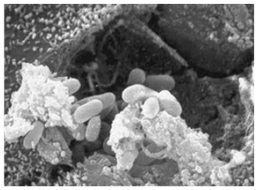
Enterocytozoon bieneusi
- Watery diarrhea
- Biliary disease (cholangitis, acalculous cholecystitis)

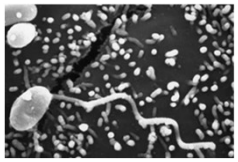
Encephalitozoon intestinalis
- Watery diarrhea
- Biliary disease
- Disseminated disease (liver, kidney, lung, sinuses)

Encephalitozoon cuniculi, hellem
- Can cause disseminated disease of multiple organs, plus eye

Many species (including *Vittaforma corneae*):
Punctate keratoconjunctivitis (contact lens use, after eye surgery, bathing in hot springs)

Diagnosis: modified trichrome stain, Calcofluor white, IFA to detect spores in stool
Treatment: albendazole (not effective for *E. bieneusi*)


Spores of *E. hellem* bursting out of a cell (CDC DpDx)


Polar tubule inserted into a eukaryotic cell (CDC DpDx)

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

Protozoan Infections that Can Reactivate in the Severely Immunocompromised

- **Chagas**
  - Encephalitis with mass lesions
  - Hepatosplenomegaly and fevers
  - Myocarditis in 40% that receive heart transplant b/c chagas disease
- **Malaria**

Some other protozoa that can cause severe disease in immunocompromised
- Cryptosporidium
- Giardia
- Microsporidia
- Babesia
- Acanthamoeba

Good luck on the exam!

Edward Mitre, M.D.
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Malaria Chemoprophylaxis

(Note: No Malaria Vaccine Approved For U.S. Travelers)

Some Regions In Central America and the 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	1 Tab/wk x 2-3 wks	1 Tab/wk	4 Weeks

**** Tafenoquine can precipitate severe hemolytic anemia in individuals that are G6PD deficient***

***** FDA black box warning mefloquine can cause neurologic symptoms, hallucinations, and feelings of anxiety, mistrust, and depression. Can also cause QT prolongation. Thus, many U.S. practitioners now reserve mefloquine for pregnant travelers to areas with chloroquine resistance.***

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P. falciparum Treatment

Excellent Review → 2022 JAMA, 328(5):460-47, PMID: 3591684

Uncomplicated P. falciparum malaria (no organ dysfunction, low parasitemia, able take PO)

- If chloroquine sensitive area → Chloroquine or hydroxychloroquine

- If not chloroquine sensitive area (most cases) → **Artemether/lumefantrine (Coartem)**
  ACTs are treatment of choice, WHO 2022 guidelines

Alternatives if artemether/lumefrantrine not available:

- Atovaquone/proguanil (Malarone), quinine + doxycycline, mefloquine

Severe Malaria

→ **IV artesunate** (CDC Malaria Hotline: 770-488-7788)

NOTES

1. Treatment failures can occur with artemether/lumefrantrine, especially when > 65 kg
   Abanyie F. et al, *Clinical Infectious Diseases* 2022 PMID: 36052468
2. Artemisinin resistance reported in SE Asia (Cambodia, Laos, Myanmar, Thailand, Vietnam), parts of Africa (Uganda, Rwanda), and in S. America (Guyuna)
3. Delayed-onset anemia in 2.7% of U.S. patients after treatment with artesunate
   Sonden K. et al, *Clinical Infectious Diseases* 2017 PMID: 27986683
4. Hypoglycemia and ARDS are complications that can occur during treatment of malaria. ARDS sometimes develops even as pt improving from malaria.

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P. vivax/P. ovale Treatment

Chloroquine x 3 days, or ACT (artemether/lumefrantrine in U.S.)

Note: PNG, Indonesia, Oceania have CLQ R P. vivax → use ACT

Then ANTIRELAPSE THERAPY with primaquine or tafenoquine

→ Need to check G6PD status before administering primaquine OR tafenoquine
(as both can cause severe hemolysis in patients with G6PD deficiency)

→ Both primaquine and tafenoquine contraindicated during pregnancy

- **Primaquine – weigh- based dosing and duration as determined by G6PD activity**

*****ALWAYS LOOK UP DOSING BEFORE ADMINISTERING*****

-> Usually 30 mg primaquine base per day x 14 days if normal G6PD activity

-> Do not exceed 30 mg primaquine base per day

-> If over 70 kg, can calculate total dose 6 mg/kg and then extend duration of 30 mg daily doses until total goal met

-> If G6PD deficient consider weekly chloroquine x 1 year

- **Tafenoquine (two 150 mg tabs once, given on 1st or 2nd day of chloroquine therapy)**
(Tafenoquine was approved for radical cure of *P. vivax* in 2018, *P. ovale* treatment is off-label)

2020 : Company (GSK) reported some failures when tafenoquine was used after ACT treatment of P. vivax.

NEW FDA LABELING: **Tafenoquine now only approved and recommended after chloroquine treatment**

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https://www.cdc.gov/malaria/hcp/clinical-guidance/treatment-uncomplicated.html

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Visceral Leishmaniasis

L. donovani *(South Asia, East Africa)*

L. infantum chagasi *(Middle East, Central Asia, Mediterranean, Central and S. America)*

Amastigotes in macrophages go to local LNs then hematogenously to liver, spleen, bone marrow

A persistent disease that can reactivate

TNF blockade, HIV CD4 < 200

- Weeks/months of fevers, chills, hepatosplenomegaly
- Pancytopenia & hypergammaglobulinemia

Diagnosis: PCR, culture, or histopathology for intracellular amastigotes

→ Bone marrow aspirate preferred, can also check LN, spleen, or buffy coat antibody to rK39 recombinant Ag

Treatment: Liposomal ampho B (FDA approved)

Miltefosine (oral) FDA approved for *L. donovani*

(Combination treatment for L. donovani in people living with HIV in SE Asia)

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African Trypanosomiasis – Treatment

July 16, 2021: Oral fexinidazole FDA approved for *T. gambiense*

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 > 6 yo and > 20kg: 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*)

If < 6 yo or < 20 kg: lumbar puncture

CSF < 5 WBC/ul → suramin

CSF > 5 WBC/ul → melarsoprol

If > 6 yo and > 20kg → oral fexinidazole (IV melarsoprol or suramin depending on CSF counts if unable to take PO)

Notes: *1. Melarsoprol associated with ~5% death rate due to reactive encephalopathy*

2. This is reduced by co-administration of corticosteroids

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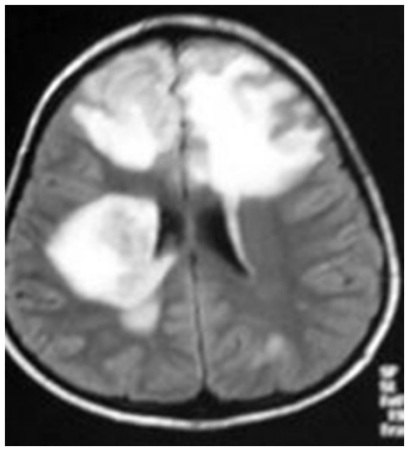
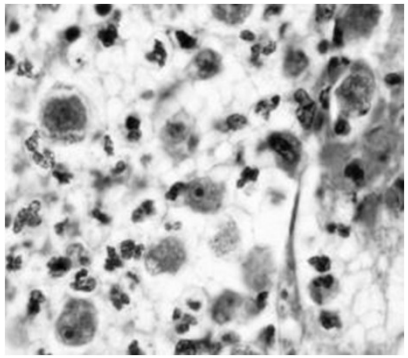
Free-living Amoebae





Naegleria fowleri (amoeboflagellate!)

- Warm freshwater exposure
- Enters through olfactory neuroepithelium
- Fulminant meningoencephalitis
- Immunocompetent children/young adults

Acanthamoeba

- Found in soil and water
- Enter through lower respiratory tract or broken skin
- Subacute granulomatous encephalitis
- Immunocompromised hosts
- Chronic granulomatous keratitis (contact lens, LASIK)

Balamuthia mandrillaris

- Likely enters through lower respiratory tract or broken skin
- Transmission by solid organ transplantation has been reported
- Subacute granulomatous encephalitis
- Normal and immunocompromised hosts

Outcome → often fatal (amphotericin B, azoles, pentamidine, others tried)

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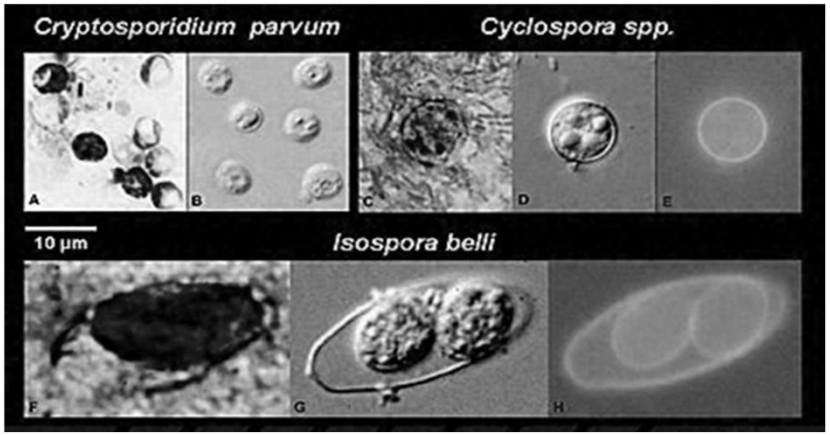
Intestinal Apicomplexa Characteristics

Pathogen	Size	Stain	Treatment
Cryptosporidium	4 µm	M acid-fast	(None) nitazoxanide or paromomycin
Cyclospora	10 µm	M acid-fast	TMP/SMX
Cystoisospora	20 µm	M acid-fast	TMP/SMX



CDC

Molecular Tests

Most stool multiplex PCR assays detect cryptosporidium AND cyclospora

But NOT cystoisospora

Stool Ag tests are commercially available for cryptosporidium

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Sunday, August 23, 2026

12

Brain Abscess, Cavernous Sinus Thrombosis, and Subdural and Epidural Empyema

Allan Tunkel, MD

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Brain Abscess, Cavernous Sinus Thrombosis, Subdural Empyema and Epidural Abscess

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

Disclosures of Financial Relationships with Relevant Commercial Interests

- List of disclosures or “None”

Question #1

- 24-year-old female who presented with pain and swelling on the right side of her jaw that had been progressing over the last several weeks. She was unable to open her mouth. She denied fever or headache and had no past hospitalizations or illnesses. The patient had not been to the dentist within 10 years.
- T 99.8^{o}F, P 88, RR 14, BP 110/80
- Exam revealed swelling and erythema along her right mandible

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Question #1

Which of the following empiric antimicrobial regimens should be initiated?

A. Ceftriaxone + metronidazole
B. Vancomycin + cefepime
C. Trimethoprim-sulfamethoxazole
D. Voriconazole
E. Liposomal amphotericin B

Predisposing Conditions for Brain Abscess

Condition	Relative Frequency (%)
Contiguous focus of infection (otitis media, mastoiditis, sinusitis, face or scalp infection, dental sepsis, osteomyelitis, penetrating head injury)	30-50
Hematogenous spread (lung abscess, empyema, congenital heart disease, bronchiectasis, infective endocarditis, compromised host, hereditary hemorrhagic telangiectasia)	~35
Cryptogenic	10-35

Principles of Brain Abscess Management

- MR imaging is the diagnostic procedure of choice; diffusion-weighted imaging increases diagnostic accuracy (sensitivity and specificity 96% for differentiation from cancers [PPV 98%; NPV 92%])
- Lumbar puncture is contraindicated
- Biopsy or aspiration (via stereotactic guidance) is needed for microbiologic diagnosis
- Begin empiric antimicrobial therapy based on underlying condition and pathogenesis of spread of infection to brain

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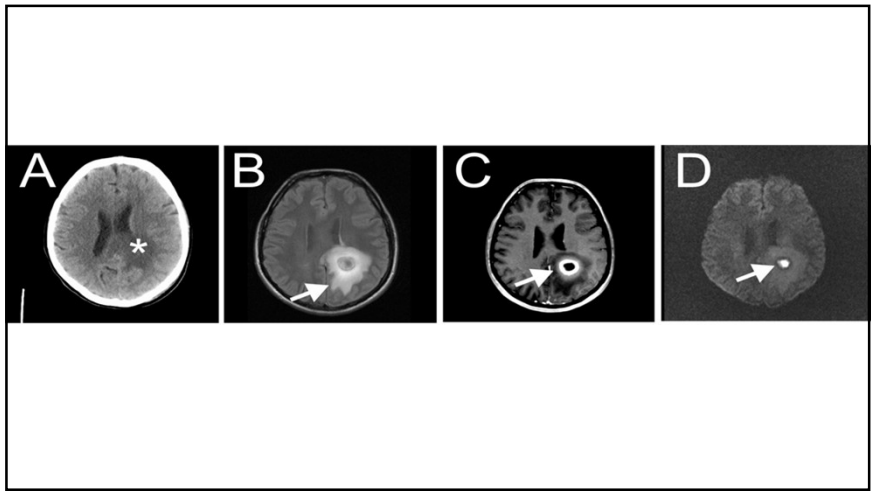

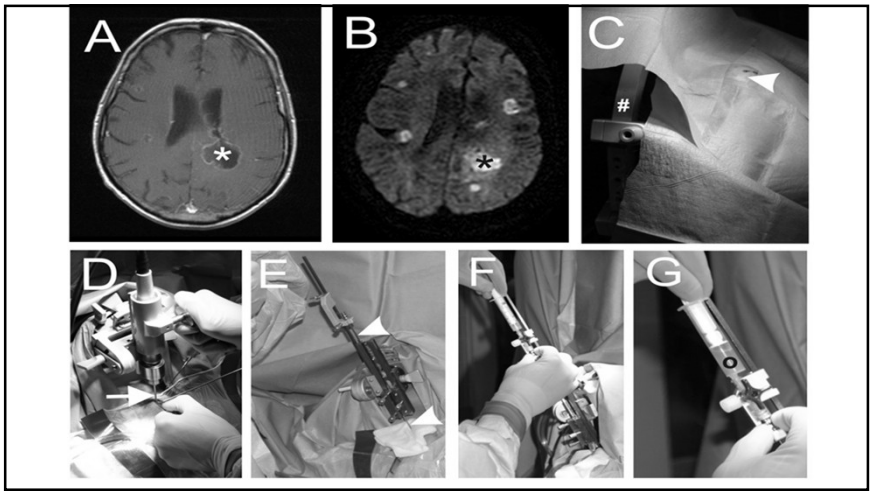

Empiric Antimicrobial Therapy of Brain Abscess

Predisposing Condition	Antimicrobial Regimen
Otitis media or mastoiditis	Metronidazole + a third-generation cephalosporin[a]
Sinusitis	Vancomycin + metronidazole + a third-generation cephalosporin[a]
Dental sepsis	Third-generation cephalosporin[a] + metronidazole
Penetrating trauma or post-neurosurgical	Vancomycin + a third- or fourth-generation cephalosporin
Lung abscess, empyema, bronchiectasis	Vancomycin + metronidazole + a third- or fourth-generation cephalosporin + trimethoprim-sulfamethoxazole[b]
Bacterial endocarditis	Vancomycin[c]

[a]ceftriaxone or cefotaxime
[b]add if *Nocardia* suspected, along with 1-2 additional agents
[c]additional agents may be used based on other likely microbial etiologies

Empiric Antimicrobial Therapy of Brain Abscess

Predisposing Condition	Antimicrobial Regimen
Unknown	Vancomycin + metronidazole + a third or fourth generation cephalosporin; or vancomycin + meropenem
Transplant recipients	Add voriconazole + trimethoprim-sulfamethoxazole (plus additional 1-2 anti-nocardial agents) if *Nocardia* suspected
HIV-infected patients	Add pyrimethamine + sulfadiazine; consider isoniazid, rifampin, pyrazinamide, and ethambutol for possible tuberculosis

12 Brain Abscess, Cavernous Sinus Thrombosis, Subdural Empyema and Epidural Abscess

Speaker: Allan Tunkel, MD, PhD

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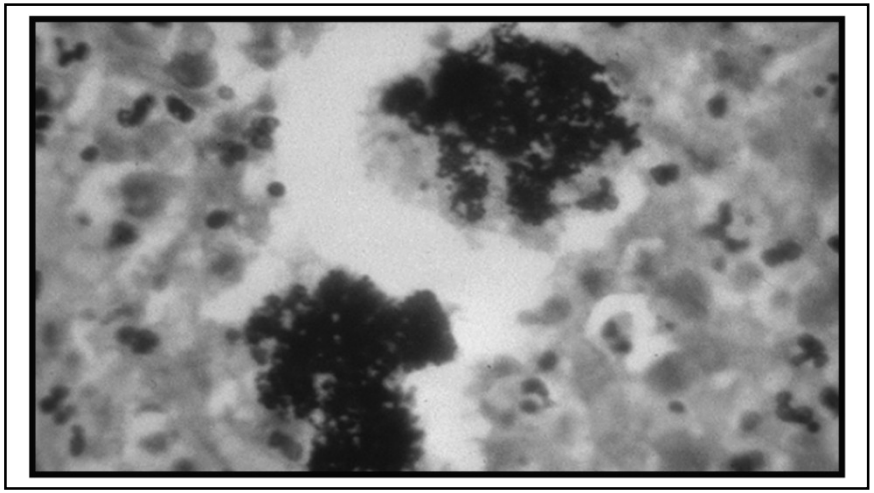
Case Study

- 21-year-old member of a motorcycle gang thrown from his bike, and suffered a depressed skull fracture
- In the OR, a large subdural hematoma was evacuated
- Discharged in 5 days
- Returned by mother 5 days later because of bizarre behavior
- No headache, afebrile



Question #2

- 78-year-old male with multiple myeloma on chronic prednisone therapy; underwent aortic valve replacement with a bioprosthesis 5 years earlier; presented with new-onset seizures
- T 100.4o F, P 96, RR 18, BP 110/70 mmHg; Exam (-)
- CT scan revealed multiple ring-enhancing lesions
- TEE - no vegetations and normal bioprosthesis
- Empirically placed on vancomycin + cefepime
- Blood cultures negative

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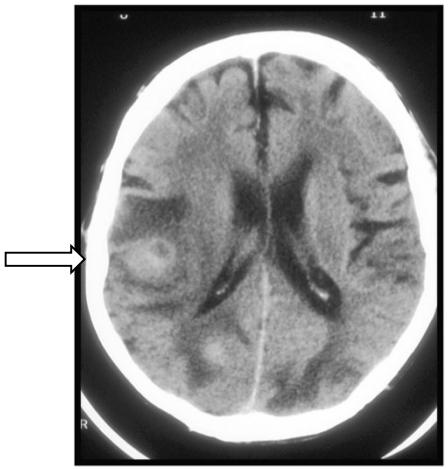
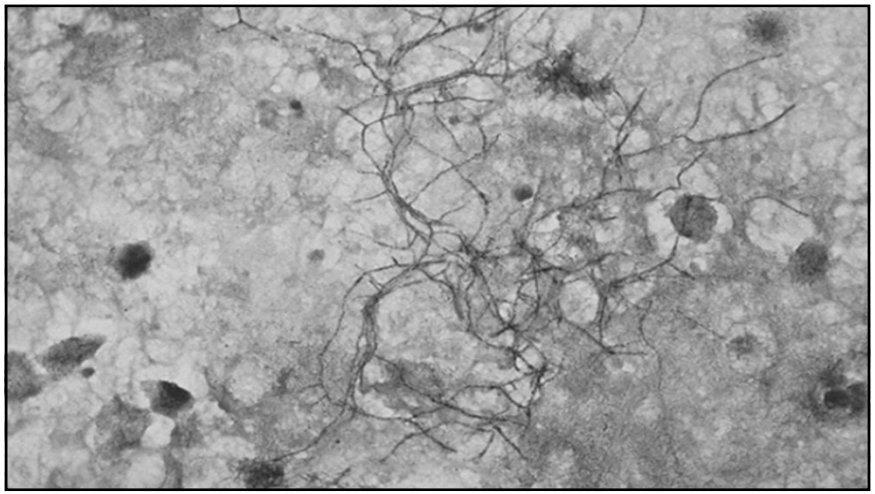
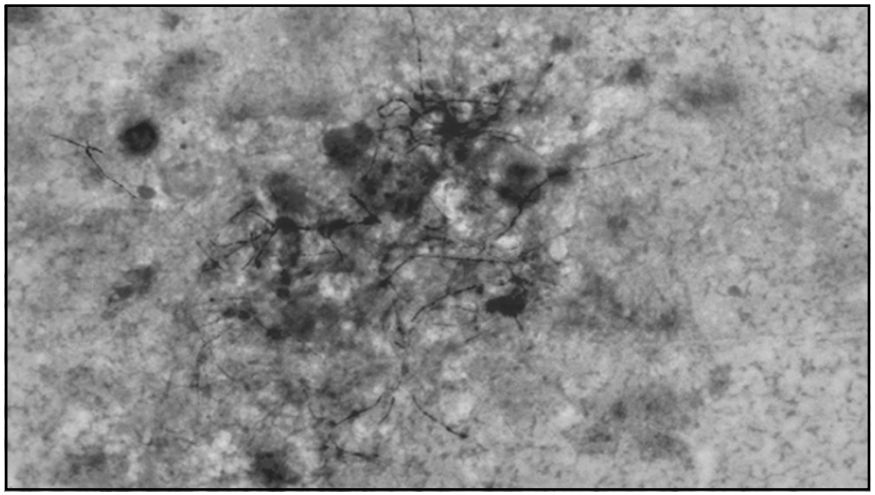




Question #2

Which of the following antimicrobial regimens should be initiated?

A. Penicillin + metronidazole
B. Trimethoprim-sulfamethoxazole + imipenem
C. Daptomycin + cefepime
D. Liposomal amphotericin B + 5-FC
E. Voriconazole



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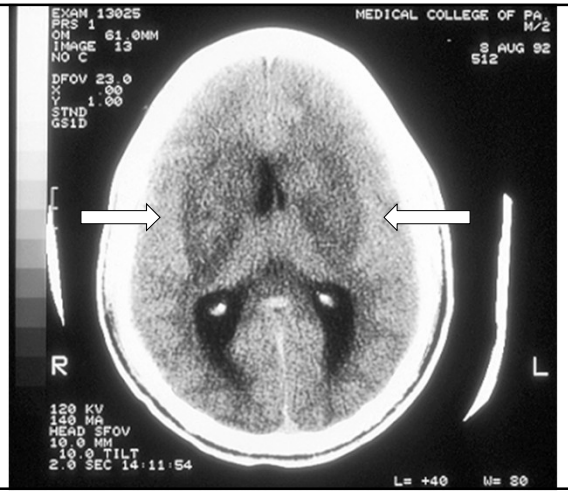
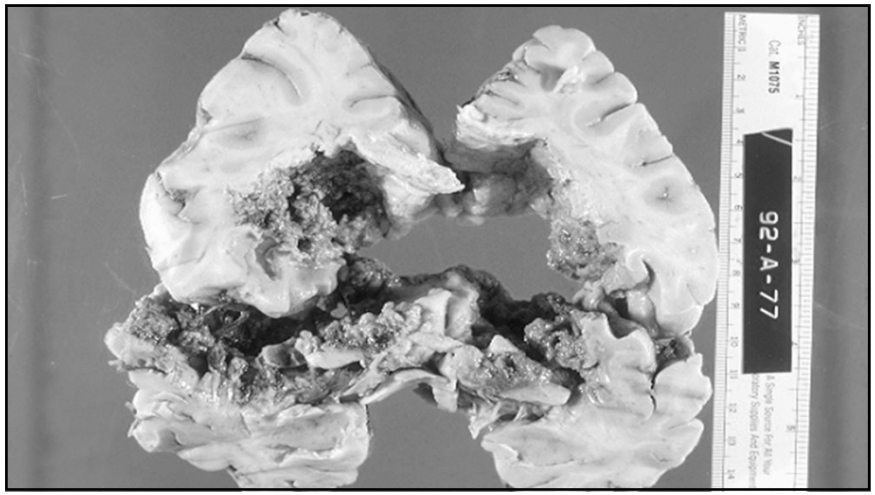
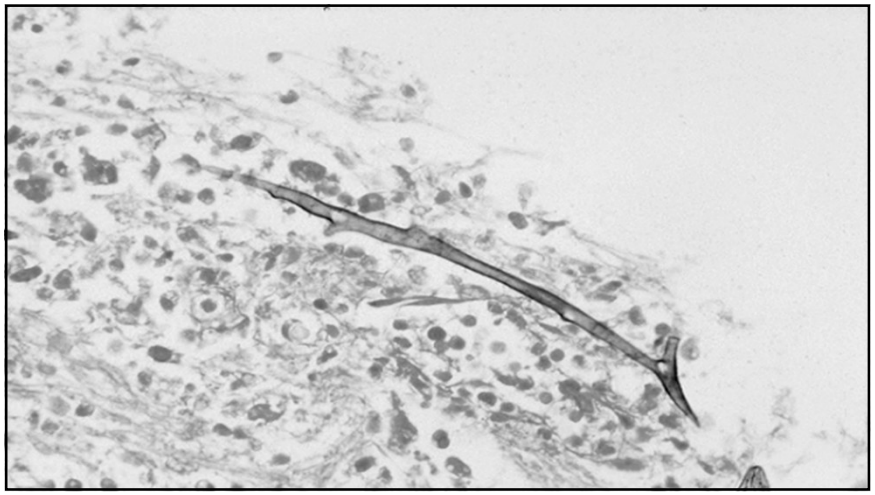
Case Study

- 24-year-old injection drug user who, while injecting intravenous drugs with his girlfriend, fell out of the second story window of his apartment. When he did not return for 48 hours, she found him unresponsive on the ground and called fire rescue
- T 103oF, P 150, RR 32, BP 110/76 mmHg
- On exam, he was comatose without evidence of head trauma
- WBC 13,000/mm3, profound metabolic acidosis







12 Brain Abscess, Cavernous Sinus Thrombosis, Subdural Empyema and Epidural Abscess

Speaker: Allan Tunkel, MD, PhD

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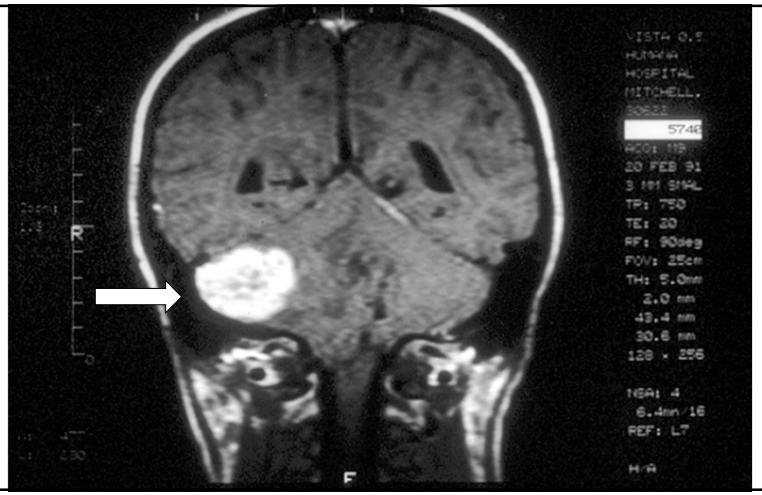
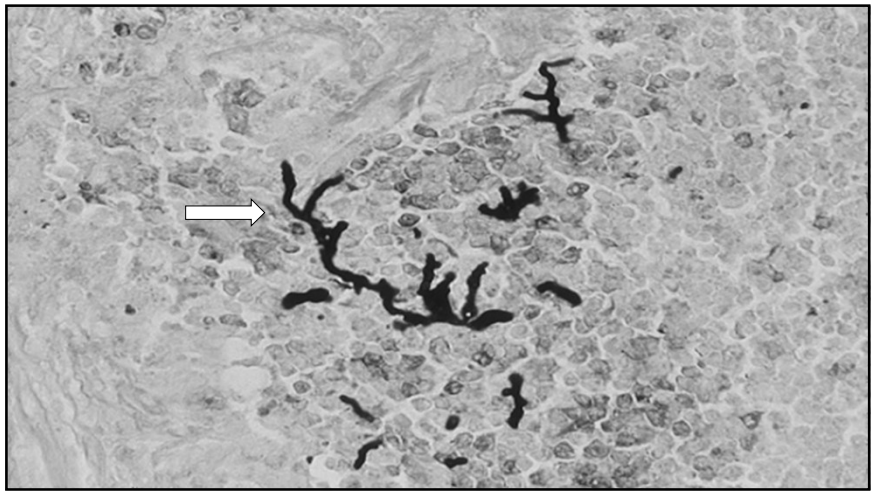
Case Study

- 11-year-old boy with chronic granulomatous disease on chronic TMP-SMX therapy noted the onset of a mild headache which lasted 10 minutes
- Two weeks later at a routine physician visit, the patient had no complaints and denied recurrence of the headache
- On examination, the patient had normal vital signs and a normal neurologic examination
- The physician ordered an MR imaging of the head





Case Study

- 80-year-old male with CLL on chronic prednisone therapy presented to the VA Hospital with sepsis and ARDS. Course complicated by VDRF and multiple nosocomial infections, including candidemia for which he received 4 weeks of IV liposomal amphotericin B. After completing the course of therapy, he developed altered mental status
- T 1010 F, P 100, RR 20, BP 120/76
- Neurologic exam left-sided hyperreflexia and Babinski

12 Brain Abscess, Cavernous Sinus Thrombosis, Subdural Empyema and Epidural Abscess

Speaker: Allan Tunkel, MD, PhD

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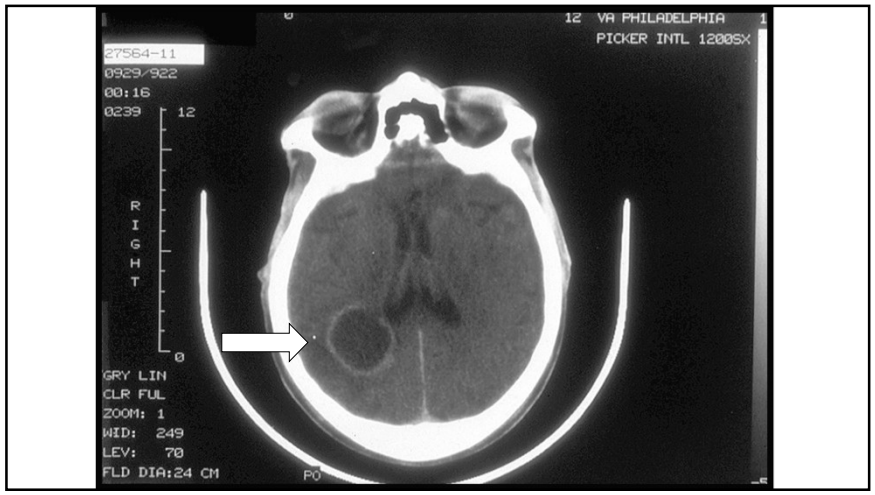

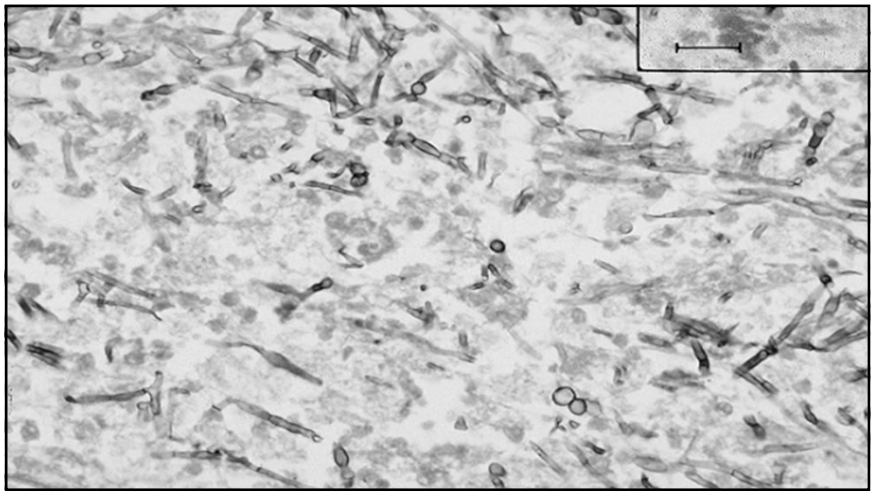

Principles of Brain Abscess Management

- Optimal management usually requires a combined medical and surgical approach (aspirate if >2.5 cm)
- Fungal brain abscess often requires combined medical and surgical therapy
- Initiate corticosteroids with evidence of cerebral edema or mass effect causing increased ICP

Antimicrobial Therapy of Brain Abscess

Organism	Antimicrobial Therapy
Actinomyces sp.[a]	Penicillin G
Bacteroides fragilis[a]	Metronidazole
Enterobacterales[a]	Third- or fourth-generation cephalosporin, or another agent based on in vitro susceptibility
Fusobacterium sp.[a]	Metronidazole
Pseudomonas aeruginosa	Ceftazidime or cefepime or meropenem
Staphylococcus aureus	Nafcillin, oxacillin, or vancomycin
Strep. milleri; [a] other streptococci[a]	Penicillin G

[a]depending on pathogenesis of infection, may be isolated as part of a mixed infection1111

12 Brain Abscess, Cavernous Sinus Thrombosis, Subdural Empyema and Epidural Abscess

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Antimicrobial Therapy of Brain Abscess

Organism	Antimicrobial Therapy
Nocardia asteroides	Trimethoprim-sulfamethoxazole + imipenem; add third drug in those with severe disease, or those failing standard therapy
Mycobacterium tuberculosis	Isoniazid + rifampin + pyrazinamide ± ethambutol

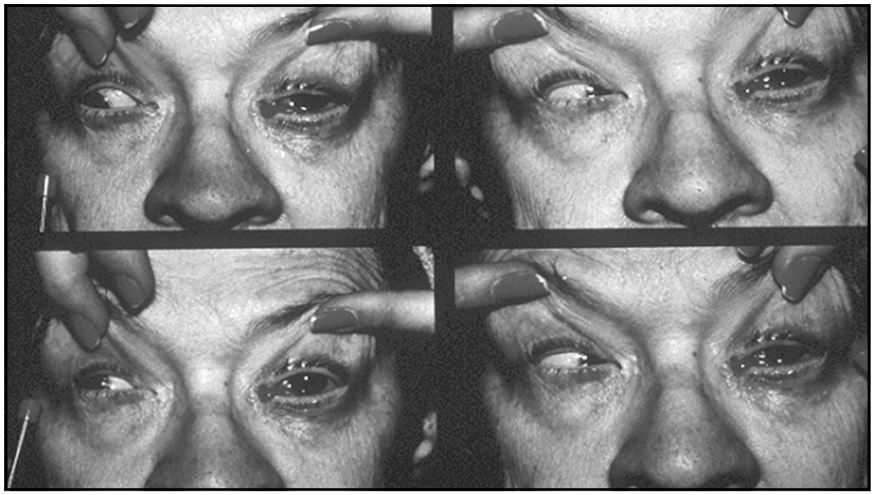
Antimicrobial Therapy of Brain Abscess

Organism	Antimicrobial Therapy
Aspergillus sp.	Voriconazole
Candida sp.	Liposomal amphotericin B[a]
Mucorales	Liposomal amphotericin B
Scedosporium spp.	Voriconazole

[a]Addition of 5-flucytosine should be considered

Question #3

- 79-year-old female is transferred from a nursing home for failure to thrive as a result of decreased oral intake. A nasogastric tube is placed via the left nares for enteral hyperalimentation
- One week into her hospital course, the patient develops fever to 101.5o F, and left periorbital edema and chemosis
- CT scan of the head without contrast reveals opacification of the sphenoid sinus



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Question #3

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

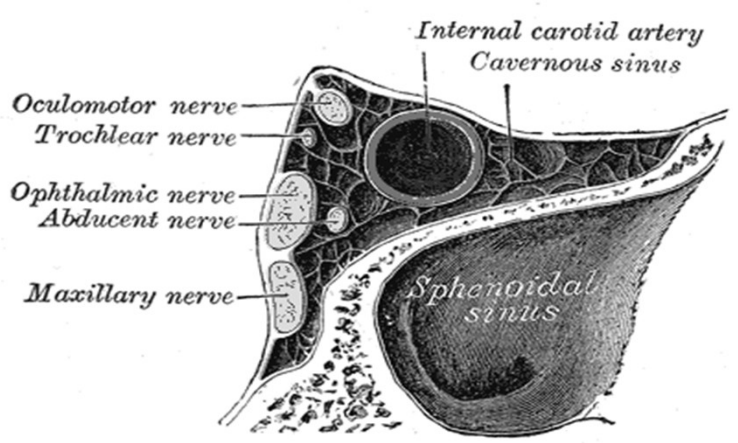
A. CT scan of the head and sinuses with contrast
B. MR imaging with MR venography
C. Cerebral angiography
D. Positron emission tomography of the head
E. Lumbar puncture

Epidemiology and Etiology of Septic Cavernous Sinus Thrombosis

Risk Factors	Etiologic Agents
Paranasal sinusitis	Staphylococci (60-70%)
Facial infection	Streptococci (~17%)
Dental infection	Gram-negative bacilli (~5%)
	Pneumococci (~5%)
	Bacteroides sp. (~2%)

Clinical Features of Septic Cavernous Sinus Thrombosis

Symptoms	Signs
Headache (52%)	Periorbital edema (73%)
Facial pain	Chemosis
Vision loss	Papillitis
Fever	Oculomotor palsies
Double vision	Proptosis



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Radiologic Findings in Septic Cavernous Sinus Thrombosis

- MR imaging
- Noninvasive diagnostic procedure of choice
- MRA and MRV can directly visualize cerebral vasculature
- Fullness in cavernous sinus region
- Paranasal sinus fluid

Management of Septic Cavernous Sinus Thrombosis

- Culture and drainage of infected sinuses
- Antimicrobial therapy (vancomycin + metronidazole + 3rd or 4th generation cephalosporin)
- Anticoagulation - Yes
- Corticosteroids - No

Question #4

- 22-year-old man with a history of paranasal sinusitis presents with fever, severe headache, neck pain, and seizure
- On physical examination, T 102^{o}F and he is lethargic
- Laboratory studies normal

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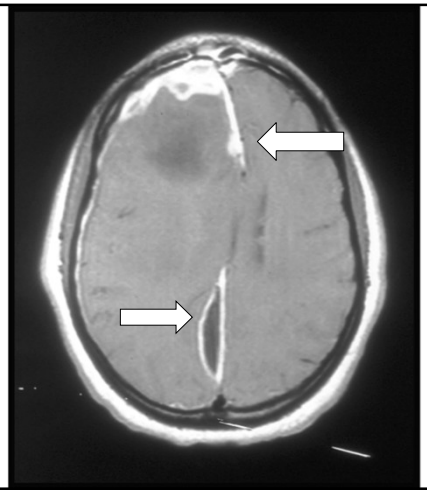

Question #4

In addition to appropriate antimicrobial therapy, what other management should be performed?

A. Lumbar puncture
B. External ventricular drain
C. Dexamethasone
D. Burr hole drainage
E. Craniotomy

Cranial Subdural Empyema and Cranial Epidural Abscess

Risk Factors	Etiologic Agents
Sinusitis (50-80%)	Staphylococci (10-15%)
Otogenic	Streptococci (25-45%)
Head trauma	Gram-negative bacilli (3-10%)
Neurosurgery	Other anaerobes (8%)
Hematogenous	Others (8%)
Meningitis	Unknown (20%)

Cranial Subdural Empyema and Cranial Epidural Abscess

Subdural Empyema
(Acute Course)

- Fever
- Headache
- Depressed consciousness
- Hemiparesis
- Seizures
- Nuchal rigidity
- Gaze palsies/ataxia

Epidural Abscess
(Indolent Course)

- Headache
- Fever
- Seizures
- Focal neurologic signs
- Altered mental state

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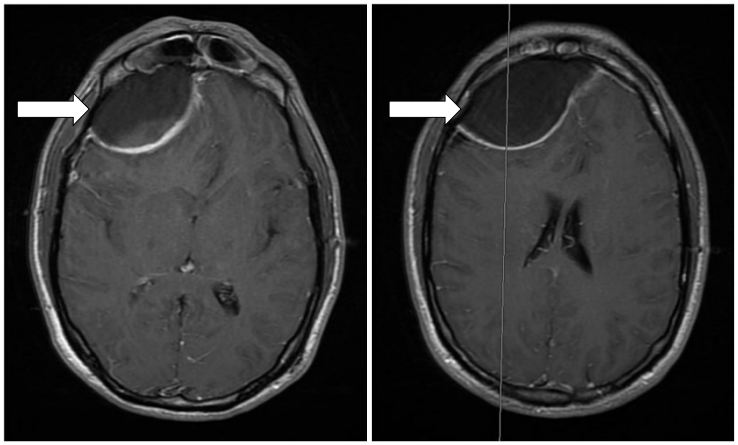


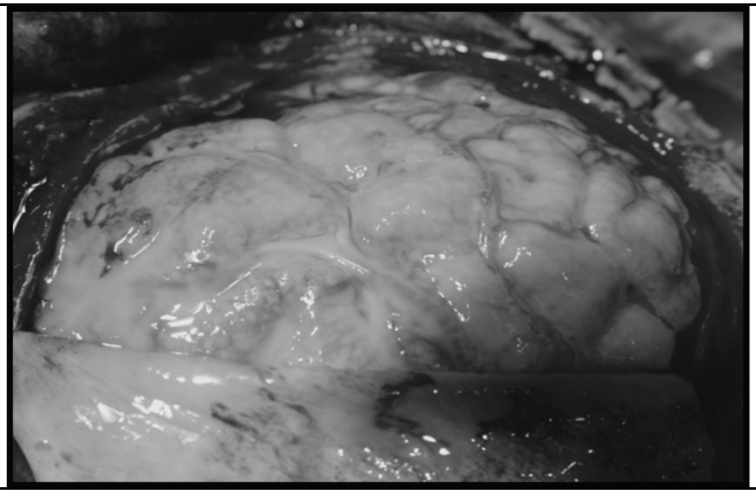
Principles of Management of Cranial Subdural Empyema

- MR imaging (diagnostic procedure of choice) provides better clarity of detail and can differentiate empyema from most sterile effusions and chronic hematomas; diffusion-weighted imaging adds to value of MRI
- Empiric antimicrobial therapy based on pathogenesis of infection
- Surgical therapy (burr holes or craniotomy) is imperative; better outcome with craniotomy

Surgical Management of Cranial Subdural Empyema

Surgical Procedure	Mortality Rate
Burr hole(s)	23.3%
Craniectomy	11.5%
Craniotomy	8.4%

Nathoo et al. Neurosurgery 2001;49:872



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Epidemiology of Spinal Epidural Abscess

- Incidence of ~5-8 infections per 10,000 hospital admissions
- Usually occurs secondary to hematogenous dissemination (~50% of cases)
- Contiguous foci (~1/3rd of cases)
- Unidentified source (20-40% of cases)
- Diabetes mellitus identified in up to 50% of patients

Etiology of Spinal Epidural Abscess

Organism	Relative Frequency (%)
Staphylococci	50-90
Streptococci	8-17
Gram-negative bacilli	12-17
Other anaerobes	2
Other	2
> 1 organism	5-10
Unknown	6

Clinical Stages of Spinal Epidural Abscess

- Back pain and tenderness at the level of infection
- Radicular pain and paresthesias
- Impaired spinal cord function; motor paresis and sensory deficits
- Complete paralysis

Pathogenesis of Spinal Epidural Abscess

- Pathogenesis of spinal cord injury
  - Direct mechanical compression by an expanding abscess (with or without vascular damage)
  - Disruption of vascular supply from septic thrombophlebitis
- Potential for neurologic impairment higher in cervical and thoracic locations

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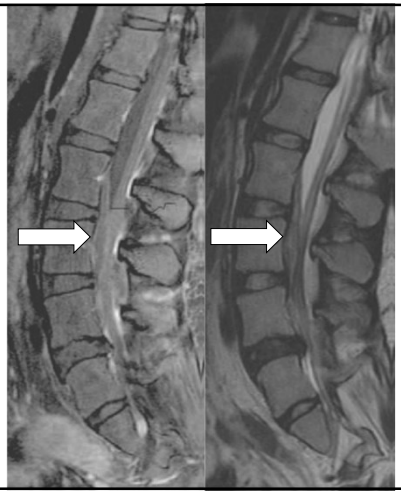
Principles of Management of Spinal Epidural Abscess

- MR imaging is the diagnostic procedure of choice; can visualize the spinal cord and epidural space, and can identify accompanying osteomyelitis, intramedullary spinal cord lesions, and joint space infection
- Microbiologic diagnosis by blood cultures or image-guided biopsy (unless surgery is imminent)



Principles of Management of Spinal Epidural Abscess

- Empiric antimicrobial therapy should include an antistaphylococcal agent (i.e., vancomycin) and coverage for gram-negative bacilli
- Surgical therapy imperative in the presence of neurologic dysfunction (best if <24-36 hours of complete paralysis)
- Nonsurgical therapy only for patients with an unacceptably high surgical risk or no neurologic deficits at diagnosis; patient must be followed carefully for clinical deterioration

Questions

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Worms You Should Know

Edward Mitre, MD

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Worms You Should Know

Edward Mitre, MD
Rockville, MD

Disclaimer: Dr. Mitre is giving this presentation in a personal capacity. The views expressed in this presentation are the sole responsibility of the presenter and do not necessarily reflect the views, opinions, or policies of the Uniformed Services University of the Health Sciences, the Department of Defense, or the United States Government.

7/28/2026

Disclosures of Financial Relationships with Relevant Commercial Interests

- None

Question #1

28-year-old female
- Recurrent crampy abdominal pain for several months
- Just returned home after living for two years in Tanzania
- Colonoscopy reveals small white papules
- Biopsy reveals an egg with eosinophilic granulomatous inflammation

Which is the most likely diagnosis?

A. Entamoeba histolytica
B. Ascaris lumbricoides
C. Wuchereria bancrofti
D. Schistosoma mansoni
E. Paragonimus westermani

Major Helminth Pathogens

TREMATODES

Blood flukes
- *Schistosoma mansoni*
- *Schistosoma japonicum*
- *Schistosoma haematobium*

Liver flukes
- *Fasciola hepatica*
- *Clonorchis sinensis*
- *Opisthorchis viverrini*

Lung flukes
- *Paragonimus westermani*

Intestinal flukes
- *Fasciolopsis buski*
- *Metagonimus yokagawai*

CESTODES

Intestinal tapeworms
- *Taenia solium*
- *Taenia saginata*
- *Diphyllobothrium latum*
- *Hymenolepis nana*

Larval cysts
- *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*
- *Dracunculus medinensis*

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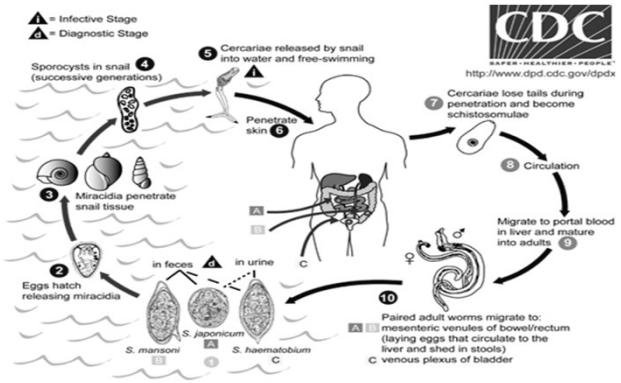
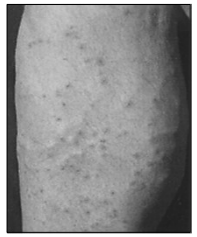
Schistosomiasis Life Cycle



Acute Schistosomiasis



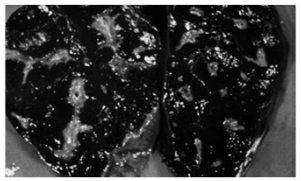
Cercarial Dermatitis (Swimmer's Itch)

- Urticarial plaques and pruritic papules
- Occurs upon re-exposure to cercariae penetrating skin in a sensitized individual
- Symptoms develop minutes to days after water exposure
- Can occur with human or avian schistosomes

Katayama Fever

- Fever, myalgias, abdominal pain, headache, diarrhea, urticaria
- Occurs in previously unexposed hosts
- Symptoms typically start 3 - 8 weeks after water exposure
- Eosinophilia, elevated AST and alkaline phosphatase
- No reliable way to confirm diagnosis acutely as serology and stool O/P frequently negative

Chronic Schistosomiasis



Schistosoma species

- *S. mansoni (Sm)*
- *S. japonicum (Sj)*
- *S. intercalatum (Si)*
- *S. mekongi (Smk)*
- *S. haematobium (Sh)*
- *S. haematobium/S. bovis hybrid (Sh/b)*

From Senegal, outbreak 2013 in Corsica, France

Intestinal and hepatosplenic disease
(**S. mansoni +** Sj, Si, Smk, Sh/b)

- Granulomatous colitis
- Portal hypertension

Genitourinary disease (S. haematobium + Sh/b)

- Granulomatous cystitis
- Bladder fibrosis and cancer
- Obstructive uropathy

Pulmonary Disease (Sm, Sh, Sj)

CNS disease

- CNS disease (eggs to brain/spinal cord, esp *S. japonicum*)

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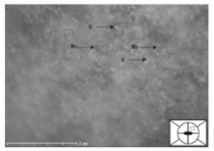
Schistosomiasis

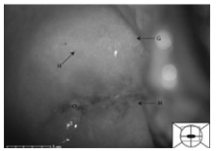
Chronic genital disease
Increasingly recognized
Primarily due to *S. haematobium*

Women (vaginal and cervical lesions)
- Pelvic pain
- Dysmenorrhea
- Dyspareunia
- Post-coital bleeding
- Endometritis/salpingitis

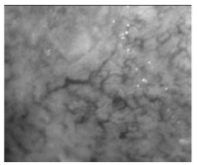
Men
- Epididymitis
- Prostatitis



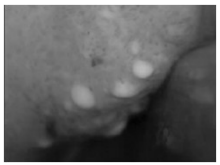
Sand Grains



Sandy Yellow Patches



Abnormal Vessels



Rubbery Papules

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WHO Female Genital Schistosomiasis Pocket Atlas

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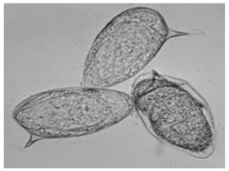
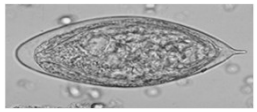
Schistosome Eggs

S. mansoni
(Lateral spine)



CDC DPDx image library

S. haematobium
(Terminal spine)



CDC DPDx image library

Question #2

A 25-year-old 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.

What is a long-term complication that can occur as a result of infection with the larval form of this parasite?

A. HTLV-1 infection
B. Bladder cancer
C. Appendicitis
D. Liver abscess
E. Seizures

Major Helminth Pathogens

TREMATODES

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- *Schistosoma mansoni*
- *Schistosoma japonicum*
- *Schistosoma haematobium*

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- *Anisakis simplex*
- *Toxocara canis/cati*
- *Baylisascaris procyonis*
- *Gnathostoma spinigerum*
- *Dracunculus medinensis*

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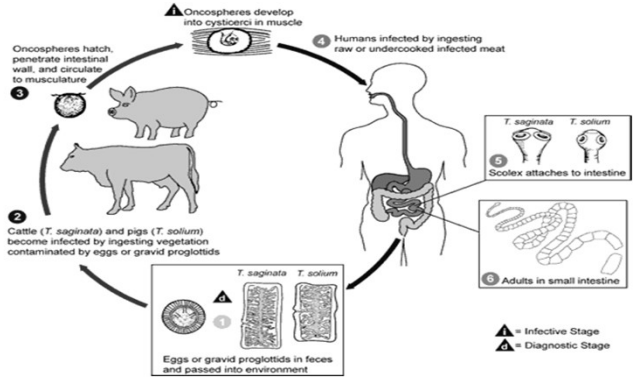
Taenia Life Cycle



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Taenia Life Cycle

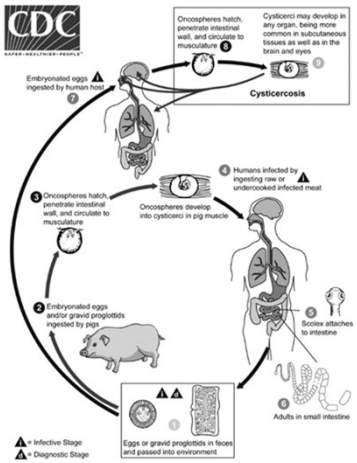
Taenia solium
- Tapeworm is acquired by eating larvae in pork
- Adult tapeworm causes few symptoms

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.



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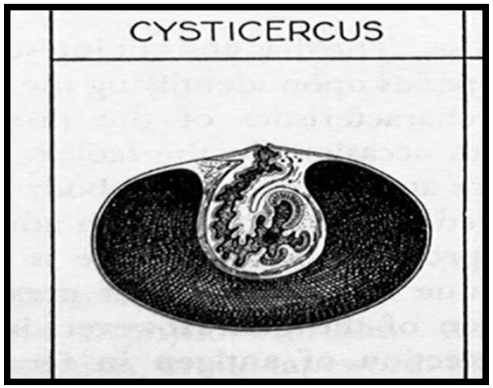
Cysticercus: a fluid filled bladder containing the invaginated head (scolex) of the larval form of a tapeworm



Neva and Brown, Basic Clinical Parasitology 6th Edition

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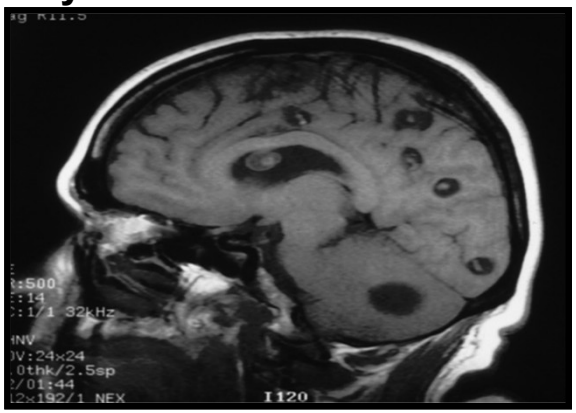
Neurocysticercosis



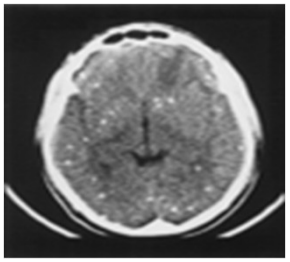
Neurocysticercosis

Can cause:

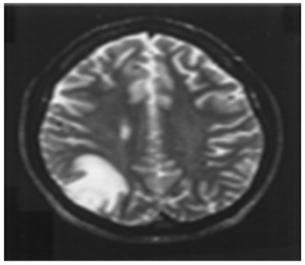
- Seizures
- Hydrocephalus
- Headaches
- Focal neurologic deficits

Neurocysticercosis

Multiple old calcifications

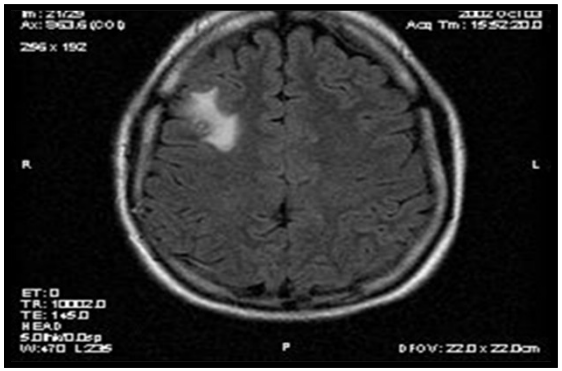


Perilesional edema – typically occurs around dying cysts and is a frequent finding on initial presentation of seizure or terrible headache.



Cysticercosis

Single Lesion Disease is Diagnostic Challenge



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Neurocysticercosis

Diagnosis:

Definitive = tissue biopsy, multiple cystic lesions each with scolex on imaging, retinal cysticercus on fundoscopy

Presumptive = suggestive lesions on imaging

Cysticercosis serology → supportive (sensitive if high burden of disease)

qPCR and antigen testing of CSF → sensitive for subarachnoid and intraventricular neurocysticercosis, and can be used to help gauge duration of treatment *(available at NIH, contact Dr. Elise O'Connell oconnellem@mail.nih.gov)*

Treatment:

Medical therapy decreases risk of future seizures, but has immediate risk of increasing seizures/brain inflammation

If hydrocephalus or diffuse cerebral edema: initial treatment with steroids and/or surgery (not anti-parasitic Rx)

If no increased ICP: 1-2 viable cysts → albendazole for 1-2 viable cysts

> 2 viable cysts → albendazole + praziquantel

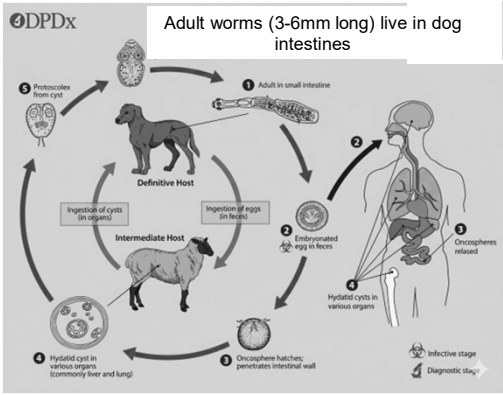
AND corticosteroids started before anti-parasitic therapy

****2017 IDSA Guidelines for Diagnosis and Treatment of Cysticercosis****

SEE ENLARGED SLIDE FOLLOWING ENTIRE PRESENTATION

Echinococcus granulosus

Adult worms (3-6mm long) live in dog intestines



Humans = Accidental hosts

Infected by ingestion of eggs in dog feces

SEE ENLARGED SLIDE FOLLOWING ENTIRE PRESENTATION

Echinococcus granulosus

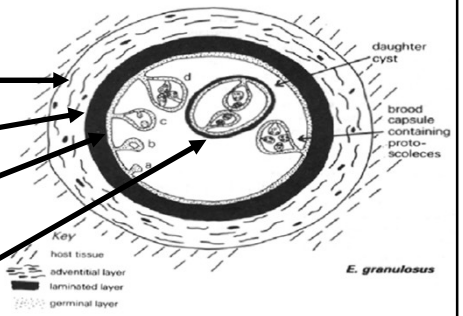
Hydatic cyst = "watery vessel"

Surrounding inflammatory response of fibrosis and chronic inflammation

Outer acellular laminated layer

Inner, nucleated germinal layer (PLURIPOTENTIAL TISSUE!)

Internal cystic fluid and daughter cysts



SEE ENLARGED SLIDE FOLLOWING ENTIRE PRESENTATION

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 tamponade
- Hematuria or flank pain due to renal cysts

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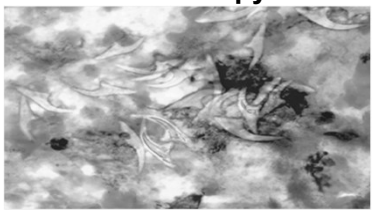
Echinococcus granulosus
Diagnosis

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

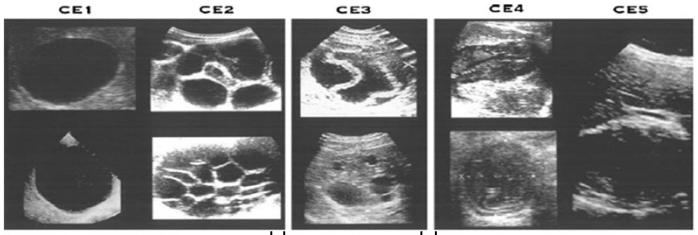
Echinococcus granulosus
Treatment

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 3d-1wk before, and 1-3 months after)

Cystic Echinococcus Treatment
Depends on Cyst Stage



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 calcified wall
---ALB +/- PAIR or Surgery---	---SURGERY---	---SURGERY--- ---PAIR if no solid matrix---	---NO TREATMENT---

SEE ENLARGED SLIDE FOLLOWING ENTIRE PRESENTATION

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*
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- *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*
- *Dracunculus medinensis*

SEE ENLARGED SLIDE FOLLOWING ENTIRE PRESENTATION

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Intestinal Helminths - Lifecycles

Strongyloides and Hookworms

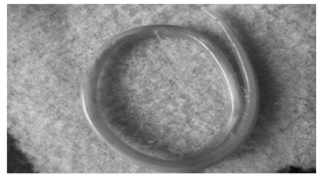
SKIN → LUNGS → GUT

Ascaris

INTESTINE → LIVER → LUNGS → INTESTINE

Ascaris lumbricoides

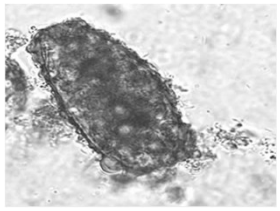
- Large numbers of worms can cause abdominal distention and pain or intestinal obstruction
- Can cause "Loeffler's syndrome" - an eosinophilic pneumonitis with transient pulmonary infiltrates
- Cholangitis and/or pancreatitis b/c aberrant migration



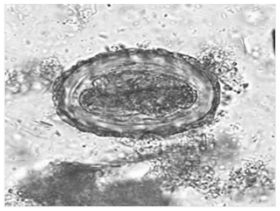
Ascaris lumbricoides
Diagnosis

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

Rx: albendazole or mebendazole

CDC DPDx

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, dyspnea, 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*)

Hookworms are still endemic in the U.S. → 35% of individuals from a rural community in Alabama had *N. americanus* in their stool samples

SEE ENLARGED SLIDE FOLLOWING ENTIRE PRESENTATION

Am. J. Trop. Med. Hyg., 97(5), 2017, pp. 1623-1628

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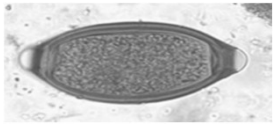
Trichuris trichiura (Whipworm)



4 cm 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

Question #3

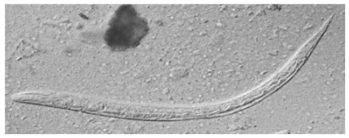
A 25-year-old female from rural Peru presents with shortness of breath, bilateral interstitial infiltrates, fever, loose stools, hypotension, and E. coli bacteremia. She has received > 4weeks of high dose corticosteroids and cyclophosphamide for a recent diagnosis of lupus nephritis.

Which of the following anthelmintic agents should be included in her treatment regimen?

A. Albendazole
B. Ivermectin
C. Praziquantel
D. Pyrantel pamoate
E. Diethylcarbamazine

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, intestinal 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

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Ivermectin

Activates nematode glutamate-gated chloride channels causing muscle paralysis

Drug of Choice

- Strongyloides
- Onchocerca volvulus (microfilaricidal only)
- Also has activity against Ascaris, whipworm, cutaneous larva migrans, gnathostomiasis AND ectoparasites such as scabies and lice

Image created with Google Imagen3

ADVERSE EFFECTS

- Altered mental status in 13-year-old boy given standard dose for scabies due to a mutation in ABCB1 (aka P glycoprotein 1 and MDR1); *NEJM 2020; 383:787-789*
- Reports of seizures, ataxia, and confusion after ingestion of large veterinary doses; *NEJM 2021; 385:2197-2198*

Question #4

A 32-year-old male 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

Blood flukes
- *Schistosoma mansoni*
- *Schistosoma japonicum*
- *Schistosoma haematobium*

Liver flukes
- *Fasciola hepatica*
- *Clonorchis sinensis*
- *Opisthorchis viverrini*

Lung flukes
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Intestinal flukes
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- *Metagonimus yokagawai*

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Tissue Invasive
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- *Brugia malayi*
- *Onchocerca volvulus*
- *Loa loa*
- *Trichinella spiralis*
- *Angiostrongylus cantonensis*
- *Anisakis simplex*
- *Toxocara canis/cati*
- *Baylisascaris procyonis*
- *Gnathostoma spinigerum*
- *Dracunculus medinensis*

SEE ENLARGED SLIDE FOLLOWING ENTIRE PRESENTATION

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

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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

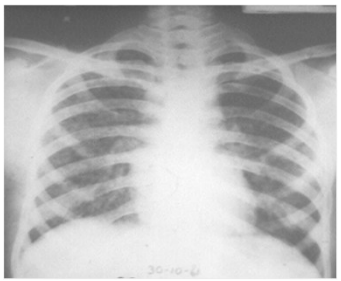
W. bancrofti and *B. malayi*

- 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

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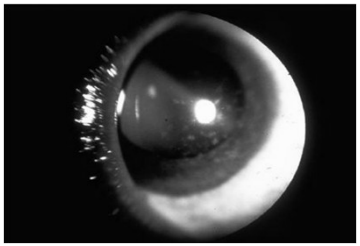
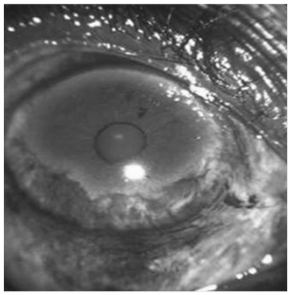
Manifestations of Onchocerciasis

Skin: nodules, pruritus, rash, depigmentation, lichenification

Manifestations of Onchocerciasis

Eye: punctate keratitis, sclerosing keratitis, chorioretinitis

Onchocerciasis

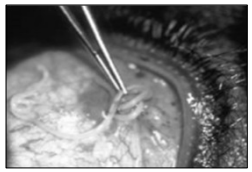
Diagnosis
- Serology
  - Anti-filarial
  - Onchocerca-specific
- Parasitologic: skin snips, nodulectomy

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



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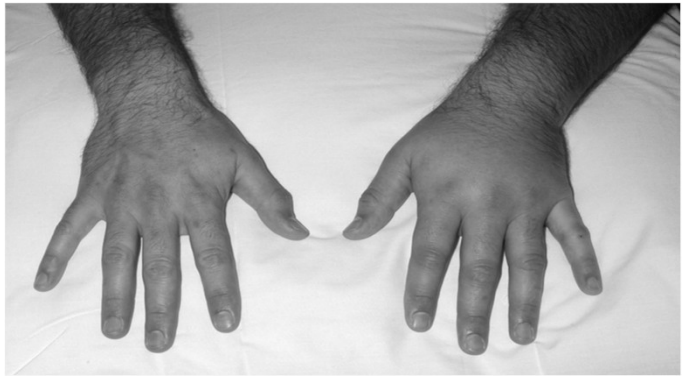
Calabar Swelling



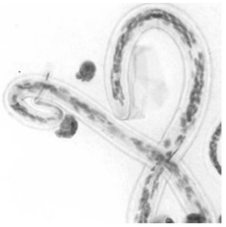
Loiasis
Diagnosis

Definitive Diagnosis

- Identification of adult worm in subconjunctiva
- Detection of Loa microfilaria in **noon blood**

Presumptive Diagnosis

- Compatible clinical picture + positive antifilarial antibodies



CDC DpDx

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 sax's, skin = Ov)
Muscle pain + eosinophilia → Trichinella
Eosinophilic meningitis → Angiostrongylus
Abdominal pain after sushi → Anisakis
Eosinophilia + F + ↑ AST/ALT in child → visceral larva migrans

Good Luck!

Ed Mitre
edwardmitre@gmail.com

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- *Dracunculus medinensis*

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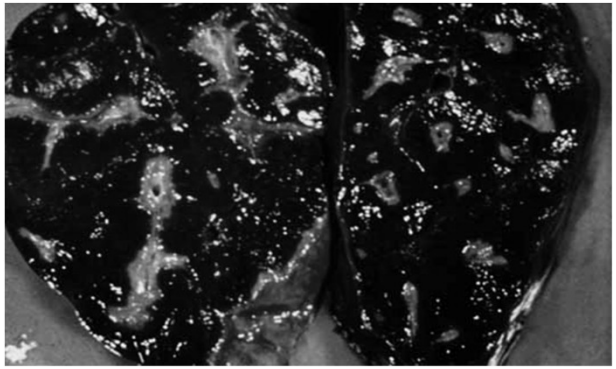
Chronic Schistosomiasis



Schistosoma species

- *S. mansoni (Sm)*
- *S. japonicum (Sj)*
- *S. intercalatum (Si)*
- *S. mekongi (Smk)*
- *S. haematobium (Sh)*
- *S. haematobium/S. bovis hybrid (Sh/b)*

  From Senegal, outbreak 2013 in Corsica, France

SEE ENLARGED SLIDE FOLLOWING ENTIRE PRESENTATION

Intestinal and hepatosplenic disease
(**S. mansoni +** Sj, Si, Smk, Sh/b)

- Granulomatous colitis
- Portal hypertension

Genitourinary disease (S. haematobium + Sh/b)

- Granulomatous cystitis
- Bladder fibrosis and cancer
- Obstructive uropathy

Pulmonary Disease (Sm, Sh, Sj)

CNS disease

- CNS disease (eggs to brain/spinal cord, esp *S. japonicum*)

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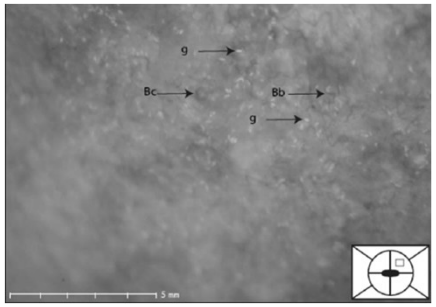
Schistosomiasis

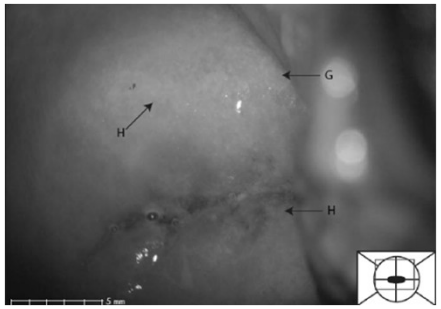
Chronic genital disease
- Increasingly recognized
- Primarily due to *S. haematobium*

Women (vaginal and cervical lesions)
- Pelvic pain
- Dysmenorrhea
- Dyspareunia
- Post-coital bleeding
- Endometritis/salpingitis

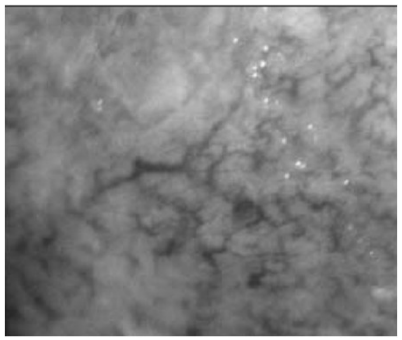
Men
- Epididymitis
- Prostatitis

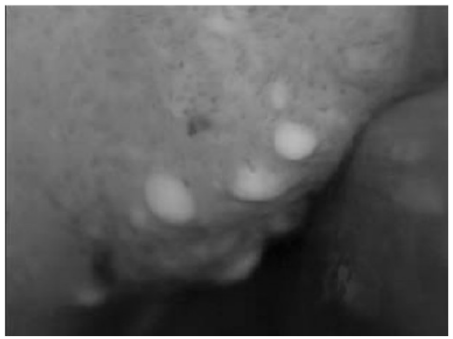


Sand Grains



Sandy Yellow Patches


Abnormal Vessels


Rubbery Papules

SEE ENLARGED SLIDE FOLLOWING ENTIRE PRESENTATION

WHO Female Genital Schistosomiasis Pocket Atlas

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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

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- *Ascaris lumbricoides*
- *Ancylostoma duodenale*
- *Necator americanus*
- *Trichuris trichiura*
- *Strongyloides stercoralis*
- *Paracapillaria philippinensis*
- *Enterobius vermicularis*

Tissue Invasive
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- *Brugia malayi*
- *Onchocerca volvulus*
- *Loa loa*
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- *Anisakis simplex*
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- *Gnathostoma spinigerum*
- *Dracunculus medinensis*

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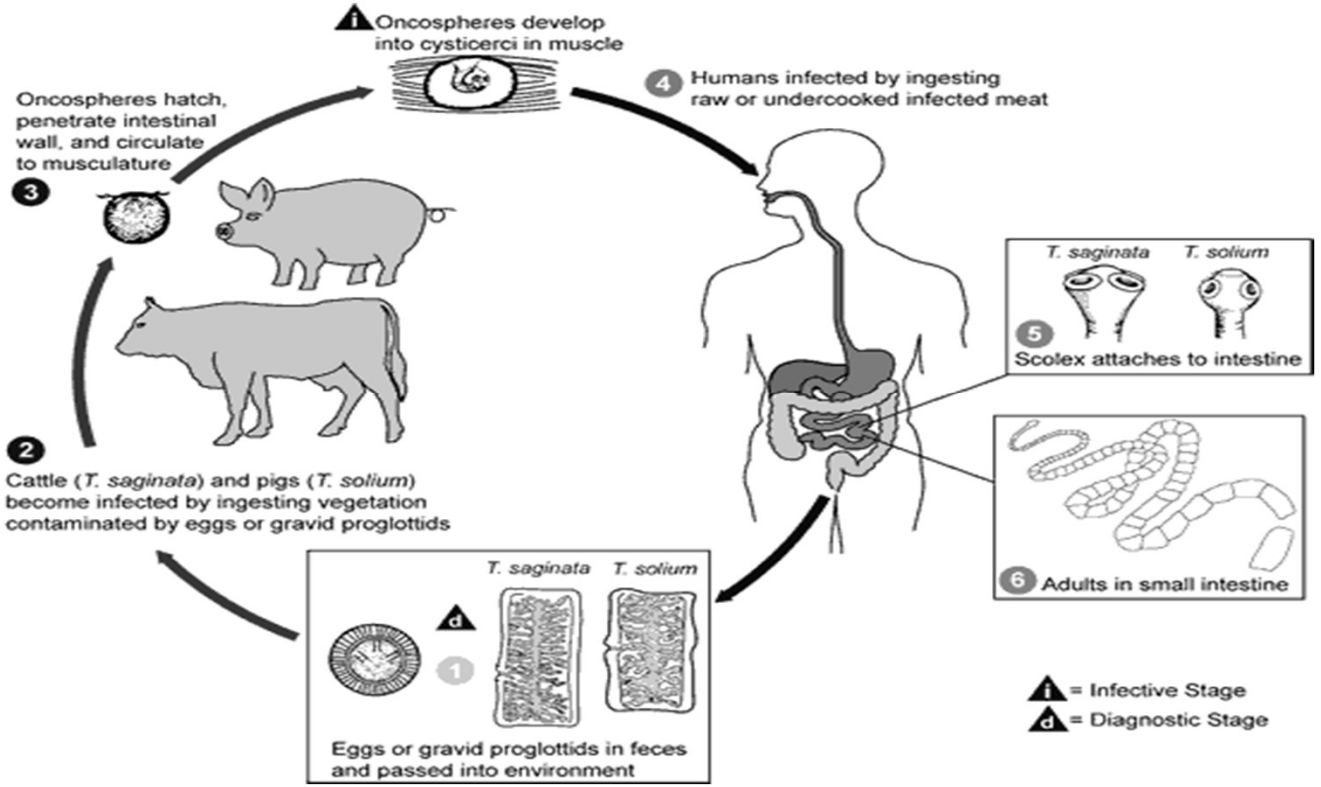
Taenia Life Cycle



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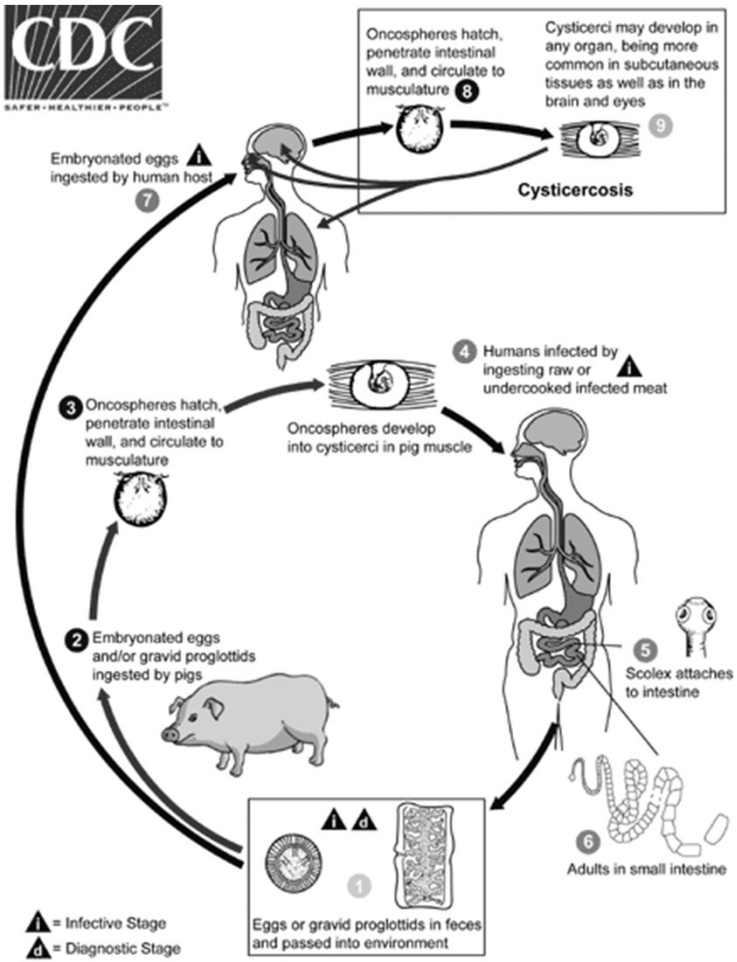

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Neurocysticercosis

Diagnosis:

Definitive = tissue biopsy, multiple cystic lesions each with scolex on imaging, retinal cysticercus on fundoscopy

Presumptive = suggestive lesions on imaging

Cysticercosis serology → supportive (sensitive if high burden of disease)

qPCR and antigen testing of CSF → sensitive for subarachnoid and intraventricular neurocysticercosis, and can be used to help gauge duration of treatment *(available at NIH, contact Dr. Elise O'Connell oconnellem@mail.nih.gov)*

Treatment:

Medical therapy decreases risk of future seizures, but has immediate risk of increasing seizures/brain inflammation

If hydrocephalus or diffuse cerebral edema: initial treatment with steroids and/or surgery (not anti-parasitic Rx)

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****

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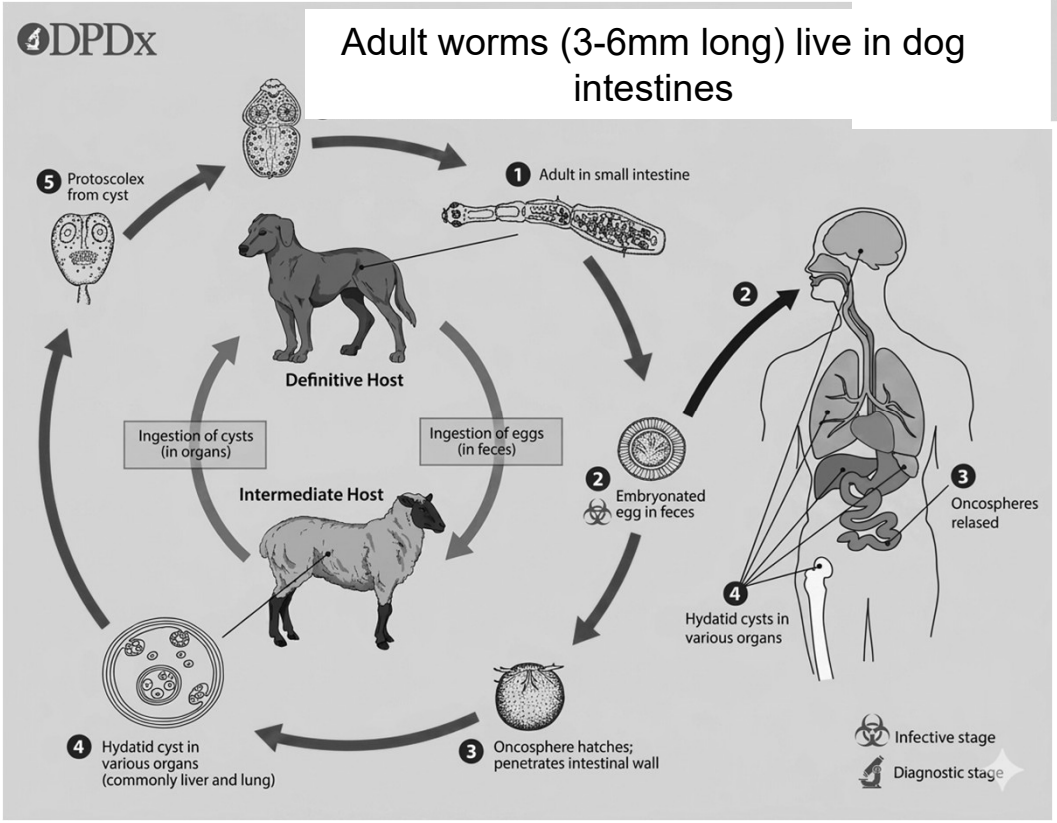
Echinococcus granulosus

Adult worms (3-6mm long) live in dog intestines



CDC

Humans =
Accidental hosts

Infected by ingestion of eggs in dog feces

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Echinococcus granulosus

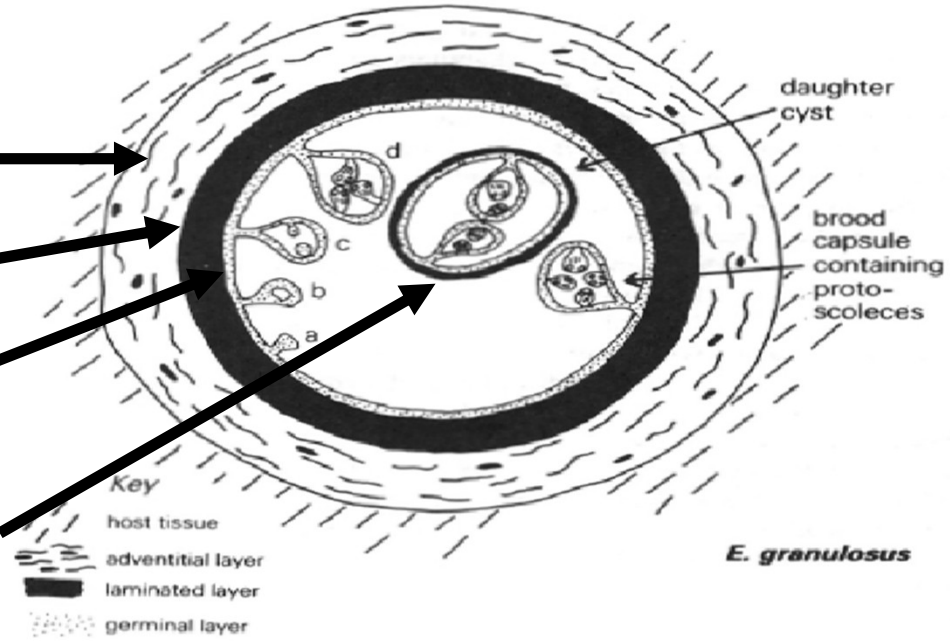
Hydatic cyst = “watery vessel”

Surrounding inflammatory response of fibrosis and chronic inflammation

Outer acellular laminated layer

Inner, nucleated germinal layer
(PLURIPOTENTIAL TISSUE!)

Internal cystic fluid and daughter cysts



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Echinococcus and Hydatid Disease 1995

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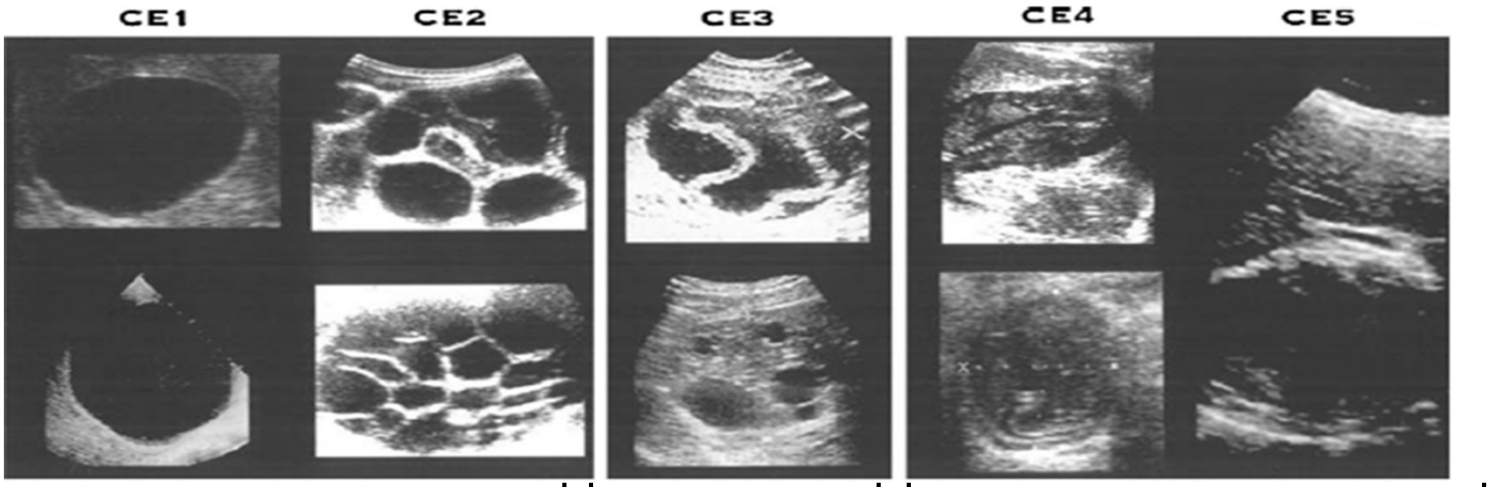
Cystic Echinococcus Treatment

Depends on Cyst Stage



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 calcified wall
---ALB +/- PAIR or Surgery---	---SURGERY---	---SURGERY--- ---PAIR if no solid matrix---	---NO TREATMENT---

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Major Helminth Pathogens

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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, dyspnea, 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*)

Hookworms are still endemic in the U.S. → 35% of individuals from a rural community in Alabama had *N. americanus* in their stool samples

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Am. J. Trop. Med. Hyg., 97(5), 2017, pp. 1623-1628

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Sunday, August 23, 2026

BR2

Board Review Day 2

Drs. Auwaerter (Moderator), Bell, Bennett, Mitre, Platts-Mills, and Tunkel

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Board Review: Day 2

Moderator: Paul Auwaerter, MD
Faculty: Drs. Bell, Bennett, Mitre, Platts-Mills, and Tunkel

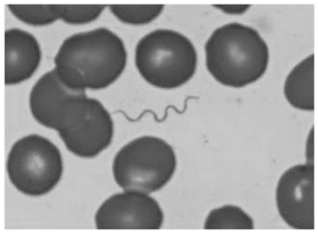
7/28/2026

#16 **This is the blood smear from a previously healthy commercial photographer with a fever after visiting Tanzania and Colorado.**

He went to Tanzania 42 to 35 days before the presentation. He spent most of the time in the city but did go to a rural orphanage where he took some photographs. He saw many rats near his hotel and in the rural area.

After returning to Chicago, he left for a week-long trip to Colorado in early July, from 14 days previously to 7 days before the presentation. He slept with his friends in his first of the season opening uncle's rustic cabin in the Rocky Mountains, white water rafting and driving an all-terrain vehicle through the woods.

#16 **About 3 days after returning to Chicago, he developed a fever, headache and myalgia.**



He came to a travel clinic the next day after developing a fever (4 days after returning from Colorado), where a blood film exam to evaluate for malaria was done.

The blood for complete blood cell count and routine chemistries was clotted.

His blood smear is shown. When he was called about his blood smear results, he said he was feeling OK, was busy, and wouldn't return to the clinic.

#16 **What is the most likely identity of this organism?**

A. ***Borrelia hermsii***
B. ***Borrelia recurrentis***
C. ***Leptospira interrogans***
D. ***Borrelia burgdorferi***
E. ***Spirillum minus***

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BOARD REVIEW DAY 2

#17 **A 52-year-old man with 35% total body surface area burns has been in the ICU for 3 weeks and recently underwent tracheostomy for prolonged mechanical ventilation. After a period of stability off antibiotics, he develops fever, hypotension, and new bilateral infiltrates on chest radiograph.**

Blood cultures and endotracheal aspirate both grow *Acinetobacter baumannii*.

The isolate is preliminarily reported as carbapenem-resistant. The patient is hemodynamically unstable and requires norepinephrine.

1 of 3

BOARD REVIEW DAY 2

#17 **Which of the following is the most appropriate empiric antimicrobial regimen pending susceptibility results?**

A. Ceftazidime–avibactam
B. Meropenem–vaborbactam
C. Sulbactam–durlobactam plus meropenem
D. Colistin plus imipenem
E. Colistin monotherapy

3 of 3

BOARD REVIEW DAY 2

#18 **A 23-year-old college student is seen for intermittent fevers, headaches and arthralgias.**

He came to the US from the Central African Republic (central Africa) two months ago to attend college.

He says his symptoms have been present for at least the last four months, and it is hard for him to concentrate on his studies.

On exam his temperature is 100.6F; he has a soft, moveable posterior cervical node 3 cm by 3 cm; and his liver and spleen are palpable.

1 of 3

BOARD REVIEW DAY 2

#18 **Which one of the following is the most likely diagnosis?**

A. Malaria
B. Rift Valley fever
C. *Rickettsia africae* infection
D. Typhoid fever
E. African trypanosomiasis

2 of 3

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BOARD REVIEW DAY 2

#19 **A 56-year-old male from Pittsburgh, PA presents to his primary care physician with fatigue. He reports no fevers, chills, sweats, chest pains, respiratory symptoms, abdominal pain, or diarrhea.**

Chest/abdomen/pelvis CT scan with contrast is normal. Blood tests reveal normal thyroid function tests as well as a normal white blood cell count and differential.

His Hgb level is low at 9 g/dL with an MCV of 106 fL.

He reports spending two weeks every summer at Lake Como in Italy where he enjoys fishing and eating freshly caught perch.

BOARD REVIEW DAY 2

#19 **Which of the following is the most likely cause of his fatigue?**

A. ***Ancylostoma duodenale***
B. ***Entamoeba histolytica***
C. ***Anisakis simplex***
D. ***Wuchereria bancrofti***
E. ***Dibothriocephalus latus*** **(aka *Diphyllobothrium latum*)**

BOARD REVIEW DAY 2

#20 **A 45-year-old man previously healthy man presents with two weeks of right upper quadrant pain, fever, and weight loss. He returned from a month-long trip to rural Mexico ten weeks ago. He recalls a self-limited episode of diarrhea while he was there that has fully resolved.**

Laboratory tests show a white blood cell count of 12,000/microL with normal eosinophil percentage. Liver enzymes are notable for an elevated alkaline phosphatase.

Ultrasound reveals a solitary 6 cm fluid-filled mass in the right lobe of the liver.

BOARD REVIEW DAY 2

#20 **Which of the following is most likely to be diagnostic?**

A. **Bacterial blood cultures**
B. **Percutaneous aspiration of the liver cyst**
C. **Serology for *Entamoeba histolytica***
D. **Stool microscopy for ova and parasites**
E. **Echinococcal serologies**

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BOARD REVIEW DAY 2

#21 A 50-year-old man was admitted for replacement of a non-functioning ventriculoperitoneal shunt that had been placed when he had obstructive hydrocephalus from cryptococcal meningitis.

A low-grade fever began several days after replacing the ventricular end and valve of the shunt.

Cerebrospinal fluid (CSF) from the shunt reservoir revealed a WBC count of 150 cells/mm^3, glucose of 40 mg/dL, and protein of 100 mg/dL. Gram stain was negative, but culture of CSF revealed a light growth of *Staphylococcus epidermidis*, susceptible to vancomycin and linezolid.

The patient's entire shunt was removed, a ventricular drain placed, and intravenous vancomycin started.

BOARD REVIEW DAY 2

#21 Which of the following is recommended prior to placing a new CSF shunt?

A. Continue vancomycin for ten days
B. Continue vancomycin, add linezolid, and treat for ten days
C. Continue vancomycin until drain cultures have been negative ten days
D. Add intraventricular vancomycin and treat for ten days

BOARD REVIEW DAY 2

#22 A 68-year-old man with HIV (CD4 = 35 cells/mm^3; viral load 50,000 copies/mL) and emphysema is brought to the emergency department with 3 days of cough productive of purulent sputum, progressive shortness of breath, and fevers.

He recently completed a course of amoxicillin-clavulanate and a steroid dose pack for a COPD exacerbation.

Medications include taking bictegravir/emtricitabine/tenofovir and prophylactic TMP-SMX, although he admits to poor adherence.

BOARD REVIEW DAY 2

#22 On physical exam his temperature is 39° C, respiratory rate is 30/min, and BP is 96/58. Room air O_2 saturation is 85% and soon required high-flow oxygen.

Initial evaluation is notable for:

- WBC 8700 cells/ mL with 85% neutrophils (prior WBC 3000 cells/mL)
- Sputum Gram stain and sputum and blood cultures: pending from offsite lab
- Chest x-ray: dense, alveolar infiltrates in the left lower and R middle lobes
- MRSA nasal swab: negative

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#22 **Empiric coverage for community-acquired pneumonia should include which pathogen in this patient?**

A. ***Bordetella bronchiseptica***
B. **Methicillin-resistant *Staphylococcus aureus***
C. ***Rhodococcus equi***
D. ***Pseudomonas aeruginosa***
E. ***Acinetobacter baumannii***

#23 **A 74-year-old woman with chronic obstructive pulmonary disease and prior stroke with residual dysphagia is admitted from home via the emergency department for acute hypoxemic respiratory failure requiring supplemental oxygen.**

On hospital day 2, she has a witnessed aspiration event and develops fever (39.1°C), worsening oxygenation, and hypotension requiring vasopressors. She is intubated and transferred to the ICU. Chest radiograph shows new right lower lobe consolidation.

Bronchoalveolar lavage (BAL) fluid cultures grow *Streptococcus intermedius*.

#23 **She is started on piperacillin–tazobactam. Over the next 72 hours, her oxygenation stabilizes and vasopressor requirements plateau, but she remains intermittently febrile with persistent leukocytosis.**

CT scan of the chest reveals multiple cavitary lesions in the right lower lobe, the largest measuring 2.1 cm, with surrounding consolidation. No single collection is amenable to percutaneous drainage.

#23 **Which of the following is the most appropriate next step in management?**

A. **Escalate antibiotics to meropenem plus vancomycin**
B. **Add clindamycin**
C. **Continue piperacillin tazobactam monotherapy**
D. **Consult thoracic surgery for surgical drainage**
E. **Perform another bronchoalveolar lavage**

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#24 **A 27-year-old woman is referred to your office because the blood bank where she recently donated notified her that a test for Chagas disease was positive, as was a confirmatory test they performed.**

She is concerned because she is 8 weeks pregnant.

She lived in a rural area of El Salvador until age 12 before moving to the USA and returned twice to visit relatives since then.

She is in good health and takes no medications.

#24 **What is the most appropriate next step in management?**

A. Start benznidazole to protect the fetus from becoming infected

B. She needs two confirmatory serologic tests to confirm chronic infection before further action

***C. Trypanosoma cruzi* PCR on her blood now and prior to delivery to detect fetal infection**

D. Prescribe benznidazole after delivery to decrease the likelihood of maternal disease later in life

E. Perform serology for *T. cruz*i infection on the infant after delivery

#25 **A 45-year-old man living on Eastern Long Island, New York had been ill for 5 days with fever (T102.7°F) and flu-like symptoms including headache. Two days ago, when he noticed an enlarging oval red rash of about 10 cm on the back of his right thigh, he was started on doxycycline for presumed Lyme disease.**

Today, while fevers have not abated though the rash is fading, he became faint on standing at home, and he is brought to the emergency department where his blood pressure is normal, but he is quite anemic.

His past medical history is only remarkable for a motorcycle accident 10 years earlier which he suffered splenic injury requiring splenectomy.

#25 **On examination, he appears ill with pulse 100/minute, blood pressure 98/70 and temperature recorded as 101°F. There is an ovoid homogenous rash over the posterior right thigh and a left upper quadrant abdominal scar.**

Laboratories:

- **Leukocyte count 3.3 x 10^9/L (50% neutrophils, 35% lymphocytes, 15% monocytes)**
- **Hemoglobin 4.7 gm/dL**
- **Platelet count 105,000 x 10^9/L**
- **Total bilirubin 3.8mg/dL**
- **ALT 110 U/L**
- **LDH 650 IU/mL**

He develops adult respiratory distress syndrome (ARDS), progressive renal failure and disseminated intravascular coagulation.

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#25 **Which of the following is the most likely cause of his progressive problems indicative of severe sepsis?**

A. ***Borrelia burgdorferi***
B. ***Francisella tularensis***
C. ***Babesia microti***
D. ***Anaplasma phagocytophilum***
E. ***Rickettsia rickettsii***

#26 **A group of adults in Detroit, Michigan develops an illness during a banquet in which they are served mahi-mahi, mushrooms, wonton soup, and corn with margarine.**

Eight of 16 people eating the meal have symptoms beginning within 20 minutes after eating fish that tastes peppery and unusual.

They experienced a burning mouth, felt flushed, had a headache, and felt dizzy. Two experienced an urticarial reaction.

The illness lasted 10 hours.

#26 **What is the likely cause of the outbreak?**

A. **Ciguatera**
B. **Monosodium glutamate toxicity**
C. **Staphylococcal food poisoning**
D. **Scombroid**
E. **Mushroom poisoning**

#27 **A previously healthy 60-year-old woman presents to the emergency room with headaches, fevers, nausea, and vomiting for the past 4 days. Two days prior to her ER presentation, she noted difficulty with balance.**

Earlier this morning, she noted left facial numbness. She denied any night sweats, photophobia, or neck stiffness. She has not traveled outside of the United States and has lived her entire life in Baltimore, Maryland.

She lives with her husband and two daughters in a row house. They own 2 cats and a dog. She denies smoking, alcohol use, or injection drug use.

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#27 On physical examination, her temperature was 38.3° C, blood pressure 120/60 mmHg, heart rate 109 beats/minute, and respiratory rate 13 breaths/minute. She was alert and oriented but appeared uncomfortable.

Higher cortical functions, extraocular movements and visual fields were intact. Limb tone, motor strength and reflexes were normal. Plantar responses were flexor.

Abnormalities included left facial hypoesthesia, right facial weakness and left gaze-evoked nystagmus. She was noted to have gait ataxia. The remainder of her physical examination was unremarkable.

#27 Her peripheral white cell count, and differential were normal.

- A comprehensive metabolic panel was normal.
- Lumbar puncture and cerebrospinal fluid (CSF) examination revealed a lymphocytic pleocytosis with 500 white blood cells/mm^3 (64% lymphocytes). CSF glucose was normal, and protein was slightly elevated. No organisms were visualized on Gram stain of the CSF. CT scan without IV contrast was unremarkable.
- Postgadolinium T1-weighted MRI images of the brain showed multiple ring-enhancing abscess-like lesions in the brainstem with mild meningeal enhancement.

#27 Which of the following is the most likely etiology of her clinical presentation?

A. Behçet disease
B. Cytomegalovirus
C. Herpes simplex virus type 2
D. *Listeria monocytogenes*
E. *Streptococcus pneumoniae*

#28 A 60-year-old man has been in intensive care unit for the past three weeks with a flare of lupus erythematosus for which he has received a short course of methylprednisolone and cyclophosphamide.

His hospital course was complicated by hospital acquired pneumonia, requiring intubation and mechanical ventilation.

He completed a one-week course of vancomycin and meropenem four days ago.

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BOARD REVIEW DAY 2

#28 After a tracheostomy, he was febrile for several hours but then defervesced with unchanged ventilatory support, PEEP of 10 and an FIO_2 of 0.4.

A tracheal aspirate and blood cultures were obtained, and he was restarted on meropenem and vancomycin.

Blood cultures were negative but tracheal aspirate had a heavy growth of *Stenotrophomonas maltophilia*, susceptible to trimethoprim-sulfamethoxazole, levofloxacin, and minocycline.

BOARD REVIEW DAY 2

#28 What do you recommend?

A. Stop meropenem and vancomycin and observe
B. Add trimethoprim-sulfamethoxazole
C. Add minocycline
D. Add minocycline and trimethoprim-sulfamethoxazole
E. Add levofloxacin

BOARD REVIEW DAY 2

#29 A 31-year-old man presents with a chief complaint of enlarged scrotum. He reports having worked as a missionary in rural areas in the northern regions of Nigeria for the past three years.

While in Nigeria he took atovaquone/proguanil daily for malaria prophylaxis during the rainy seasons. He had two episodes of *Giardia* infection and one febrile episode that resolved with empiric treatment for both typhoid fever and malaria.

He did substantial work outdoors and reports having been frequently bitten by mosquitoes.

BOARD REVIEW DAY 2

#29 He routinely ate fresh produce and meats, and recalls having eaten a few dishes prepared with fresh goat milk.

He had intermittent interactions with livestock but no animal bites or scratches and reports that he was careful to only drink boiled or bottled water.

Ultrasound reveals a collection of anechoic fluid around both testes, consistent with a bilateral hydrocele.

BR2 Board Review - Day 2

Moderator – Paul Auwaerter, MD

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BOARD REVIEW DAY 2

#29 **Which of the following is the most likely cause of this condition?**

A. ***Wuchereria bancrofti***
B. ***Brugia malayi***
C. ***Loa loa***
D. ***Onchocerca volvulus***
E. ***Dirofilaria immitis***

3 of 4

BOARD REVIEW DAY 2

#30 **A 45-year-old man with no significant past medical history is involved in a motor vehicle accident in which he suffers a high-impact blunt force trauma to the head.**

On evaluation, he is found to have a basilar skull fracture and is medically managed. Three days later, he is noted to have fluid coming out of his right nostril.

Testing of the fluid is positive for beta-2-transferrin confirming that it is cerebrospinal fluid (CSF). The patient is doing well and is recovering well from his skull fracture.

1 of 4

BOARD REVIEW DAY 2

#30 **On physical examination, he is afebrile and vital signs are normal.**

He is alert and oriented to person, place and time, and has no neurological deficits.

His laboratory studies reveal a normal leukocyte count. MRI of the brain does not show a fluid collection or air fluid level.

2 of 4

BOARD REVIEW DAY 2

#30 **Which of the following interventions is appropriate?**

A. **Immediate surgical intervention to repair the leak**
B. **Surgical intervention if the leak does not stop after 7 days**
C. **Administration of prophylactic intravenous vancomycin**
D. **Administration of prophylactic intravenous vancomycin and cefepime**

3 of 4

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Sunday, August 23, 2026

14

Encephalitis Including West Nile and Rabies

Allan Tunkel, MD

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Encephalitis Including West Nile and Rabies

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Disclosures of Financial Relationships with Relevant Commercial Interests

- None

Encephalitis
Definitions

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

Encephalitis
Epidemiology

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

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Encephalitis
Etiology

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

Encephalitis
Etiology

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

Reasons Etiology not Identified

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

General Approach

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

Tunkel et al. Clin Infect Dis 2008;47:303
Bloch et al. Clin Infect Dis 2023;doi.org/10.1093/cid/ciad306
El Zibaoui et al. Curr Op Infect Dis 2026;39:208
Binks, et al. Lancet 2026;407:1968

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Question #1

- 50-year-old man presents with a several day history of fever, headache, and personality change with progression to confusion
- On exam, temperature is 101oF; he is disoriented and unable to follow commands
- CT scan of the head without contrast is negative
- CSF analysis reveals a WBC of 80/mm3 (95% lymphs), glucose 70 mg/dL (serum 100 mg/dL), protein 120 mg/dL; Gram stain is negative
- 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

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

Question #2

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

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

Herpes Simplex Encephalitis

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

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Herpes Simplex Encephalitis

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

Herpes Simplex Encephalitis

- Cerebrospinal fluid (CSF) findings
  - Lymphocytic pleocytosis (mean of 100 cells/mm3)
  - Presence of red blood cells (25% never have RBCs)
  - Elevated protein
  - Absent pleocytosis (<5/mm3) in up to 25% of patients on initial 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

*Habis et al. Clin Infect Dis 2025;81:179

Herpes Simplex Encephalitis

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

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Other Herpesviruses

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

Other Herpesviruses

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

Question #3

- 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
- No significant past medical history
- On presentation, he is somnolent and unable to provide a complete history, although denies headache and stiff neck

Question #3

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

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Question #3

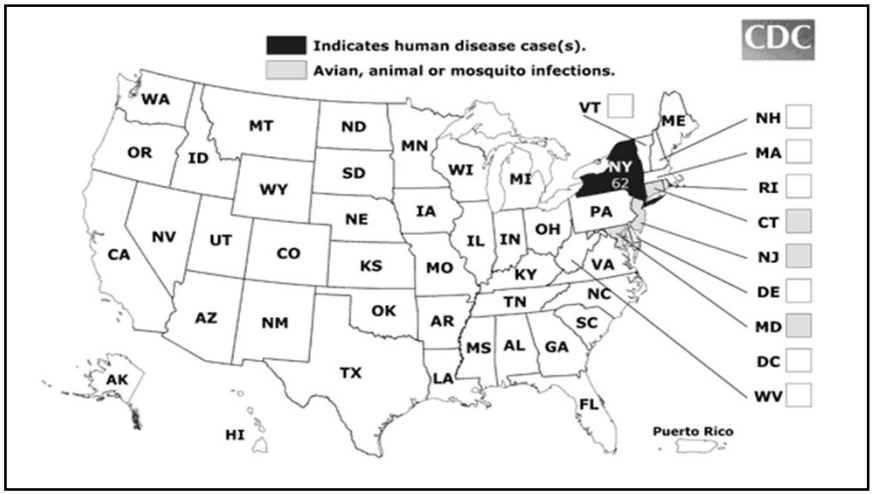
Which of the following tests is most likely to establish the etiology of this patient's encephalitis?

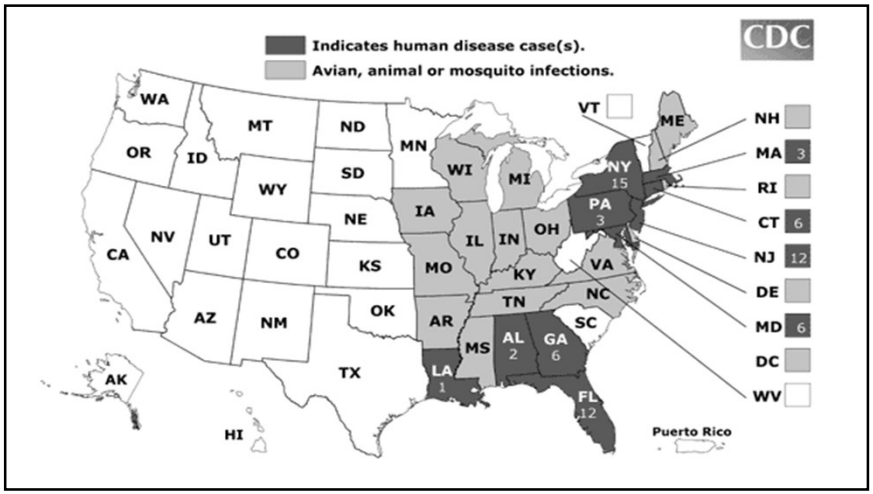
A. Serum IgM
B. Serum polymerase chain reaction
C. Cerebrospinal fluid IgM
D. Cerebrospinal fluid polymerase chain reaction
E. Brain MRI

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

Gould et al. JAMA 2025;334:618





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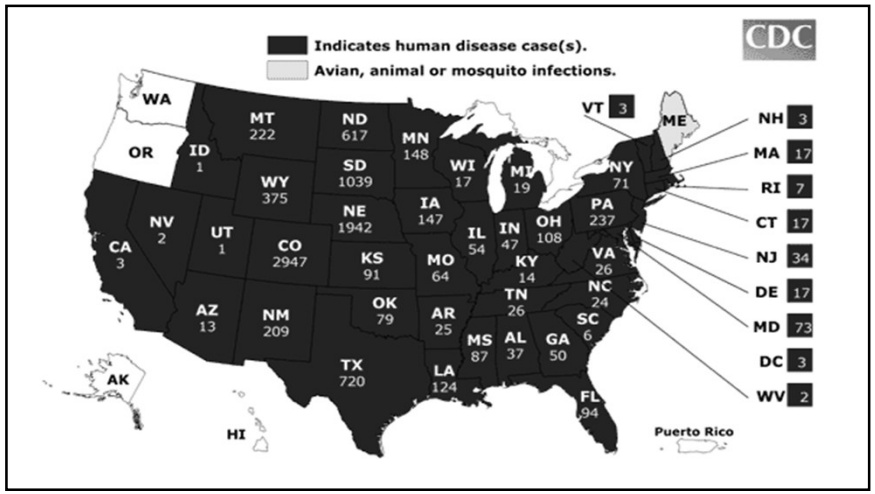

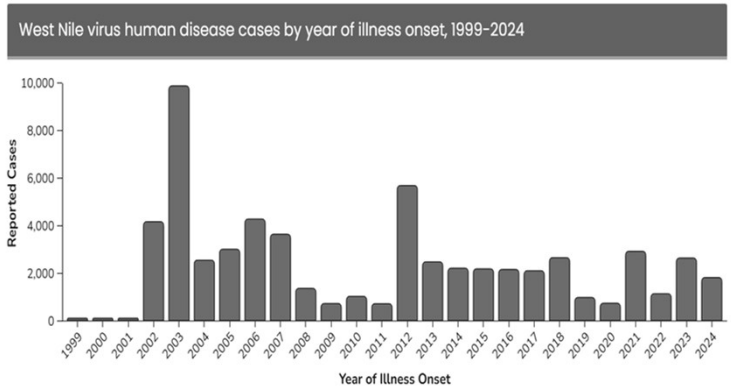

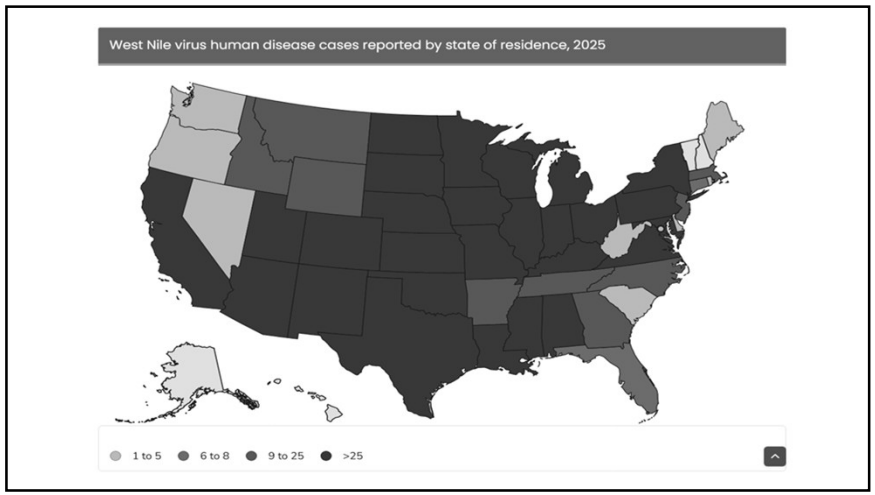

West Nile Virus Clinical Syndromes

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

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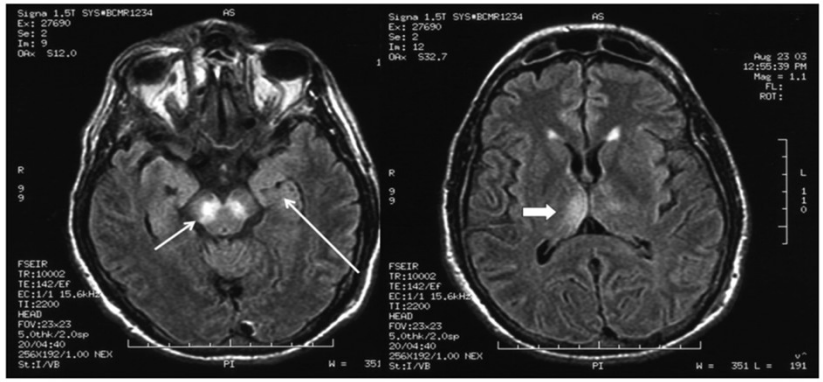
West Nile Virus Encephalitis

- 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 overall, but may be more sensitive in immunocompromised patients)
  - Neuroimaging



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
  - Serology; CSF IgM

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Other Arboviruses

- 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, as well as lower brainstem, cerebellum and spinal cord
  - Serology; CSF IgM; PCR if immunocompromised; 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

- 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/mm3)

Measles Virus

- Primary encephalitis
  - Up to 1 per 1,000 infections
  - Usually appears within a few days (typically 5 days) of rash
  - Fever, headache, stiff neck, drowsiness, convulsions, coma
  - Rapidly progressive and fatal in ~15%
- Acute disseminated encephalomyelitis
  - Up to 1 per 1000 infections
  - Usually appears ~2 weeks after exposure
  - Demyelinating disease; post-infectious autoimmune response
  - Fever, fatigue, headache, nausea, vomiting
  - 10-20% mortality

Measles Virus

- Inclusion body encephalitis
  - Unvaccinated children and adults; immunocompromised
  - Symptoms 1-6 months after exposure;
  - Decreased consciousness, focal signs, seizures
- Subacute sclerosing panencephalitis
  - Acquisition of measles before 2 years of age
  - 6-10 years after infection (range 3-35 years)
  - Behavioral changes, cognitive impairment at presentation
  - Myoclonus, seizures, neurologic deterioration (coma and death) later

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BioFire® FilmArray® Meningitis/Encephalitis Panel

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

- Allows unbiased or agnostic pan-species molecular diagnostics
- 204 patients (58 with meningitis or encephalitis), NGS identified an infectious cause in 22% not identified by clinical testing*
- 220 CNS infections, 40% identified by conventional methods and NGS, 22% by NGS alone and 36% only by conventional methods**
- Possible role in testing of enigmatic cases

*Wilson et al. NEJM 2019;380:2327
**Benoit et al. Nature Med 2024;30:3522

Question #4

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

Question #4

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

A. Rabies immune globulin at the bite site
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

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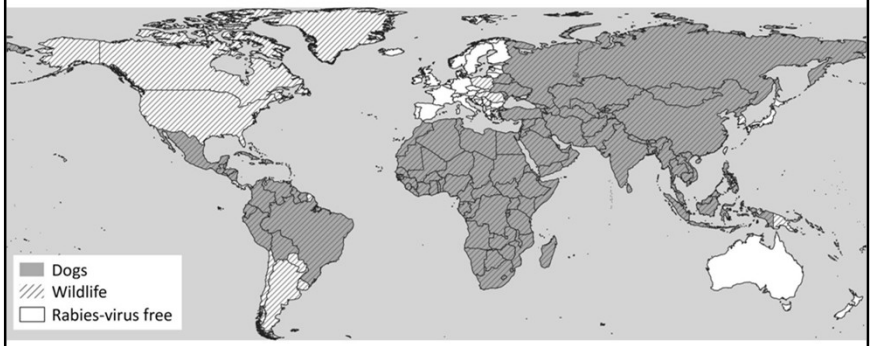
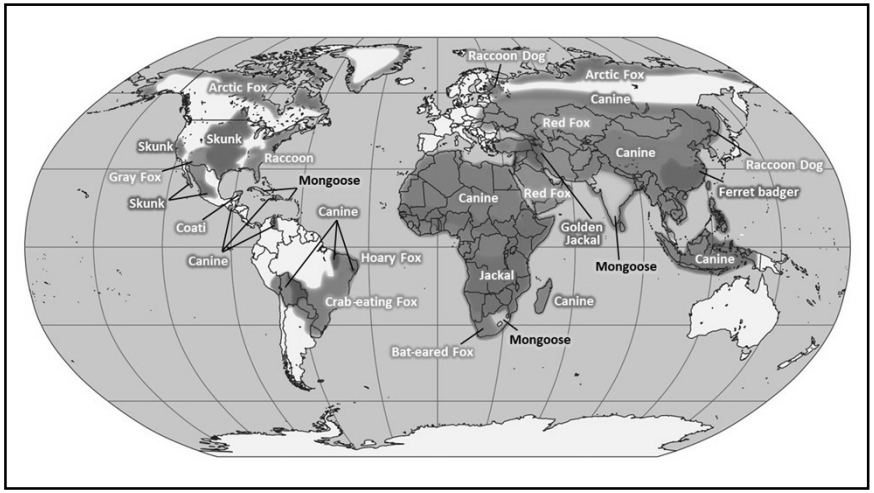
Rabies

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





Rabies

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

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Rabies

- Diagnosis
  - Culture and RT-PCR of saliva
  - Immunofluorescent detection of viral antigens and RT-PCR in nuchal biopsy
  - CSF antibodies and RT-PCR
  - Brain biopsy (antigen detection/Negri bodies)
- Therapy
  - Supportive (especially critical care)
  - Milwaukee Protocol has failed in at least 64 cases
  - Post-exposure prophylaxis (rabies immune globulin at bite site and vaccine)

Question #5

- 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/mm3, with normal glucose and protein
- Brain MRI is normal

Question #5

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

Question #5

Which of the following studies should now be performed?

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

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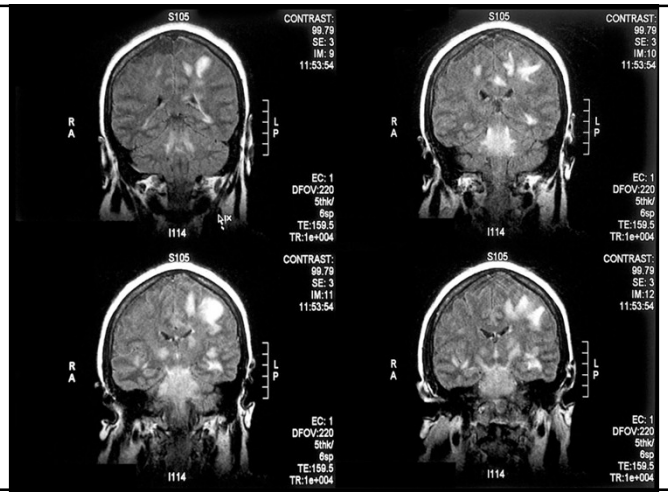
Encephalitis
Noninfectious Etiologies

- Acute disseminated encephalomyelitis (ADEM)
  - 10-15% of encephalitis cases in US
  - Post-infectious
  - Symptoms 2-4 weeks after trigger
  - MRI bilateral asymmetric T2 hyperintensity in subcortical and deep white matter
- Approximately 20-30% of encephalitis cases are due to autoimmune conditions (e.g., anti-N-methyl-D-aspartate receptor [Anti-NMDAR] encephalitis



Anti-NMDAR Encephalitis

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

Anti-NMDAR Encephalitis

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

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Anti-NMDAR Encephalitis

- CSF analysis
  - Mild pleocytosis (median WBC 23/mm3); normal glucose and protein
  - Specific IgG antibodies to GluN1 subunit of the NMDAR in CSF and serum
  - Viral causes of encephalitis (e.g., HSV) are associated with development of NMDAR antibodies*

*Armangue et al. Brain 2023;146:4306

Anti-NMDAR Encephalitis

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

Anti-NMDAR Encephalitis

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

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Questions

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Syndromes in the ICU That ID Physicians Should Know

Taison Bell, MD

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Syndromes in the ICU that Infectious Disease Physicians Should Know

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Division of Infectious Diseases and International Health

8/5/2026

Disclosures of Financial Relationships with Relevant Commercial Interests

- List of disclosures or "None"

Exam Blueprint: Critical Care Topics ~8-10%

- Critical Care Medicine
- Systemic inflammatory response syndrome (SIRS) and sepsis
- Ventilator-associated pneumonias
- Noninfectious pneumonias (eosinophilic and acute respiratory distress syndrome [ARDS])
- Bacterial pneumonias
- Viral pneumonias
- Hyperthermia and hypothermia
- E-cigarette or vaping product use–associated lung injury (EVALI)

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

Question #1

What proportion of patients in the ICU develop fever during their stay?

A. Serum RPR
B. Serum VDRL
C. Serum treponemal EIA
D. Darkfield microscopy on a specimen obtained from the oral ulcer
E. Darkfield microscopy on a specimen obtained from the vulvar ulcer

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Extreme Hyperpyrexia (T>41.5C)

All Potential Medical Emergencies

Heat Stroke

- Lack of hydration and/or inability to sweat
  - Exertional (football player in August)
  - Non-exertional (Elderly)

Drugs

- Cocaine, amphetamines, ecstasy, anti-parkinson, beta blockers, antipsychotics, anti-depressants, calcium channel blockers, etc.

Three Specific Syndromes You Should Recognize

Question #2

- You are called to the PACU to see a 29-year-old previously healthy male with a fever of 41.6°C who is 1 hour post-op from an arthroscopy for a rotator cuff injury.
- He initially did well post operatively except for some nausea that was treated.
- The patient is somnolent, flushed, diaphoretic, and rigid. His blood pressure has risen from 130/70 to 180/100 but is now dropping.
- He is given one ampule of Narcan but does not respond.

Which of the following would you give to reverse this syndrome?

A. Antihistamines
B. High-dose corticosteroids
C. Dantrolene
D. IVIG
E. Dilantin

Malignant Hyperthermia

- **Syndrome – Rare (~700 cases/year) but 5-10% mortality**
  - Early signs: Steep rise in CO2, tachycardia, tachypnea, muscle rigidity/contraction (masseter spasm)
  - Late signs: Hyperthermia, acidosis, hyperkalemia, cardiac arrythmias
- **Genetic defect in the RYR1 or (less commonly) CACNAS1S gene**
  - Ca++ transport in skeletal muscle
  - Autosomal dominant
    - (Excessive calcium accumulation)
- **Triggers**
  - **Classic: Volatile anesthetics (halothane, sevoflurane, desflurane), succinylcholine**
  - **Usually < 1 hour after trigger (up to 10 hours)**
- **Management—Usually By Anesthesiologist/Intensivist**
  - Dantrolene-
    - **Muscle relaxant-inhibits calcium ion release necessary for muscle contraction**

Neuroleptic Malignant Syndrome (NMS)

- **Frequent trigger = haloperidol**
  - Any “neuroleptic” (antipsychotic)
  - Lead pipe rigidity
  - Antiemetics such as metoclopramide
  - Withdrawal of antiparkinson drugs (L dopa)
- **Onset variable: 1-3 days/within first 2 weeks**
  - Time of drug initiation
  - When dose changed
- **Management**
  - Dantrolene or
    - (Administer for up to 10 days)
  - Dopamine agonists (bromocriptine and others)

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Serotonin Syndrome

Clinical Characteristics of Serotonin Syndrome	
Pathogenesis	Excess Serotoninergic Activity • Therapeutic drugs, drug interactions, self poisoning
Triggers	• Linezolid = MAO Inhibitor • SSRI inhibitors (Bupropion) • Antiemetics (Granisetron) • Tricyclic antidepressants (amitriptyline)
Clinical Manifestations	• Acute onset (within 24 hrs of new drug/drug change) • Hyper-reflexive>bradyreflexia • Nausea, vomiting, diarrhea, tremors followed by shivering
Treatment	• Withdraw offending medication • Consider benzodiazepines and cyproheptadine

What to Look for on the Exam

	Malignant Hyperthermia	NMS	Serotonin Syndrome
Trigger	Succinylcholine or inhaled halogenated anesthesia	Withdrawal of L Dopa in Parkinsons or Neuroleptic Drugs	SSRIs, Antiemetics, Linezolid, Lithium, Street Drugs
Onset	Rapid onset in perioperative period **(usually 1 hr)**	Subacute over **1-3 days**	**6-24 hours** of starting a drug or increasing dose
Exam	Masseter spasm, Lead pipe rigidity	Mental status change with dysautonomia, catatonia, mutism, stupor, coma	Shivering, myoclonus, n/v/d, hyper-reflexia, flush skin
Labs	Severe hypercarbia, **rhabdomyolysis**	**CK rise, rhabdomyolysis**	Nothing classic

Hypothermia: <35°C

- **Causative Drugs**
  - Beta blockers (metoprolol) Antidepressants
  - Alpha blockers (clonidine) Antipsychotics
  - Opioids Aspirin
  - Ethanol Oral hypoglycemics
- **Syndrome**
  - Hypotension due to fluid shifts
  - Consider adrenal or thyroid insufficiency
- **Treatment**
  - "ABC"s
    - Airway, Breathing, Circulation
  - Rewarming

  *Give broad spectrum antibiotics empirically if they fail to raise temperature 0.67C/hour

Question #3

- You are called to the medical ICU to see a 47 y/o woman with alcoholic cirrhosis
- Admitted 3 days ago for encephalopathy after missing lactulose doses
  - On HD#3 developed low grade fever, ARDS and Shock due to aspiration
    - Started on vancomycin and piperacillin-tazobactam
  - Daily fevers to 38.5°C and a persistent low-dose levophed requirement
    - Labs: mild hyponatremia and hyperkalemia. Metabolic acidosis
    - Micro: all cultures negative at 48 hours
    - Radiology: Chest Xray unchanged, Abdominal CT non-diagnostic

Which of the following would most likely contribute to reversal of shock and reduced time in ICU?

A. Discontinue vancomycin
B. Add antifungal therapy
C. Stress dose corticosteroids
D. Dantrolene
E. IVIG

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Acute Adrenal Insufficiency

- Patients with chronic adrenal insufficiency typically have normal or low body temperature
- Fever can occur during adrenal crisis, in the absence of infection:
  - Mechanism: the loss of cortisol's suppressive effect on inflammatory cytokines leading to fever and other systemic symptoms
  - Therapy:
    - Hydrocortisone 100mg bolus followed by 240mg/24 hrs in 4 doses or contin infusion
    - Rapid fluid resuscitation: Normal Saline: 1000 ml initially and then PRN
    - Management of glucose and electrolytes

Differential Diagnosis of Shock

Ohm's Law

MAP = CO x SVR

Cardiogenic (flow)
- MI/CHF/Tamponade
- PE
- Tension PTX
- Hypovolemia

Distributive (resistance)
- Sepsis
- Toxic shock syndrome
- Aspiration
- Anaphylaxis
- Neurogenic
- **Adrenal insufficiency**

Question #4

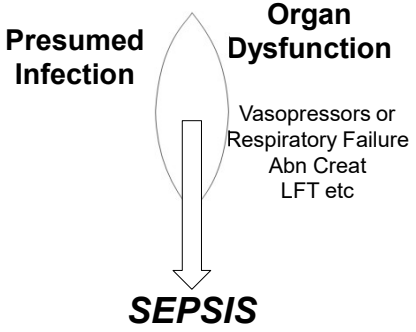
A patient with end stage renal disease on dialysis through a tunneled hemodialysis catheter is admitted to the medical ICU with altered mental status, hypotension (BP 80/50 mmHg), and fever.

- On exam he has obvious purulence at the catheter site.
- The line is replaced to a different site
- The patient is given a single initial bolus dose of vancomycin and a single initial bolus dose of piperacillin-tazobactam.

Which of the following is an evidence-based intervention to improve survival?

A. Serial lactate measurements q-1-h to assess adequacy of resuscitation
B. Serial procalcitonin levels to determine adequacy of antimicrobial regimen
C. Serum Beta D Glucan to determine whether micafungin should be added to initial antimicrobial regimen
D. Prolonged infusion of subsequent doses of piperacillin-tazobactam
E. Continuous (24 hr/day) infusion of vancomycin

Definition of Sepsis



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Surviving Sepsis Guideline Recommendations: What Do You Need to Know

- Few recommendations based on strong evidence
- Most ID related recommendations are common sense

Surviving Sepsis Guidelines* (2021 and 2026)
Strong Recommendations – Potentially Testable

- **Mean Arterial Pressure >65 mm Hg by continuous monitoring**
  - Invasive or non-invasive
- **Timing of Antibiotics**
  - Septic Shock-Within 1 Hour
  - Sepsis without Shock-Within 3 Hours
- **Blood cultures before antibiotics**
- **Pathogen Specific Rapid Diagnostic Tests**
  - Multiplex nucleic acid amplification tests to identify blood culture isolates
  - Nucleic acid amplification tests to identify antibiotic resistance genes in blood culture isolates

*With a few modifications!

Surviving Sepsis Guidelines* (2021 and 2026)
Strong Recommendations – Potentially Testable

- **Norepinephrine as Pressor of Choice**
  - Add Vasopressin if inadequate response
- **Prolonged infusion of beta-lactams for maintenance----Not initial dose**
  - Higher efficacy for organisms with higher MICs-suspected or confirmed
  - Especially for antipseudomonal beta lactams e.g. piperacillin-tazobactam, meropenem,, cefepime, ceftolozane-tazobactam. Ceftazidime-avibactam, meropenem-vaborbactam, and cefiderocol
- **Crystalloids for Resuscitation (e.g., Ringers Lactate) rather than Normal Saline**
- **PK/PD monitoring for selected antimicrobials**
- **Hydrocortisone for severe community acquired pneumonia**
- **Hydrocortisone for septic shock**
  - Shock reversal better documented than survival benefit

*With a few modifications!

Surviving Sepsis Guidelines* (2021 and 2026)
Strong Recommendations – Potentially Testable

- O2 Saturation Target: 90-96%
- Proton pump inhibitor if risk for stress ulcer bleeding
- Early enteral feeding (within 72 hours)
- Insulin therapy if glucose >180 mmols/L
- Venous thromboembolic prevention with low mol wt Heparin

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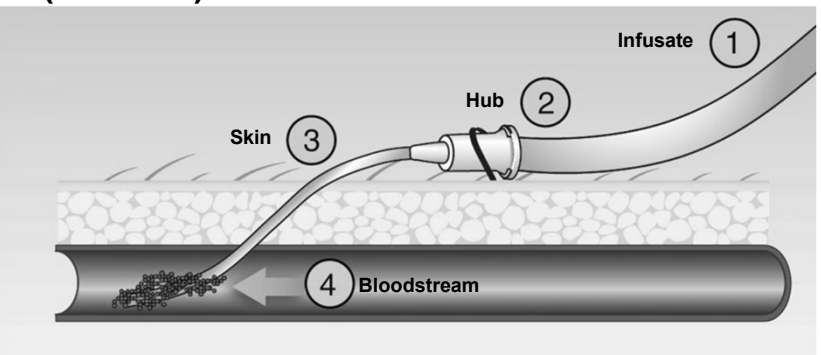
Watch For Questions About De-Escalation of Antimicrobials

- Use culture results to narrow spectrum
- Consider “shorter” courses if clinical response good and no major risk factors for poor outcome

Severe Community Associated Pneumonia Remember Therapy for Pseudomonas

- For severe CAP, if risk factors for Pseudomonas infection are present
  - CD4 count ≤50 cells/mm3, or Neutropenia, preexisting lung disease, use of corticosteroids, severe malnutrition, hospitalization within the past 90 days, residence in nursing home, chronic hemodialysis
- Treat with antipseudomonal beta-lactam (Mero, Pip Tazo, Cefepime) plus
  - Either ciprofloxacin (400 mg every 8 hours) or levofloxacin (750 mg/day)
- Treat with anti-MRSA agent
  - Only if risk factors present (e.g. influenza, recent antibiotics) and/0r
  - Nasal swab MRSA positive

Catheter Related Blood Stream Infection (CLABSI)



Antiseptic Techniques: Catheter Insertion

(See Michael Klompas Lecture)

Hand Hygiene	• **Soap/water or alcohol-based rub before/after insertion** • **Sterile gloves while inserting**
Skin Prep	• **Chlorhexidine solution before insertion and during dressing changes** • **Allow to fully dry before insertion**
Barrier	• **Maximum barrier protection: cap, mask, sterile gown, sterile gloves and full sterile drape**

CID 2011:52 (1 May)

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Remove the Catheter!

- **On the Board Exam**
  - It's almost never wrong to remove/replace catheter
- **<u>Syndromes</u> Requiring Removal**
  - Septic shock
  - Septic thrombophlebitis/Venous obstruction
  - Endocarditis
  - Positive blood cultures>72 hrs after appropriate abx
- **<u>Organisms</u> Requiring Removal**
  - Staph aureus
  - Atypical mycobacteria
  - Candida species
  - Cutibacterium acnes
  - Pseudomonas aerug
  - Bacillus species
  - Malassezia
  - Micrococcus

Antimicrobial Lock Therapy & Impregnated Catheters

Catheter salvage: for long-term catheter CRBSI with line retained → antibiotic lock + systemic therapy ×10–14 days

Best evidence for uncomplicated CoNS; still remove line for S. aureus, PsA, or Candida

Prevention: prophylactic antimicrobial lock for long-term catheters with recurrent CRBSI (e.g. hemodialysis)

Antimicrobial-impregnated catheters: consider when CLABSI rates stay high despite basic prevention

Mermel et al., CID. 2009
Buetti et al., Infect Control Hosp Epidemiol. 2022

Life Threatening Rashes/Exfoliation

Stevens Johnson Syndrome and Toxic Epidermal Necrolysis

Rash Characteristics	Erosive mucositis of oral, urogenital, and ocular sites SJS: <10% BSA; TEN: >30% BSA (body surface area)
Onset	4-28 days after drug exposure
Other Features	Fever, partial or full thickness injury with painful necrolysis, pulmonary and GI manifestations
Lab Findings	Leukopenia, no eosinophilia
Risk Factors	Anticonvulsants, infection (mycoplasma), GVHD, HIV
Treatment	Withhold offending agent, supportive care Steroids and IVIg are controversial

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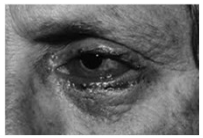
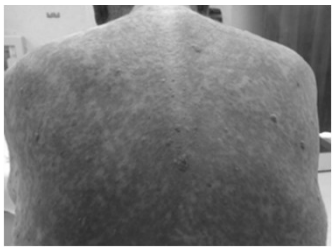
Stevens Johnson and Toxic Epidermonecrolysis



- "Positive Nikolsky sign"
  - Slight rubbing of the skin results in exfoliation of the outermost layer
  - NOT specific for Stevens Johnson and TEN
    - Staph scalded skin syndrome (mostly children, no mucosal involvement)
    - Pemphigus
    - Graft vs Host
    - Paraneoplastic syndromes

DRESS: Morbilliform Rash with Facial Edema and Eosinophilia

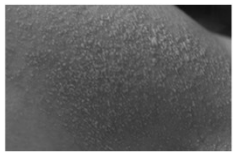


DRESS (Drug Induced Hypersensitivity Syndrome)

Rash Characteristics	Morbilliform involving >50% BSA, inflamed, facial edema, infrequent mucosal involvement
Onset	1-3 (up to 6) weeks after drug exposure
Other Features	Fever, Lymphadenopathy, other organ involvement in 80% (liver, kidney, pancreas, heart, lung) Herpesviridae reactivation (HHV6)
Lab Findings	Eosinophilia, lymphocytosis/lymphopenia, atypical lymphs
Classic Meds	Anticonvulsants (esp. lamotrigine), Vancomycin, Raltegravir, Dapsone, other Sulfas, anti-TB RIPE
DDx	Mycoplasma, viral hepatitis, mononucleosis, SLE
Treatment	Withhold offending agent, supportive care Controversial: Steroids, CsA, IVIg. Mortality is high

Acute Generalized Exanthematous Pustulosis (AGEP)

- Acute diffuse pustular skin eruption starting on face
  - T cell-mediated neutrophilic inflammation
  - Arises suddenly hours or days after initiating new drug
    - Starts on face and spreads to extremities with facial edema
    - Fever, mild leukocytosis and eosinophilia
    - Mucosal involvement unusual
  - Often caused by antimicrobials
    - Often: Sulfonamides, Chloroquine, Ampicillin, Quinolones
    - Occasionally: Mycoplasma, Viruses
- Treatment
  - Supportive +/- Corticosteroids



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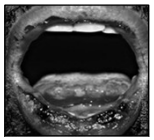
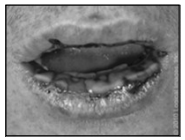
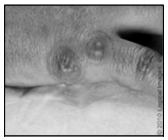
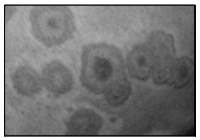
Febrile Exanthematous Drug Eruptions

SJS/TEN	AGEP	DRESS
• Severe blistering • Mucosal involvement	• Pustular lesions • Rare Mucosal	• Facial edema • Rare mucosal • Eosinophilia
• Fever	• Fever	• Fever
• Steroids • IVIG controversial	• Steroid rx controversial	• Steroid rx controversial
• SJS: <10% BSA • TEN: >30% BSA	• Common ddx: psoriasis	• > 50% BSA

Erythema Multiforme: Rarely Life Threatening

- Immune mediated
- Distinctive target lesions that are usually asymptomatic
  - Febrile prodrome in some cases
- Often associated with oral, ocular, and genital mucosal lesions
- Less severe than DRESS or SJS or TEN
- Causes: Infection > Drugs
  - Infections: HSV, Mycoplasma, many others
  - Cancer, autoimmune, drugs, etc.
- Self Limiting in 10-14 days

Two Topics Specifically Mentioned on ABIM ID Blueprint

Near Drowning/Submersion Injuries

- Prophylactic Antibiotics
  - Not indicated unless water grossly contaminated
  - Steroids not indicated
- Etiologic Agents
  - Water borne organisms common
    - Pseudomonas, Proteus, Aeromonas
- Therapy for Pneumonia
  - Directed at identified pathogens

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E-cigarette or Vaping Product Use Associated Lung Injury (EVALI)

- Primarily associated with e-cigarettes and vaping products, particularly THC-containing compounds
- Clinical presentation similar to community acquired pneumonia
- Exact cause believed to be related to direct lung injury → inflammatory response
- Treatment: supportive care, cessation of e-cigarette use

MMWR. 2019;68(46):1076

Summary: What To Look For on Exam

- **Hyper-pyrexia syndrome**
  - Use of dantrolene
- **Prevention of CLABSI, VAP, UTI, Surgical wound infection**
  - See Klompas lecture
- **Apparent Septic Shock**
  - Non-infectious cause-adrenal insufficiency, thyroid storm, anaphylaxis, neurogenic
- **Management of Septic Shock**
  - Time to antibiotics
  - Prolonged infusion of beta lactams
- **De-escalation of Antibiotics**
  - Based on culture results or MRSA screening
- **E-cigarette and pulmonary infiltrates**
- **Near Drowning**
  - Use of antibiotics for prophylaxis or therapy

Thank You

- Good luck!
- Please give feedback
- Contact
  - taison.bell@virginia.edu
  - Twitter/X: @TaisonBell (but don't bother)

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Sunday, August 23, 2026

16

Ticks, Mites, Lice, and the Diseases They Transmit

Paul Auwaerter, MD

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Ticks, Mites, Lice, and The Diseases They Transmit

Paul G. Auwaerter, MD

Johns Hopkins University School of Medicine

8/6/2026

Disclosures of Financial Relationships with Relevant Commercial Interests

- Research: Pfizer (investigational Lyme disease vaccine)
- Consulting: medical-legal, Tonix Pharmaceuticals, Tarsus Pharmaceutics

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
- 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

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Tick-borne Diseases of North America General Principles II

Seasonal but not always

Geography informs etiology, but it is evolving for many

Lab tip-offs:

- Thrombocytopenia
- Leukocytosis or leukopenia
- Elevated LFTs

Doxycycline is preferred therapy for most

- (All ages including children, e.g., RMSF, ehrlichiosis…ex. Lyme < 8 yrs)

Prognosis is worse at age extremes < 10 and > 60 yrs

Tick vectors

- Ticks cause 95% of vector-borne disease in the US
- Co-infections in some patients

The Major Tick-borne Diseases of North America

- **Lyme disease (separate talk)**
- Rocky Mountain spotted fever (RMSF)
- Ehrlichioses
- Anaplasmosis
- Babesia spp.
- Relapsing fever (Borrelia 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*
  - *R. rickettsii* subsp. californica
- Coxiella burnetii (rarely from ticks)
- Tularemia
  - (< 10% tickborne)
- Other Borrelia
  - *B. miyamotoi*
  - *B. mayonii*

Ticks: Arachnids, Not Insects

- Number of species
  - >900 species or subspecies worldwide
    - 90 species in North America, handful cause most human infections
- Hematophagous arthropods
  - Parasitize every class vertebrates ≅ entire world
- Two major families
  - Ixodidae, >700 species (hard ticks, attach & engorge)
  - Argasidae, >190 species (soft ticks, bite multiply & briefly)
- Four basic life stages
  - egg → larva → nymph → adult
- Vectors of human disease
  - #1 mosquitos
  - #2 ticks

Parola, Raoult CID 2001; 32:897-928
Guglielmone, Zootaxa 2010;2528:1-28
Eisen, Ticks Tick Borne Dis 2022;12(6):102025

16 Ticks, Mites, Lice and The Diseases They Transmit

Speaker: Paul Auwaerter, MD

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Top Ticks in North American that Transmit Human Pathogens (Ixodidae)

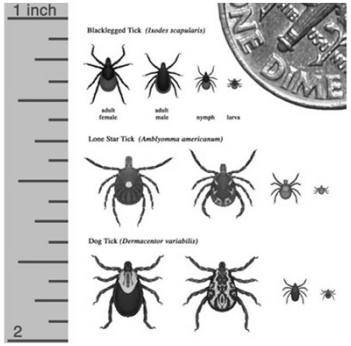
#1 *Ixodes scapularis*
Black-legged tick

#2 *Amblyomma americanum*
Lone star tick

#3 *Dermacentor variabilis*
Dog tick

#4 *Ixodes pacificus*
Western black-legged tick

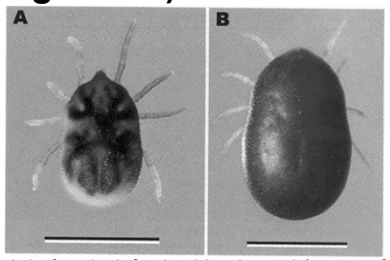
#5 *Dermacentor andersoni*
Rocky Mt wood tick



SEE ENLARGED SLIDE FOLLOWING ENTIRE PRESENTATION

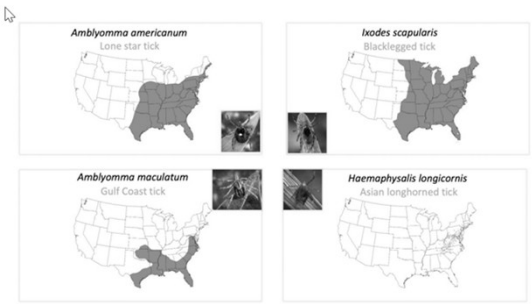
Eisen, Ticks Tick Borne Dis 2022;12(6):102025

Ornithodoros hermsii nymphal Tick Soft tick (Argasidae)



- A: shows the nymph before its infective blood meal (vector of tick-borne relapsing fever)
- B: shows it after feeding
- These are soft ticks that feed briefly at multiple spots—DO NOT remain attached
- Scale bars = 2 mm

Expanding Range and Ticks New to the US



I. Scapularis
Ticks that carry B. burgdorferi and bite humans mostly northern tick populations

H. Longicornis
May carry multiple pathogens, participation in transmitting to Humans occurs but uncertain to what degree

SEE ENLARGED SLIDE FOLLOWING ENTIRE PRESENTATION

Molaei, JID 2022;226(3):370-373

Selected Tickborne Diseases in the US

Home | Data Summary | Cases by Year | Cases by Month

Tickborne Disease Surveillance Data Summary

Total Reported Cases by Tickborne Disease, 2019-2022

Disease	2019	2020	2021	2022
Lyme disease	34,945	18,010	24,611	62,551
Anaplasmosis	5,655	3,639	6,744	5,633
Spotted fever rickettsioses	5,207	1,175	1,278	1,271
Ehrlichia chaffeensis ehrlichiosis	2,093	1,180	1,347	1,557
Babesiosis	2,418	1,827	1,915	
Tularemia	274	150	162	167
Undetermined ehrlichiosis/anaplasmosis	185	50	77	95
Powassan virus disease	43	21	24	47
Ehrlichia ewingii ehrlichiosis	43	21	19	25
Total	**50,863**	**26,073**	**36,177**	**71,346**

← New 2022 CDC Surveillance Definition for Lyme disease

CDC, https://www.cdc.gov/ticks/data-research/facts-stats/tickborne-disease-surveillance-data-summary.html#:~:text=During%202019%2D2022%2C%20state%20and,to%20CDC%20over%20the%20years. (accessed5/15/25)

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Speaker: Paul Auwaerter, MD

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New Regions for Common Tickborne Infections

Range expanding for:

- Lyme disease
  - Upper Midwest
  - South along Appalachians
- Babesiosis
  - Expanding w/i Lyme disease range
- Ehrlichioses
  - *E. chaffeensis*, northward

CDC, https://www.cdc.gov/ticks/tickbornediseases/overview.html
Accessed 1/16/23

SEE ENLARGED SLIDE FOLLOWING ENTIRE PRESENTATION

Question #1

62-year-old M, 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 an electrical lineman for a utility company. He lives with his family in an older adobe home with dogs. There is a faint maculopapular rash on the extremities. No tick bite recalled.

Which of the following is the most likely diagnosis?

A. Human Monocytic Ehrlichiosis (HME)
B. Human Granulocytic Anaplasmosis (HGA)
C. Babesiosis
D. Rocky Mountain Spotted Fever (RMSF)
E. Tularemia

Rickettsial Species: Two Major Groups (Not a Comprehensive Rickettsial List)

Spotted Fever Group (SFG)

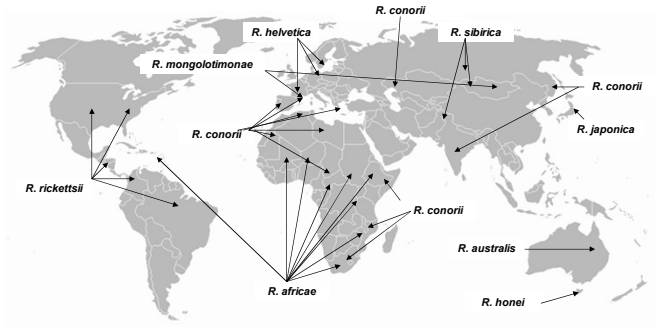
- RMSF (*R. rickettsii*)
  - *R. rickettsii* subsp californica (prev 364D)
- *R. parkeri*
- *Rickettsia sp.*
- Rickettsialpox (*R. akari*)
- *R. conorii*
- *R. africae*
- *R. japonica*
- *R. australis*

…many more

Typhus Group

- Epidemic typhus
  - *R. prowazekii*
    - Body louse
    - Worldwide
- Murine/endemic typhus
  - *R. typhi*
    - Rat flea
    - Temperate--tropical, usually
- *R. felis*

Tick-borne Rickettsia Worldwide: Many Species



➢ 24 species causing human disease. List continues to grow.

SEE ENLARGED SLIDE FOLLOWING ENTIRE PRESENTATION

Parola, Clin Microbiol Rev 2013;26(4):657-702

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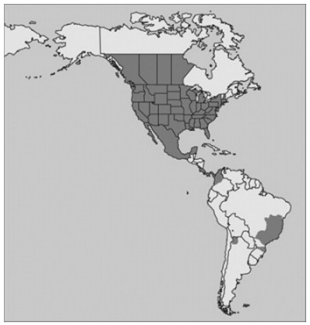
Approximate Geographic Distribution of *R. rickettsii* in the American Continents



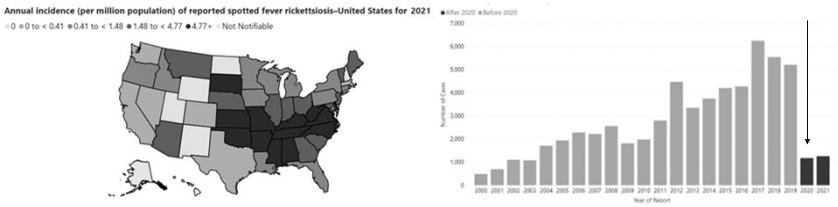
- Seen in all lower 48 states
- Mexico
- Parts of Canada
- Central and South America

Ongoing epidemic in Northern Mexico (2015-present)

Alavarez-Hernandez, Lancet ID 2017;17(6):e189-196
Tinoco-Gracia, EID 2018;24(9):1723-25

CDC Changes:

- 2010: RMSF to "spotted fever rickettsioses" 2010 due to lack of serologic specificity includes RMSF, *R. parkeri*, Pacific Coast tick fever, Rickettsialpox, and others
- 2020: SFG criteria changes w/ IFA titer raise to ≥ 1:128 from 1:64 to raise specificity, elimination of IFA IgM ELISA



SEE ENLARGED SLIDE FOLLOWING ENTIRE PRESENTATION

Source: CDC https://www.cdc.gov/rocky-mountain-spotted-fever/data-research/facts-stats/index.html

SFR in the United States

Incidence/Case Fatality 1920-2019

https://www.cdc.gov/rocky-mountain-spotted-fever/data-research/facts-stats/index.html (accessed 7/19/26)

Risk Factors for Fatal RMSF ('99-'07)

- Native Americans
- Age extremes: 5-9, 70+
- Alcoholism, chronic lung dz
- Delay in doxycycline:
  - Treatment after 5 days illness
- Immunosuppression

SEE ENLARGED SLIDE FOLLOWING ENTIRE PRESENTATION

Regan JJ, CID 2015; 60(11)1659-1666

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

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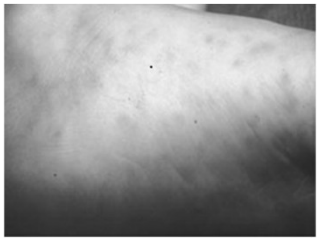
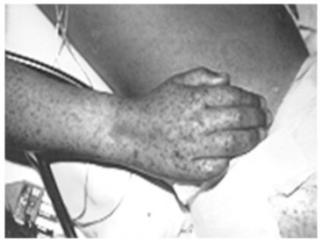
Rocky Mountain Spotted Fever

Early: Rash Absent or Maculopapular
Starts On Extremities



Later Rash: Petechial



Fulminant RMSF Gangrenous Features
(Usually Seen with Multi-organ Failure)

RMSF Diagnosis and Treatment

Start treatment upon suspicion: DON'T WAIT

- Mortality 4% if doxycycline w/i 5d of symptom onset; 35% if > 5d.

Labs: leukocytosis, thrombocytopenia, transaminitis, hyponatremia

Dx:

- Preferred:
  - Skin bxp immunohistochemistry (DFA): timely diagnosis, ~70% sensitive.
  - PCR: *R. rickettsii*-specific (blood less sensitive)
    - Skin bxp or swab (more sensitive, contact local health department → CDC)
- Acute/convalescent serology

Jay R. J Vector Borne Dis 2020;57(2):114-120

Outcome: RMSF According to Day Doxycycline Started after Sx Onset

	% mortality
• Day 1-5	0
• Day 6	33
• Day 7-9	27-50

Most lethal of Rickettsial infections: "Black measles"

In the US, mortality with treatment is ~2-5% (higher with delay in starting doxycycline)

Clin Infect Dis 2015; 60:1659-66

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RMSF Diagnosis and Treatment

Other diagnostic issues

- Serology:
  - Acute/convalescent samples
    - Not usually of timely clinical value
  - IFA : gold standard; cross-reacts w/ other SFG species
    - May be helpful in confusing cases
    - IgG is best to confirm
    - IgM with low specificity
- False positives (especially IgM) common
  - GA blood donor study: 11.1% IgG > 1:64, but only 28% fit case definition for hx SFGR
  - Background seroprevalence up to 20% in some regions, e.g., Carolinas
- Asx infection common
  - Single IgG titer insufficient for reliable diagnosis
- Both RMSF IgM & IGG can persist
- May mislead, result in unnecessary treatment

Straily A, JID 2020;221:1371
Ursery L. PLOS One May 2025

Pacific Coast Tick Fever

New Name:

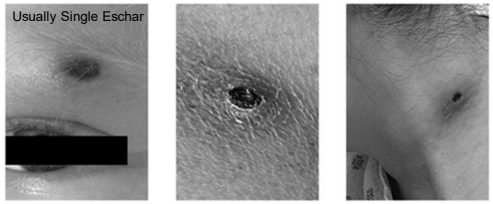
Rickettsia rickettsii subsp *californica* (proposed)
(previously Rickettsia 364D/*R. philipii)*

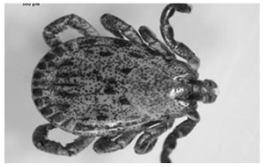
Described in 1966

Transmitted by
Pacific Coast tick
(*Dermacentor occidentalis*)

Southern Oregon → Northern Baja

Common symptoms:
- Eschar
- Fever
- Headache
- Usually mild infection





Dermacentor occidentalis

SEE ENLARGED SLIDE FOLLOWING ENTIRE PRESENTATION

Padgett K PLOS Neg Trop Dis 2016
Paddock CF JID 2025:231(4):849-858

Question #2

31-year-old M from the Tidewater (SE) region of Virginia presents in June with a 3-day history 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: Gulf Coast ticks (*A. maculatum*) transmit most
  - Southeastern US, Gulf Coast
- AKA "Maculatum fever"
  - Also seen in Central and South America, including Argentina, Uruguay, parts of Brazil
- Symptoms 2-10 d post-bite
  - Headache, myalgia
  - Skin
    - Faint salmon-colored rash
    - Single or multiple eschars
- Diagnosis
  - Spotted fever group serology,
  - Immunohistochemistry
  - PCR or culture from skin bxp or swab of eschar

MMWR Morb Mortal Wkly Rep 2016; 65(28): 718-9
Kelman, Infection 2018;46(4):559-563
Scott, Trends in Micro 2022;30(5):511-512

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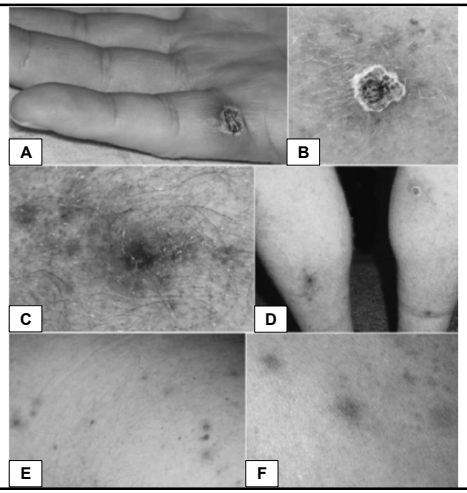
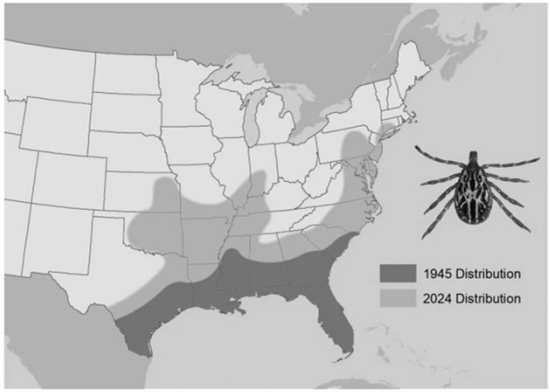
Examples of *R. parkeri*-associated Rashes



Source: CDC



A. maculatum (Gulf Coast Tick range); first human case of *R. parkeri* in CT (2024)
Connecticut Agricultural Experimental Research Station, 2024

Question #3

22-year-old M upstate NY July c/o HA and fever x 3d now confused. No known tick bite but an outdoorsman. Exam without meningism or rash. Labs normal.
Admitted, doxycycline, CTX, vancomycin started. Head CT: normal
LP: WBC 130 60%P, 40%L, glucose: nl, protein 65 mg/dL (elevated).

Which of the following is the most likely etiologic agent?

A. Anaplasma phagocytophilum
B. Ehrlichia chaffeensis
C. Heartland virus
D. Powassan virus
E. Borrelia miyamotoi

POWV: Reported cases mostly neuroinvasive
Tick-borne flavivirus infection

- Mostly present in Spring-Summer
  - But can be year-round
  - Related to nymphal Ixodes scapularis
- All ages, median 62 years, 72% male, incubation 1-5 weeks
- Clinical Syndromes
  - Neuroinvasive (90%)
    - Encephalitis (72%)
    - Meningitis (16%)
    - Other neurologic (2%)
  - Non-Neuroinvasive (10%)

- Hospitalized (90%)
- Death (11%, most > 50 years)
- Neurologic sequelae ~50%

SEE ENLARGED SLIDE FOLLOWING ENTIRE PRESENTATION

Krow-Lucal ER. Vect Borne Zoo Dis 2018; 18(6):286-290
https://www.cdc.gov/powassan/data-maps/historic-data.html

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Powassan Virus Diagnosis & Care

- Antibody testing best sensitivity
  - CT or MRI may be normal; severe cases often with cerebellar changes (70%)
  - CSF: IgM POWV
    - Commercial, State Public Health labs & CDC
    - Needs confirmation by plaque-reduction neutralizing test to r/o cross-reactivity with other flaviviruses
- Other:
  - Viral RNA serum, CSF, tissue
    - Performs best early in illness
  - Immunohistochemistry, fixed tissue
- Treatment: supportive care
- Prognosis: mortality ~ 10%, neurologic sequelae 50%

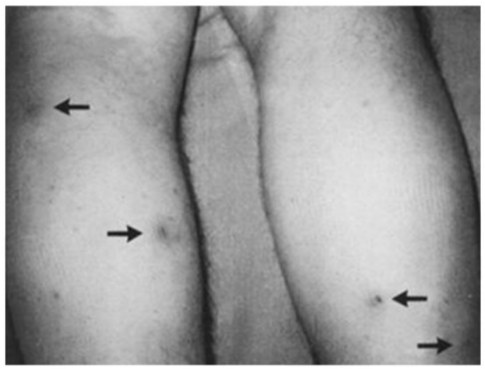
Piantadosi A. Inf Dis Clin N Am 2022;36(3):671-688

Question #4

- 28-year-old F 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

Question #4

Four Inoculation Eschars (Arrows)



Question #4

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

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Range of *R. africae*
African Tick Bite Fever (green)

Range of *R. conorii*
Mediterranean Spotted Fever

Figure 4

Figure 4. Distribution of the cases of Mediterranean spotted fever (MSF) in the world and incidence of the disease in countries where MSF is endemic.

SEE ENLARGED SLIDE FOLLOWING ENTIRE PRESENTATION

Rovery, EID 2008;14(9)

Clinical Characteristics of *R. africae* Infection

	%
Fever ≥ 38.5º	88
Neck muscle myalgia	81
Inoculation eschars	95
Multiple eschars	54
Lymphadenopathy	43
Rash (vesicular)	46 (45)
Death	0

Raoult D, et al. N Engl J Med 2001; 344:1504-10

African Tick Bite Fever

- Seroprevalence:
  - High in residents, R. africae, 30-56%
- Amblyomma ticks (cattle, ungulates)
  - Clusters of cases, multiple eschars
- Incubation period 6-7d
- Dx:
  - Biopsy or swab: PCR or MIFA
  - Serology
- Rx: doxycycline
- Complications unusual

Rickettsioses and The Returning Traveler Common Cause of Fever After Malaria, Typhoid

- Most common: 280 travelers (1996-2008)
  - Spotted fever group (83.5%)
    - 87.5% acquired in sub-Saharan Africa
- Others
  - Scrub typhus (5.7%)
  - Q fever (3.6%)
  - Typhus group (2.5%)
  - Human granulocytic ehrlichiosis (0.4%)

Jensenius M, EID 2009;15(11)

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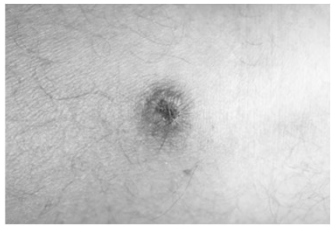
Question #5

- 48-year-old M presents in October with fever and rash
- Supervisor for apartment building in Queens, NY. Lives in cellar apartment
- Exam: T 39^0C
- Brown-black 8mm eschar on RLE
- ~30 papulovesicular lesions on trunk



Question #5

Which of the following Is the most likely etiologic agent?

A. R. rickettsii
B. R. parkeri
C. R. akari
D. R. conorii
E. Borrelia recurrentis

Rickettsialpox

Organism
- *R. akari*

Reservoir
- House mouse

Vector
- Mouse mites

Clinical
- Single eschar
- Rash: papulovesicular (20-40) or maculopapular

Diagnosis
- PCR swab eschar/vesicle

Treatment
- Doxycycline

Maculopapular rash due to R. akari (CDC)

Partial DDx of Vesicular Rash

- HSV
- VZV
- Poxviruses
  - Mpox
- Rickettsialpox
- African tick bite fever
- Queensland tick typhus

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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

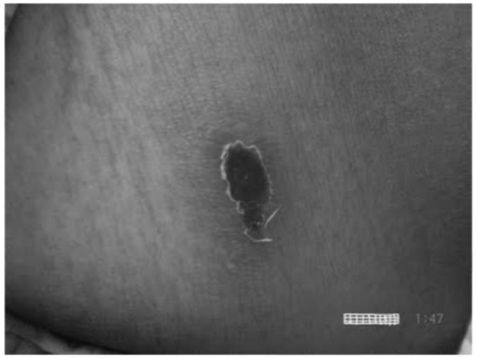
Scrub Typhus

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% in severe/untreated infection



Eschar is often associated with regional lymphadenitis

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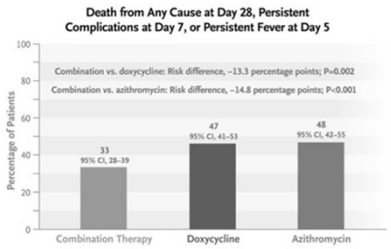
Scrub Typhus Treatment

- Treatment
- Doxycycline 100 mg PO BID x 7d
  - Alt: azithromycin
- Combination: appears superior and safe
  - Doxycycline 200 mg IV twice daily day 1 (load), then 100 mg twice daily x 6d
  - PLUS
  - Azithromycin 500 mg IV twice daily d1, then 500 mg daily x 6d
- Benefits severe scrub typhus w/ organ involvement



Jang MO, AAC 2014;58(3):1488-93
Varghese GM, NEJM 2023;388:792-803

Question #6

- 31M presents in January with 3d fever, HA, malaise, and myalgia
- Works as counselor at wilderness camp in Pennsylvania
- Flying squirrels common at camp, including residing in the walls of his cabin
- Exam is notable only for fever (39.60; no rash), tachycardia (P110)

For which of the following is a diagnostic test most likely to be positive?

A. Murine typhus
B. Epidemic typhus
C. RMSF
D. Tularemia
E. Relapsing fever

If You Read a Question with "Flying Squirrel" You Say "Epidemic typhus" or "*R. prowazekii*"

- Rare infection in the US
  - 1976-2001, 39 cases
- Generally East Coast
- None with louse exposure (the classic vector) in N. America
  - Not "epidemic" but sporadic
  - Most with flying squirrel exposure (Glaucomys volans)

Lewisboro Field Guide, phot Steve Geller

MMWR 2003; 9 (10); Lancet ID 2008;8(7):417

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
- Jarisch-Herxheimer risk ~37-100%

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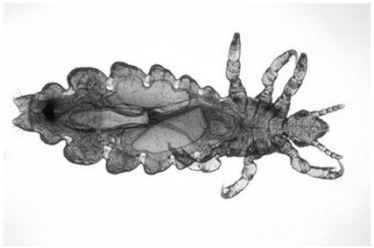
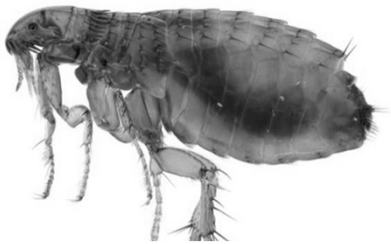
Vectors of Diseases (In this Module)



Body louse infestation = pediculosis
Pediculus humanus humanus



Human flea infestations
Oriental rat flea (*Xenopsylla cheopsis*) and the cat flea (*Ctenocephalides felis*)

Typhus: Two Forms

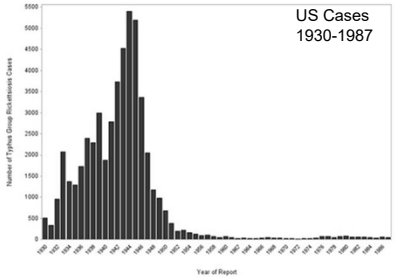
	Epidemic	Endemic
Organism	***R. prowazekii***	***R. typhi***
Vector	Louse (body>>head)	Flea (rat, cat)
Who	War refugees, crowded conditions/poor hygiene	Worldwide (U.S. Southern California, Texas, Hawaii)
Severity	Lethal	Usually milder, some fatalities
Treatment	Tetracycline Doxycycline (preferred) Chloramphenicol	Tetracycline Doxycycline
Prevention	Boil clothes; delouse (malathion, permethrin)	Flea prevention (cats, domestic animals) Reduce rodent population
Recrudesce	Brill-Zinsser Disease (years-decades)	None known

SEE ENLARGED SLIDE FOLLOWING ENTIRE PRESENTATION

Murine (or Endemic) Typhus

- In the US, mostly seen in
- California, Hawaii, and Texas
- Agent: *Rickettsia typhi*
- Infected cat/rat flea feces → skin
- Most don't recall a flea bite
- Usually non-specific febrile infection
  - Underdiagnosed
  - ~50% with rash
  - Occasional severe disease:
    - Meningoencephalitis
    - Pneumonitis
    - Shock

Historically, decline w/ better sanitation
No longer reportable since 1987



Dittrich, Lancet Global Health 2015;3:e104; Blanton Am J Trop Med 2017;96(1):53
CDC, accessed 7/6/2026 https://www.cdc.gov/typhus/about/murine.html

CDC Centers for Disease Control and Prevention
CDC 24/7: Saving Lives, Protecting People™
Search

Morbidity and Mortality Weekly Report (*MMWR*)

Fleaborne Typhus–Associated Deaths — Los Angeles County, California, 2022

Weekly / August 4, 2023 / 72(31);838–843

Incidence:
2010: 1
2022: 171
- Deaths 3 (autopsies)
- HLH
- Myocarditis
- Septic shock
- ➢ Late or no doxycycline

Case fatality usually < 1.0%
LA Series: 1.8%

Suspect: exposure to rodents, cats
Homeless

→Doxycycline

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Murine (or Endemic) Typhus

Consider especially febrile illness:
- CA, TX, Gulf coast

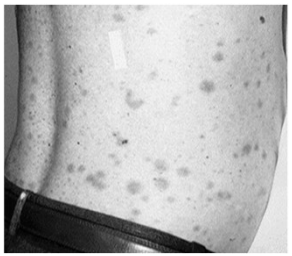
Dx:
- Serology *R. typhi* (IFA)
- Acute/convalescent, 4x rise
- Cross-reacts with R. prowazekii and SFG rickettsia

PCR
- Blood, often negative

Treatment:
- No RCTs
  - Doxycycline (preferred)
    - Azithromycin: open-label trial found azithromycin inferior to doxy
  - Alternatives: limited data
    - Chloramphenicol
    - Levofloxacin
    - Ciprofloxacin

Dittrich, Lancet Global Health 2015;3:e104; Blanton Am J Trop Med 2017;96(1):53
Newton, CID 2019;68(1 March):739

Flea-borne Spotted Fever/rickettsiosis
R. felis



Found globally; underdiagnosed
Discovered in 1990
- Cat fleas

Often lumped in with murine typhus
Usually mild illness but can be severe
- Fever, headache
- Rash variable (macular)
- Eschar in 12%

Dx:
- RMSF serology is often reactive
  - Acute/convalescent R. typhi serology
- PCR (tissue)

Treatment: doxycycline

Martinez MAC, Resp Rep Trop Med 2021;12:1-15

Other Location-specific Tick-borne Rickettsioses: Partial

Queensland tick typhus, *R. australis*
- Australia-Queensland, New South Wales, Tasmania, coastal areas of eastern Victoria

North Asian tick fever, R. sibirica
- 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. raoultii*:
- Europe and Asia

Far-Eastern tick-borne rickettsiosis, *R. heilongjiangensis*:
- Far East Russia and northern China

Oriental spotted fever, *R. japonica*:
- Japan

Thai tick typhus, *R. honei*:
- Thailand, Australia, Tasmania, Flinders Island

Australian spotted fever:
- *R. marmionii*

Question #7

- 43F visited southern Missouri on vacation, returns 7d later with fever, headache and diffuse myalgia x 3d
- Physical examination: no findings
- Laboratory evaluation
- WBC: 2.1/mm³ (80% PMNs, 10% lymphocytes, 8% monocytes
- Hemoglobin: 13 g/dL, hematocrit: 38%
- Platelets: 105,000/mm³
- AST: 364 U/L, ALT: 289 U/L Tbili 2.7
- Renal function: normal

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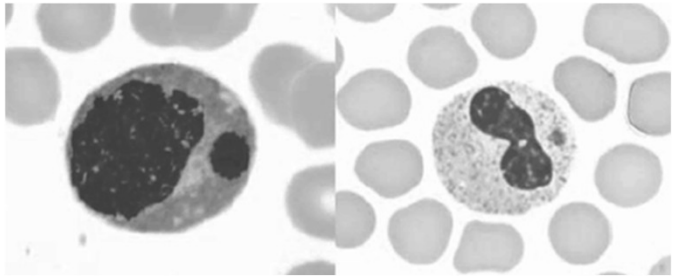
Question #7

Which of the following is the most likely etiologic agent?

A. Anaplasma phagocytophilum
B. Ehrlichia chaffeensis
C. Borrelia hermsii
D. Babesia divergens
E. Borrelia burgdorferi

Morulae



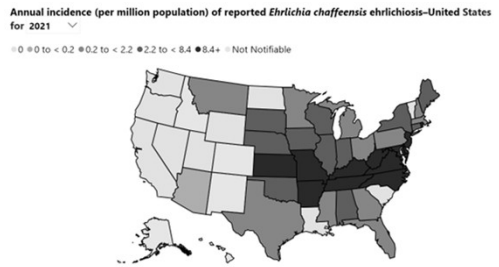
HME **HGA**

Seen 2%-38 Monocytes / Seen 20%-75% PMNs/Bands

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



SEE ENLARGED SLIDE FOLLOWING ENTIRE PRESENTATION

Source: CDC https://www.cdc.gov/ehrlichiosis/data-research/facts-stats/index.html (accessed 6/22/24)

Other Ehrlichia (Less Common)

Organism	Vector	Geography	Risk	Mortality
E. ewingii (aka canine Ehrlichia)	Amblyomma americanum (Lone star tick)	Most cases in Southcentral US	Immune compromised	Low
Ehrlichia muris eauclairensis (former Ehrlichia muris-like [EML] agent)	Ixodes scapularis (black-legged tick)	Wisconsin, Minnesota	Elderly, immune compromised	Low

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Human Granulocytic Anaplasmosis

Anaplasma phagocytophilum

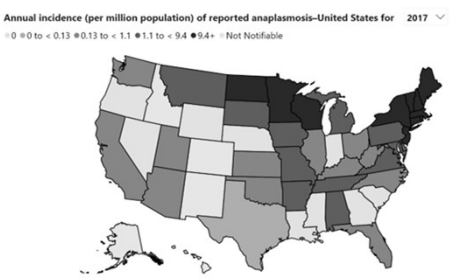
Vector: *Ixodes scapularis*

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 *E. chaffeensis* may account for much of Southern state representation

SEE ENLARGED SLIDE FOLLOWING ENTIRE PRESENTATION

Source: CDC https://www.cdc.gov/anaplasmosis/hcp/statistics/index.html (accessed 6/22/24)

Borrelia miyamotoi (AKA Hard Tick Relapsing Fever HTRF)

Unusual vector: Ixodes ticks

- Epidemiology = Lyme disease
- Appears similar to HGA (rash infrequent)
- Severe infection may be sepsis-like
- Meningoencephalitis in immunocompromised
- ↓ WBC, ↓ PLT, ↑ LFTs

Diagnosis: PCR, blood smear (observing spirochetes), serology

Treatment: similar to Lyme disease

Telford, Clin Microbiol Infect 2015

https://www.cdc.gov/relapsing-fever/about/about-htrf.html (accessed 7/19/26)

Tickborne Relapsing Fever US

***Borrelia spp.* (mainly *B. hermsii*)**

- Ornithodoros soft ticks (brief, painless)

Epidemiology

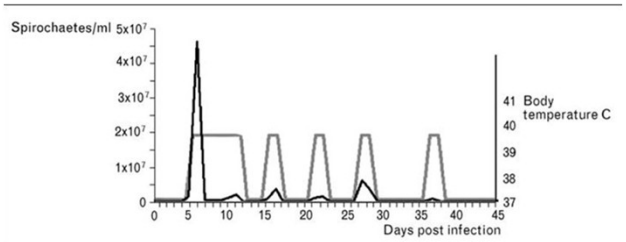
- Western states; 14-45 cases/yr
- Rustic housing and rodents
- Elevation 1500-8000 feet

Clinical Manifestations

- Fever (relapsing), HA, myalgia, N/V
  - Can be severe: ARDS
- Laboratory
  - AKI, ↓ platelets,
  - Dx: blood microscopic exam, PCR
- Rx: PCN, doxycycline
  - Jarisch Herxheimer reaction in 54%

FIGURE: Cases* of soft tick relapsing fever (n=210), by county of exposure – United States, 2012-2021

Beeson AM MMWR 2023;72(23):777-781



Relapsing Fever: recurrent bacteremia (black line) correlates with sudden fever (grey).

After initial bacteremia, relapses are lower and fever duration somewhat shorter.

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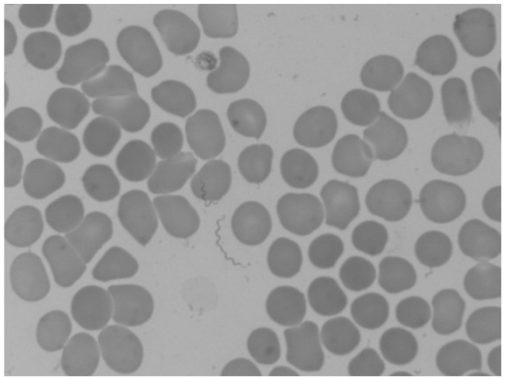

Diagnosis: observation of spirochetes in blood film

Question #8

- 48F c/o headache and fatigue worsening over 2 months since May tick bite
  - PMH: negative
  - SH: Married, works from home, has a dog, resides in suburban eastern PA
  - Treated with doxycycline for Lyme disease, no benefit
- Physical examination: afebrile, normal vital signs, no findings
- Laboratory evaluation :
  - WBC: 7.0 cells/mm³ (70% PMNs, 18% lymphocytes, 12% monocytes
  - Hemoglobin: 11.8 g/dL, hematocrit: 35%
  - Platelets: 145,000/mm³
  - ALT: 22 U/L
  - Babesia IgG 1:128 (positive ≥ 1:64)
  - Blood smear: no parasites

Question #8

What is 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

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Vannier et al, NEJM 2012 366;2397

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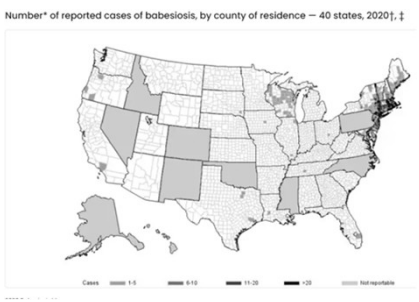
Babesia in the US



- Not reportable in all states
- Occurs within Lyme disease geography, but is more limited
- Vector:
  - *B. microti* → *Ixodes scapularis*
  - *B. duncani* → *Dermacentor albipictus*
    - (likely, west coast only)
    - < 20 documented cases
- 1500-2500 cases/yr

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https://www.cdc.gov/babesiosis/maps-graphs (accessed 7/20/26)

Babesia Species

- Malaria-like parasite, resides in RBCs
- Geography: Babesia microti (most cases in U.S.)
  - Nantucket, Martha's Vineyard, Long Island, Mid-Atlantic/New England, upper Midwest (similar to Lyme disease)
- Range of illness: Asx to "flu-like" to fatal
- **Was a** common cause of blood transfusion-related infection in US
  - Though decreasing through screening
    - But question may still appear on the boards

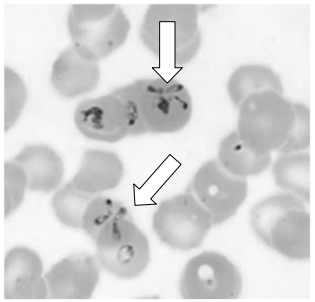
Severe Babesiosis

- n=34, Long Island NY
- Clinical manifestations
  - 41% Multi-organ failure
    - ARDS, DIC, CHF, ARF
- Risk factors:
  - age >60
  - splenectomy,
  - immunosuppression (e.g., HIV, rituximab)
- Labs
  - increased LTFs,
  - thrombocytopenia
  - anemia (Hb<10),
  - parasitemia (>10%)
- Immunocompromised mortality
- > 20%

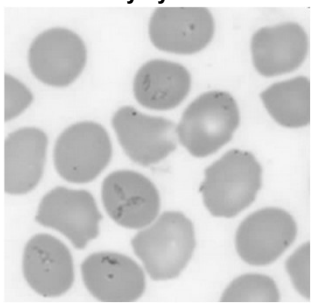
Hatcher JC, et al. Clin Infect Dis 2001; 32:1117-25

Babesiosis: Smear Diagnosis

Maltese Cross Tetrads



Species Level Identification only by PCR



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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 500-1000 mg IV q24h
    - Step down with improvement to lower dose azithromycin
    - Previous: quinine + clindamycin (now an alternative)
  - Duration: 7-10d (may require longer for persistent parasitemia or immunosuppressed)
- Blood exchange transfusion: severe hemolysis, > 10% parasitemia or 5-10% + organ compromise
  - *B. divergens*, many require
  - *B. microti*, some cases
  - Evidence for benefit, observational w/ 78% lower adjusted odds of death/readmission^
- Mild-moderate severity
  - Azithromycin PO plus atovaquone PO

Krause et al CID 2021; 72 (2) e49- 65; ^STOP-BABESIOSIS
JAMA Internal Medicine. 2026;186(5):597–607

Colorado Tick Fever

Transmission *D. andersoni*
- 4,000-10,000 feet

Agent: Coltivirus

Sx: range from
- Mild febrile flu-like illness
  - May include rash: maculopapular or petechial
- Rare: severe illness multi-system, neuroinvasive disease

Labs:
- ↓ WBC, atypical lymphocytes
- ↓ plt

Dx: samples to state lab, some commercial lab testing
- Not a reportable illness

Diagnostic Testing
Preliminary diagnosis of Colorado tick fever (CTF) is based on signs and symptoms, places and dates of travel, activities, and history of potential tick exposure. Acute samples should be tested by reverse-transcriptase polymerase chain reaction (RT-PCR) to detect viral RNA as antibody production is delayed until 14–21 days after onset of symptoms.

Timing of specimen collection	Specimens	Preferred Test
<14 days after symptom onset	Serum (CSF if suspected CNS involvement)	RT-PCR for viral RNA
≥14 days after symptom onset	Serum (CSF if suspected CNS involvement)	Antibody testing*; consider RT-PCR for samples from days 14-21

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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

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Question #9

- A 59-year-old man from Missouri presents with fever (390), headache, myalgia, anorexia, nausea, one week after removing an engorged tick from his groin. No travel
- Exam: unremarkable except ill appearing, no rash
- Lab: WBC 2300, PLT 42,000, ALT 111
- Suspect ehrlichiosis (but no morulae on blood smear)

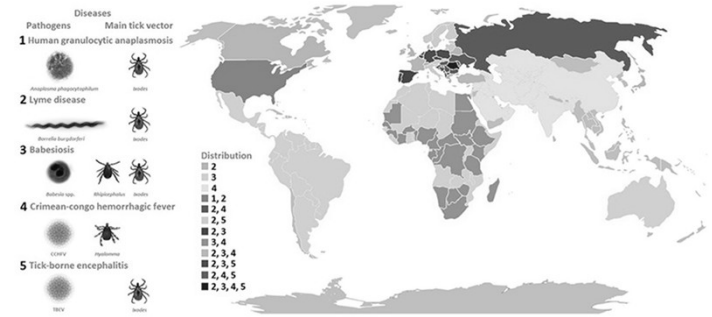
Question #9

After sending appropriate diagnostic tests the patient has not improved after three days of doxycycline.

Which of the following is the most likely etiologic agent?

A. *R. rickettsii*
B. *B. burgdorferi*
C. *R. parkeri*
D. Heartland virus
E. Severe fever with thrombocytopenia syndrome virus

But Wait: There's More (#4) and More (#5)



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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 (no tache noire)
  - Give doxycycline, even for kids
- Blood smear may be helpful
  - Morulae: PMNs = Anaplasma, Monocytes = Ehrlichia
  - Spirochete: relapsing fever Borrelia or *B. miyamotoi*
  - Erythrocyte inclusions: Babesia

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Tick-borne Infections:
Some Testable Points

Babesia:

- No longer a common cause of blood transfusion infection in the US
- Splenectomy or immunocompromise = severe infection risk

Co-infections in the US: may complicate some infections, especially after a black-legged tick (*I. scapularis*) bite

- Lyme disease + Babesia OR Lyme disease + HGA mostly

Flying squirrels: epidemic typhus

Rodent-infested urban house: Rickettsialpox

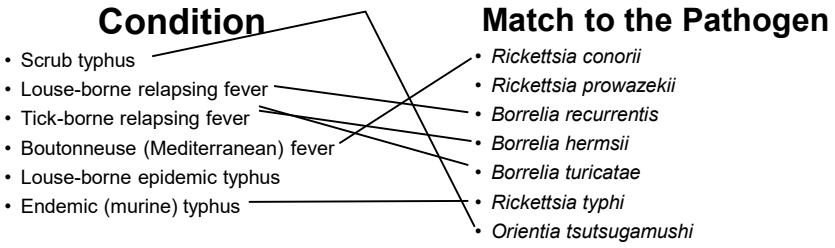
- Mouse mites.
- Tache noire first → > dozen papules/vesicles

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-like)	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 (Rare)	Yes	Cytopenias Transaminitis
Babesiosis	*B. Microti*	Ne, Ny, Ma, Mw	No	No	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 (Single)	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

SEE ENLARGED SLIDE FOLLOWING ENTIRE PRESENTATION



16 Ticks, Mites, Lice and The Diseases They Transmit

Speaker: Paul Auwaerter, MD

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Top Ticks in North American that Transmit Human Pathogens (Ixodidae)

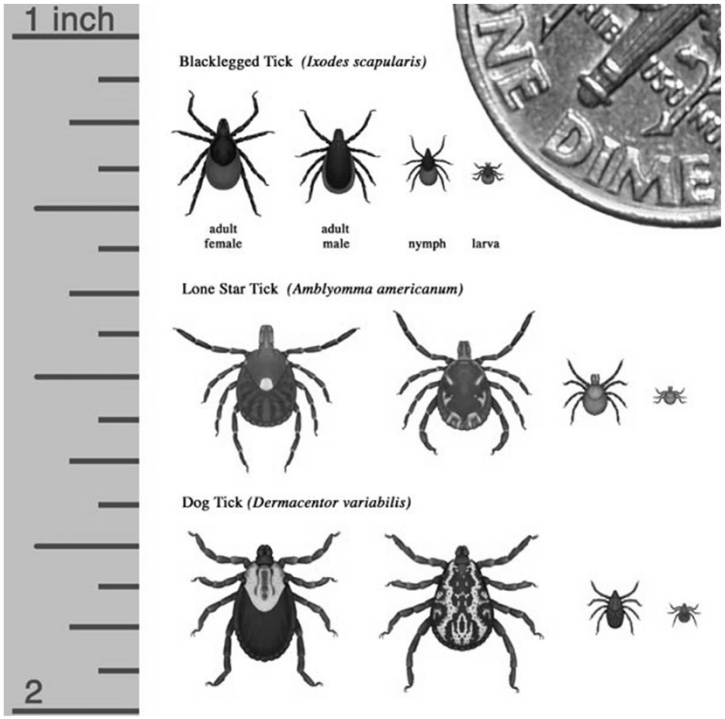
#1 *Ixodes scapularis*
Black-legged tick

#2 *Amblyomma americanum*
Lone star tick

#3 *Dermacentor variabilis*
Dog tick

#4 *Ixodes pacificus*
Western black-legged tick

#5 *Dermacentor andersoni*
Rocky Mt wood tick



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Eisen, Ticks Tick Borne Dis 2022;12(6):102025

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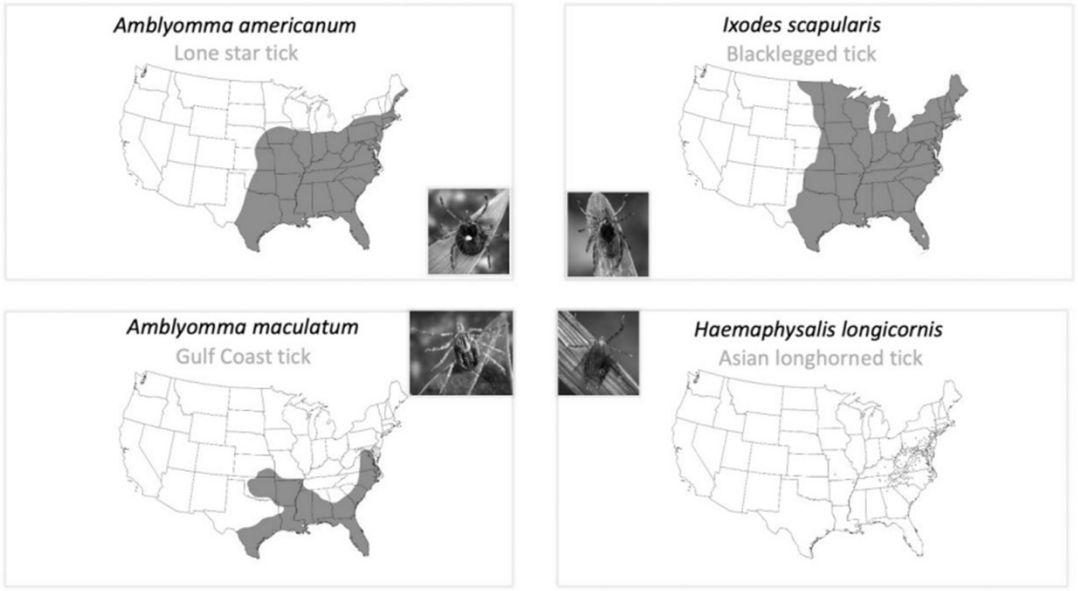
Expanding Range and Ticks New to the US



I. Scapularis

Ticks that carry B. burgdorferi and bite humans mostly northern tick populations

H. Longicornis

May carry multiple pathogens, participation in transmitting to Humans occurs but uncertain to what degree

SEE ENLARGED SLIDE FOLLOWING ENTIRE PRESENTATION

Molaei, JID 2022;226(3):370-373

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Selected Tickborne Diseases in the US

Tickborne Disease Surveillance Data Summary

Total Reported Cases by Tickborne Disease, 2019-2022

Disease	2019	2020	2021	2022
Lyme disease	34,945	18,010	24,611	62,551
Anaplasmosis	5,655	3,639	6,744	5,633
Spotted fever rickettsioses	5,207	1,175	1,278	1,271
Ehrlichia chaffeensis ehrlichiosis	2,093	1,180	1,347	1,557
Babesiosis	2,418	1,827	1,915	
Tularemia	274	150	162	167
Undetermined ehrlichiosis/anaplasmosis	185	50	77	95
Powassan virus disease	43	21	24	47
Ehrlichia ewingii ehrlichiosis	43	21	19	25
Total	**50,863**	**26,073**	**36,177**	**71,346**

New 2022 CDC Surveillance Definition for Lyme disease

CDC, https://www.cdc.gov/ticks/data-research/facts-stats/tickborne-disease-surveillance-data-summary.html#:~:text=During%202019%2D2022%2C%20state%20and,to%20CDC%20over%20the%20years. (accessed5/15/25)

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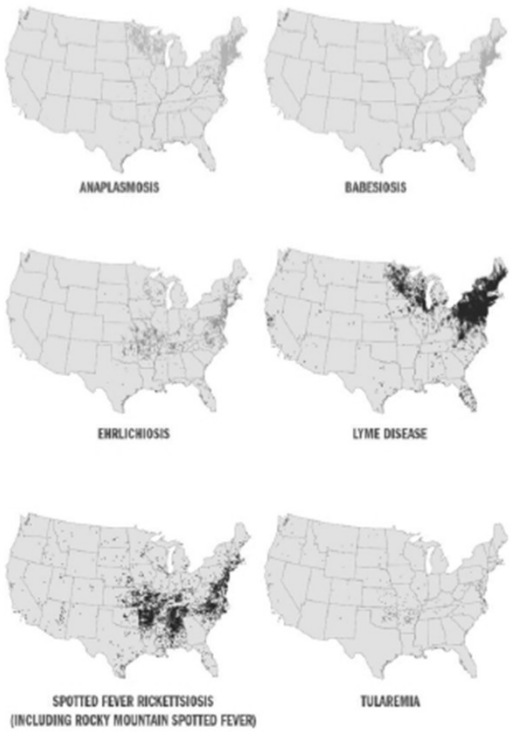
New Regions for Common Tickborne Infections



Range expanding for:

- Lyme disease
  - Upper Midwest
  - South along Appalachians
- Babesiosis
  - Expanding w/i Lyme disease range
- Ehrlichioses
  - *E. chaffeensis*, northward

CDC, https://www.cdc.gov/ticks/tickbornediseases/overview.html
Accessed 1/16/23

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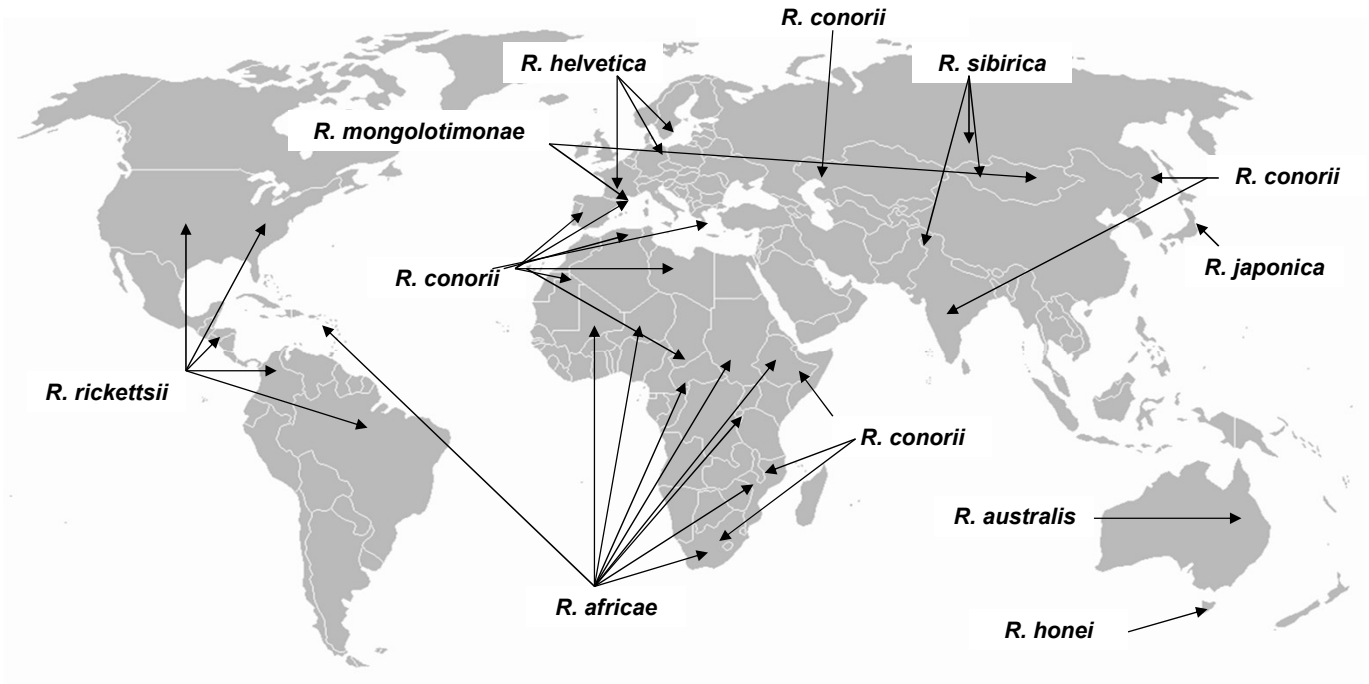
Tick-borne Rickettsia Worldwide: Many Species



- 24 species causing human disease. List continues to grow.

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Parola, Clin Microbiol Rev 2013;26(4):657-702

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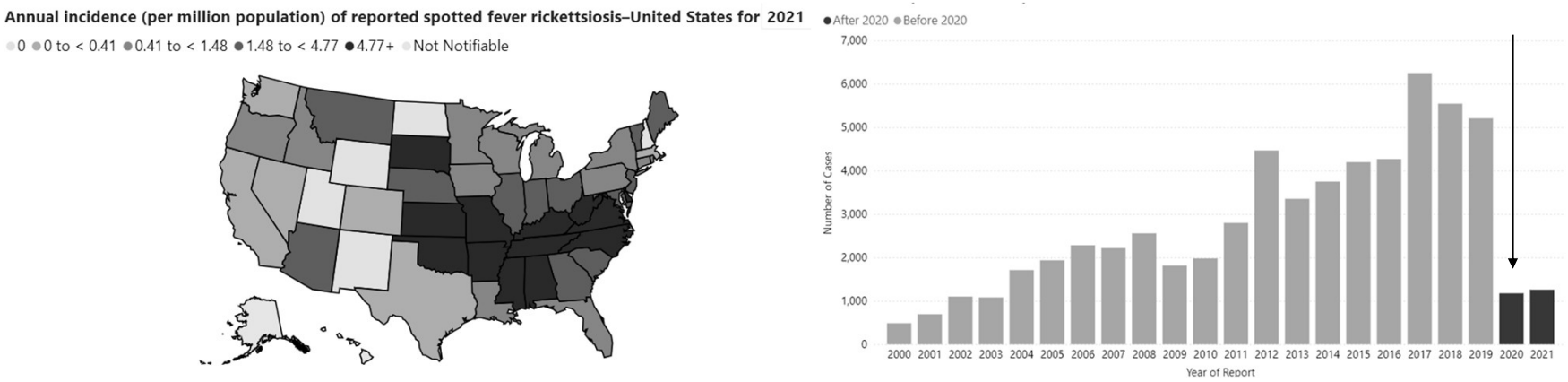
CDC Changes:

- 2010: RMSF to “spotted fever rickettsioses” 2010 due to lack of serologic specificity includes RMSF, *R. parkeri*, Pacific Coast tick fever, Rickettsialpox, and others
- 2020: SFG criteria changes w/ IFA titer raise to ≥ 1:128 from 1:64 to raise specificity, elimination of IFA IgM ELISA



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Source: CDC https://www.cdc.gov/rocky-mountain-spotted-fever/data-research/facts-stats/index.html

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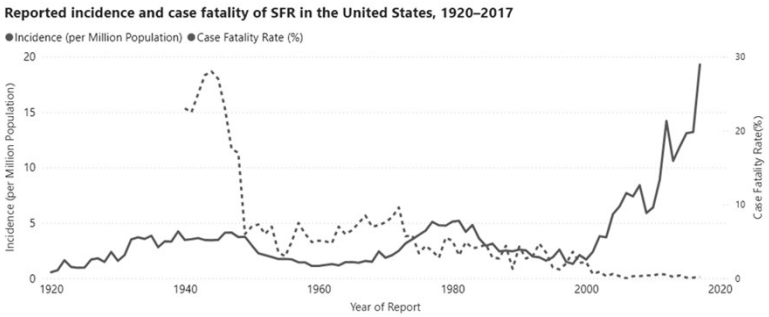
SFR in the United States

Incidence/Case Fatality 1920-2019



https://www.cdc.gov/rocky-mountain-spotted-fever/data-research/facts-stats/index.html (accessed 7/19/26)

Risk Factors for Fatal RMSF (’99-’07)

- Native Americans
- Age extremes: 5-9, 70+
- Alcoholism, chronic lung dz
- Delay in doxycycline:
  - Treatment after 5 days illness
- Immunosuppression

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Regan JJ, CID 2015; 60(11)1659-1666

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Pacific Coast Tick Fever

New Name:

Rickettsia rickettsii subsp *californica* (proposed)

(previously Rickettsia 364D*/R. philipii)*

Described in 1966

Transmitted by

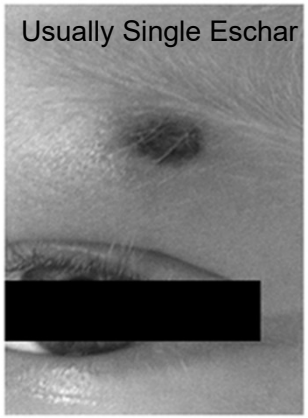
Pacific Coast tick

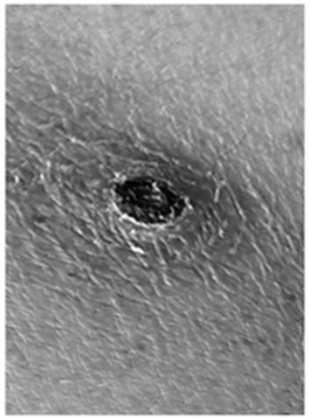
(*Dermacentor occidentalis*)

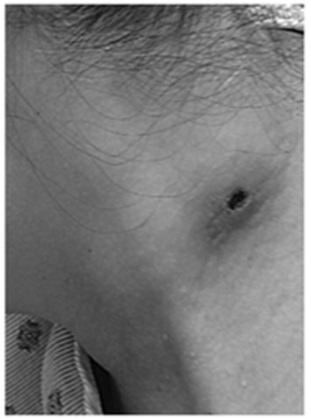
Southern Oregon → Northern Baja

Common symptoms:

- Eschar
- Fever
- Headache
- Usually mild infection







Dermacentor occidentalis

Padgett K PLOS Neg Trop Dis 2016
Paddock CF JID 2025:231(4):849-858

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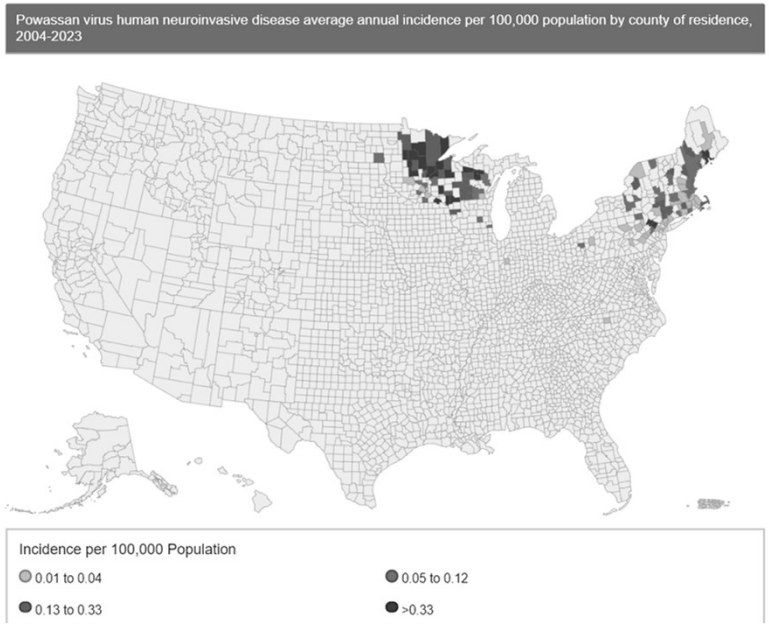
POWV: Reported cases mostly neuroinvasive
Tick-borne flavivirus infection

- Mostly present in Spring-Summer
  - But can be year-round
  - Related to nymphal Ixodes scapularis
- All ages, median 62 years, 72% male, incubation 1-5 weeks
- Clinical Syndromes
  - Neuroinvasive (90%)
    - Encephalitis (72%)
    - Meningitis (16%)
    - Other neurologic (2%)
  - Non-Neuroinvasive (10%)



- Hospitalized (90%)
- Death (11%, most > 50 years)
- Neurologic sequelae ~50%

Krow-Lucal ER. Vect Borne Zoo Dis 2018; 18(6):286-290
https://www.cdc.gov/powassan/data-maps/historic-data.html

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Range of *R. africae*
African Tick Bite Fever (green)

Range of *R. conorii*
Mediterranean Spotted Fever

Figure 4

Figure 4. Distribution of the cases of Mediterranean spotted fever (MSF) in the world and incidence of the disease in countries where MSF is endemic.

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Rovery, EID 2008;14(9)

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Typhus: Two Forms

	Epidemic	Endemic
Organism	***R. prowazekii***	***R. typhi***
Vector	Louse (body>>head)	Flea (rat, cat)
Who	War refugees, crowded conditions/poor hygiene	Worldwide (U.S. Southern California, Texas, Hawaii)
Severity	Lethal	Usually milder, some fatalities
Treatment	Tetracycline Doxycycline (preferred) Chloramphenicol	Tetracycline Doxycycline
Prevention	Boil clothes; delouse (malathion, permethrin)	Flea prevention (cats, domestic animals) Reduce rodent population
Recrudesce	Brill-Zinsser Disease (years-decades)	None known

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Human Monocytic Ehrlichiosis (HME)

E. chaffeensis

Vector: Lone star tick

Rash: ~30%

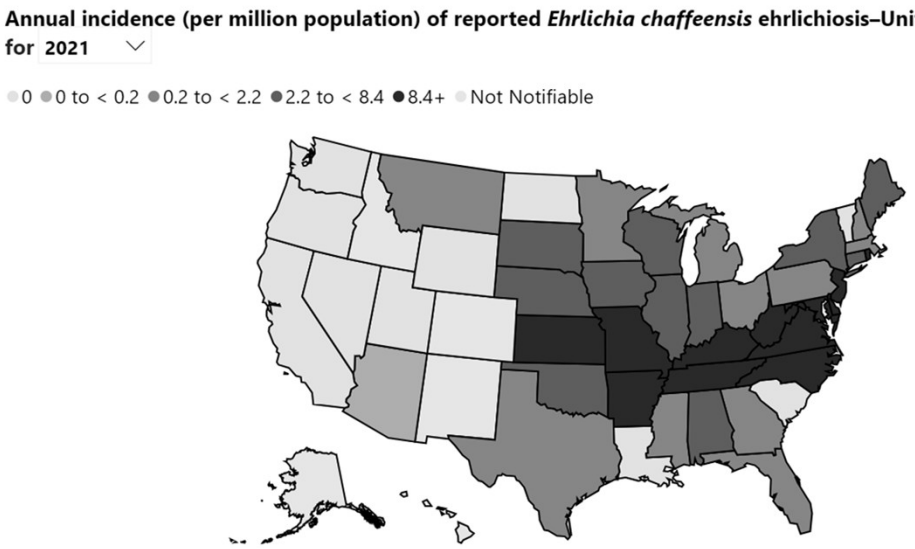
- Maculopapular or petechial

Labs: LFTs ↑, leukopenia, thrombocytopenia

Mortality: 2.7%

Diagnosis

- PCR
- Morulae (2-38%)
- Serology: acute/convalescent
- Treatment: doxycycline



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Source: CDC https://www.cdc.gov/ehrlichiosis/data-research/facts-stats/index.html (accessed 6/22/24)

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Human Granulocytic Anaplasmosis

Anaplasma phagocytophilum

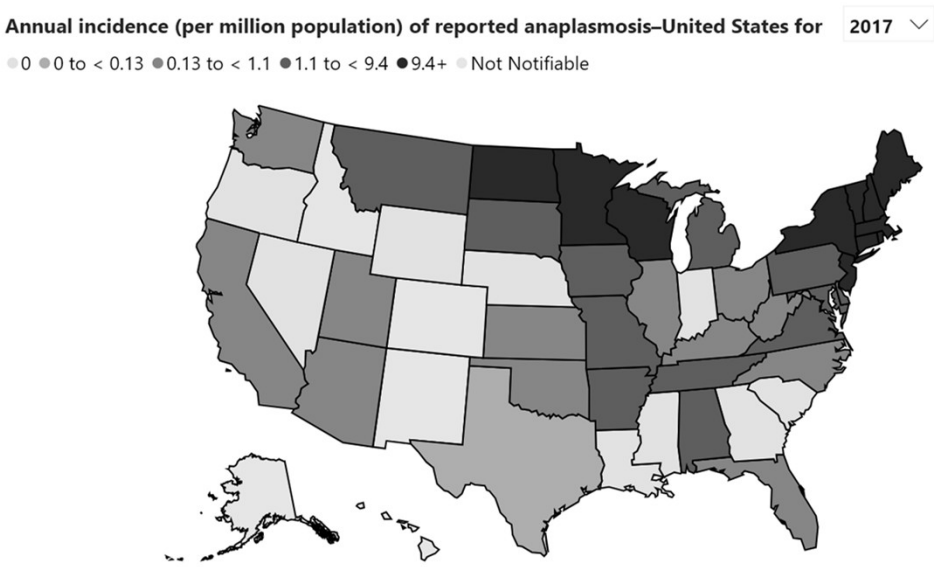
Vector: *Ixodes scapularis*

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 *E. chaffeensis* may account for much of Southern state representation

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Source: CDC https://www.cdc.gov/anaplasmosis/hcp/statistics/index.html (accessed 6/22/24)

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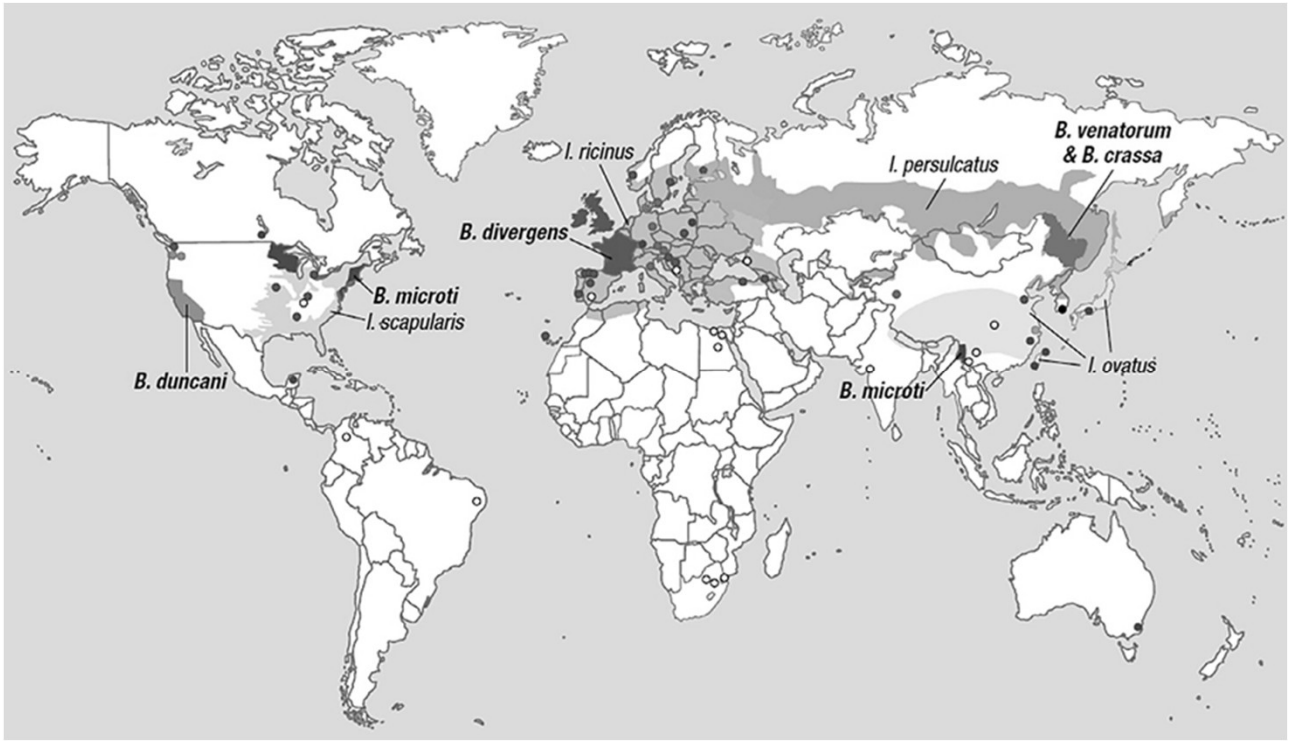
Babesia spp: Global



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Vannier et al, NEJM 2012 366;2397

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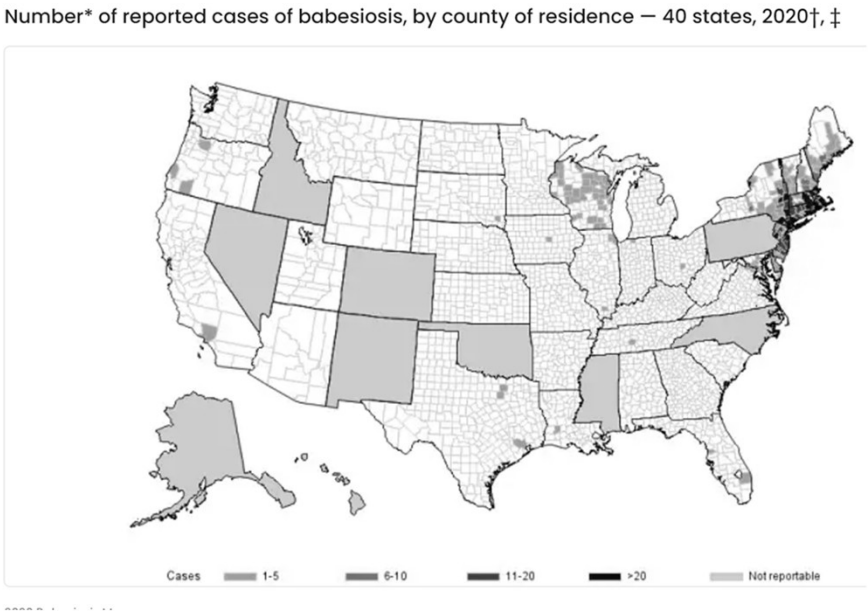
Babesia in the US



- Not reportable in all states
- Occurs within Lyme disease geography, but is more limited
- Vector:
  - *B. microti* → *Ixodes scapularis*
  - *B. duncani* → *Dermacentor albipictus*
    - (likely, west coast only)
    - < 20 documented cases
- 1500-2500 cases/yr

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https://www.cdc.gov/babesiosis/maps-graphs (accessed 7/20/26)

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Colorado Tick Fever

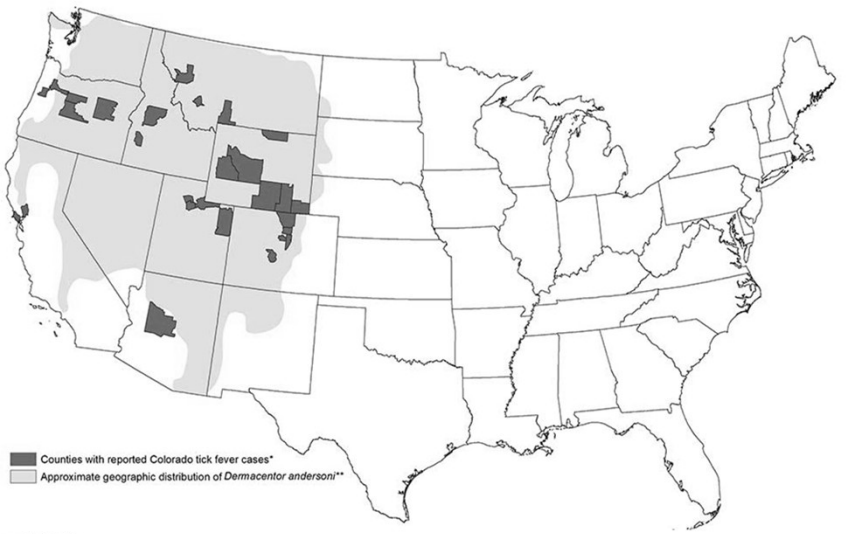
Transmission *D. andersoni*
- 4,000-10,000 feet

Agent: Coltivirus

Sx: range from
- Mild febrile flu-like illness
  - May include rash: maculopapular or petechial
- Rare: severe illness multi-system, neuroinvasive disease

Labs:
- ↓ WBC, atypical lymphocytes
- ↓ plt

Dx: samples to state lab, some commercial lab testing
- Not a reportable illness



Diagnostic Testing

Preliminary diagnosis of Colorado tick fever (CTF) is based on signs and symptoms, places and dates of travel, activities, and history of potential tick exposure. Acute samples should be tested by reverse-transcriptase polymerase chain reaction (RT-PCR) to detect viral RNA as antibody production is delayed until 14–21 days after onset of symptoms.

Timing of specimen collection	Specimens	Preferred Test
<14 days after symptom onset	Serum (CSF if suspected CNS involvement)	RT-PCR for viral RNA
≥14 days after symptom onset	Serum (CSF if suspected CNS involvement)	Antibody testing*; consider RT-PCR for samples from days 14-21

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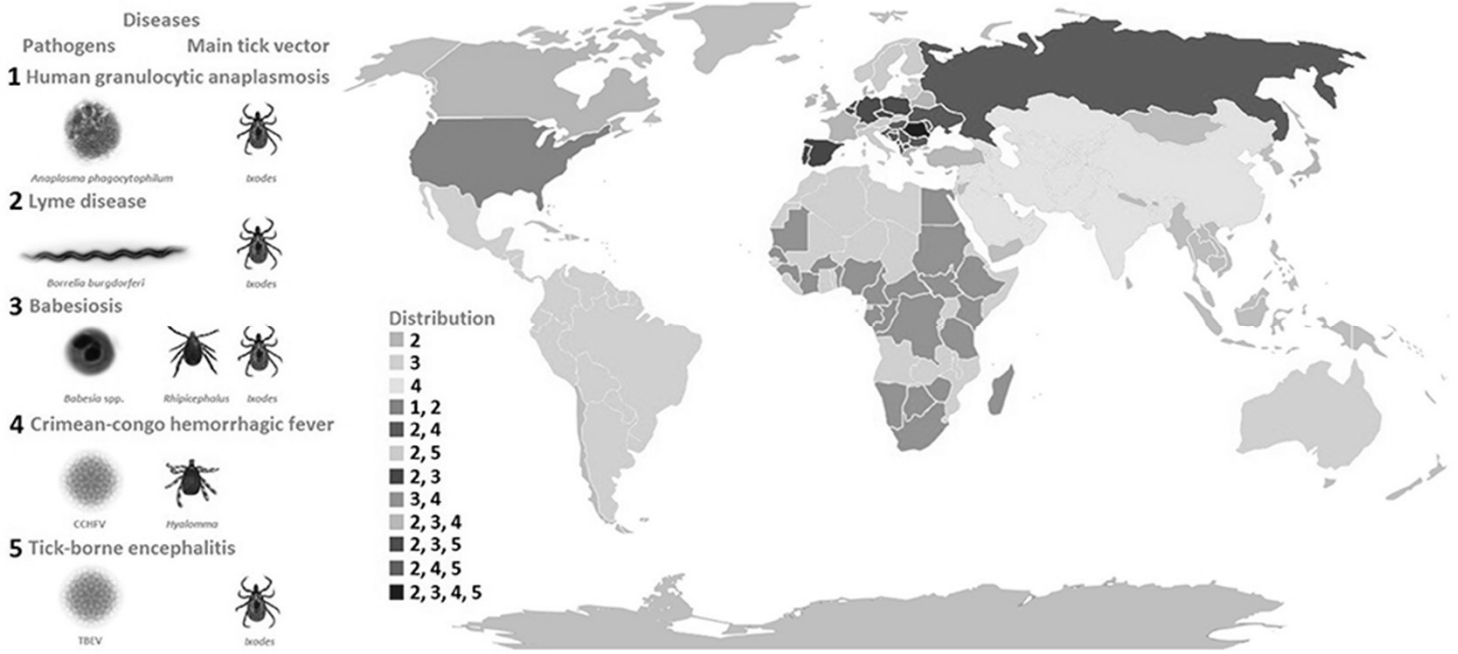
But Wait: There's More (#4) and More (#5)



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Front Cell Infect Microbiol, 2017;7:114

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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-like)	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 (Rare)	Yes	Cytopenias Transaminitis
Babesiosis	*B. Microti*	Ne, Ny, Ma, Mw	No	No	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 (Single)	Yes (V)	No	Mouse Exposure
Scrub Typhus	*O. Tsutsugamushi*	India, Asia, N. Australia	Yes	Yes	Yes	Serious

C	Central
EM	Erythema Migrans
HGA	Human Granulocytic Anaplasmosis
HME	Human Monocytic Ehrlichiosis
MA	MidAtlantic
MW	Mid-West
N	North
NE	New England
NY	New York
RMSF	Rocky Mountain Spotted Fever
S	South
SC	South Central
SE	Southeast
STARI	Southern Tick Associated Rash Illness
TBRF	Tick-borne Relapsing Fever
V	Vesicular
W	West

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Sunday, August 23, 2026

17

GI Infections
Part I

James Platts-Mills, MD

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GI Infections Part 1

James A. Platts-Mills, MD
University of Virginia

8/2/2026

Disclosures of Financial Relationships with Relevant Commercial Interests

- None

Question #1

- The morning after families had arrived at a camp for a week-long retreat, approximately one-third of participants had developed nausea (65%), vomiting (44%), abdominal cramps (85%) and diarrhea (94%) during the night.
- The night prior, they shared a meal which consisted of a casserole containing macaroni, frozen mixed vegetables, ground beef, turkey, and gravy.
- The mean onset of symptoms was 11 hours after the meal. All affected persons were substantially improved within 24 hours after onset and there were no secondary cases.

Which one of the following is most likely responsible for this outbreak?

A. *Staph aureus*
B. *Clostridium perfringens*
C. Enterotoxigenic *E. coli*
D. *Listeria monocytogenes*
E. Norovirus

Major Gastrointestinal Illness Syndromes

Food poisoning: starts < 24 hours from exposure, short duration, causes are *Staph aureus* toxin, *B. cereus* toxin, *Clostridium perfringens*

Watery diarrhea/vomiting: > 24 hours after exposure, lasts for a few days to a week: viral etiology most likely but differential remains broad esp. *diarrheagenic E. coli, Salmonella, Campylobacter*

Colitis/Dysentery: decreased volume, increased frequency, abdominal pain and cramping, tenesmus, bloody stools: *Campylobacter/Shigella* (Fever + blood), *Yersinia/Salmonella* (Fever), Shiga toxin-producing *E. coli* (Blood), *E. histolytica* (Blood + fever with liver abscess only)

Persistent diarrhea (>14 days duration): *Cryptosporidium, Giardia*, broader differential in immunocompromised patients (including norovirus)

Diarrhea + severe systemic manifestations (high fever, rigors, severe abdominal pain, headache, sepsis): consider invasive *Salmonella, Listeria, Campylobacter*

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Question #2

- An outbreak of illness was reported among approximately 50 persons eating at an area restaurant.
- The illness consisted of nausea (97%), vomiting (97%), abdominal cramps (86%), chills (78%), muscle aches (67%), fever (64%), headache (61%) and watery diarrhea (58%).
- The median incubation period was 31.3 hours; one person was hospitalized and 10 sought medical care. The illness lasted approximately 48-72 hours.

What is the most likely cause of the outbreak?

A. Norovirus
B. Shiga toxin-producing E. coli 0157:H7 (STEC)
C. Campylobacter
D. Enterotoxigenic E. coli (ETEC)
E. Pre-formed Staphylococcus aureus enterotoxin

Major Gastrointestinal Illness Syndromes

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Question #3

- A previously healthy 30-year-old male went to India for a one-week work trip and developed diarrhea and fever on the fifth day of travel.
- After 36 hours of watery diarrhea, they experience increasing abdominal pain and frequent small-volume bowel movements containing blood and mucous.

Which of the following would be the most appropriate empiric therapy for this patient?

A. Ciprofloxacin
B. Azithromycin
C. Nitazoxanide
D. No antibiotic therapy recommended
E. Rifaximin

Question #4

- A 45-year-old male with no past medical history develops watery diarrhea 4 days into a two-week trip to South Asia.
- He has had to limit his activities but is able to eat and drink and has access to a bathroom in his hotel room.

Which of the following would be the most appropriate empiric therapy for this patient?

A. Ciprofloxacin
B. Azithromycin
C. Nitazoxanide
D. No antibiotic therapy recommended
E. Rifaximin

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Empiric Therapy for Traveler's Diarrhea (IDSA Guidelines)

- ***Recommendation:*** Do **not** treat most cases of traveler's diarrhea – reserve treatment for **severe diarrhea** (incapacitating/completely prevents planned activities and/or dysentery) or for **high-risk patients**
- ***Rationale:*** Benefit (reduction in duration of diarrhea several days to one or two days) is no worth the drawbacks (cost, potential side effects, and promotion of bacterial resistance)
- If treating, favor **azithromycin** or **rifaximin** (but not if features of invasive disease) >> ciprofloxacin due to resistance and adverse effect profile

Question #5

- A 38-year-old male presents to a clinic in Ohio in mid-July with a 3-week history of watery diarrhea, severe fatigue, abdominal cramping, and an 8-pound weight loss.
- He describes a week of explosive watery diarrhea followed by intermittent symptoms over the subsequent two weeks. He denies recent international travel.
- He reports eating at a national fast-food chain during a recent road trip through the Midwest.
- A routine stool ova and parasite (O&P) examination ordered by his primary provider last week was negative, but a multiplex gastrointestinal PCR panel is positive for *Cyclospora cayetanensis*.

Which is the best choice of therapy for this patient?

A. Metronidazole
B. Nitazoxanide
C. Trimethoprim-sulfamethoxazole
D. No antibiotic therapy recommended
E. Ciprofloxacin

High-yield Points on Antibiotic Therapy for Diarrhea

- **No antibiotic therapy**: Mild-moderate disease in immunocompetent patients with *Salmonella, Campylobacter*, diarrheagenic *E. coli* and all shiga-toxin producing *E. coli* infections
- **Azithromycin and ciprofloxacin**: Treatments of choice for mild-moderate *Shigella, Campylobacter* (dysentery), *Salmonella* (>50, valve disease, severe atherosclerosis)
- **In hospitalized patients/severe disease**, targeted therapy is typically ceftriaxone (*Shigella, Salmonella, Yersinia*) or meropenem (*Campylobacter*)
- **Trimethoprim-Sulfamethoxazole**: Treatment of choice for mild-moderate *Yersinia enterocolitica, Aeromonas, Plesiomonas, Cyclospora*
- **Doxycycline**: Treatment of choice for *Vibrio*
- **Ampicillin**: Treatment of choice for *Listeria*

Question #6

- A 35-year-old female presents for a post-travel evaluation six weeks after return from a trip to Costa Rica. During travel, she had fever and diarrhea and self-administered azithromycin 500mg PO x 3 days.
- Since returning, she has had intermittent abdominal pain, bloating, and loose stools.
- A multiplex PCR panel including common bacteria, viruses, and intestinal protozoa is negative.

Which of the following would be the most appropriate next step in management for this patient?

A. Serologic testing for Celiac disease
B. Referral for endoscopy
C. Initiate treatment with nitazoxanide
D. Reassurance and expectant management
E. Modified acid-fast stain of a stool sample

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Post-infectious Irritable Bowel Syndrome

- ~10-30% of patients will develop IBS after acute gastroenteritis, which can be persistent, in particular after bacterial diarrhea (*Campylobacter, Shigella, Salmonella*).
- Can persist for months to years but generally follows a progressively improving course.
- Treatment options include rifaximin, low FODMAP diet, loperamide, anti-depressants – questions related to IBS management probably out of bounds for ID boards!

Role of Diagnostics (IDSA Guidelines)

Recommendation: Consider diagnostic testing (NAAT panels preferred) for

- Diarrhea accompanied by 1) **fever**; 2) **bloody or mucoid stools**; 3) **severe abdominal pain/cramping/tenderness**; 4) **sepsis**; 5) **immunocompromised patients** (include testing for *Cryptosporidium, Cyclospora/Isospora*, microsporidia, MAC, CMV)
- Diarrhea + concern for an **outbreak** or if in a population with public health implications (e.g., **food workers, healthcare workers**)

A Typical GI Pathogen Panel (Additional Stool-based Diagnostic Needed)

BACTERIA:
- *Campylobacter (jejuni, coli, and upsaliensis)*
- *Clostridium difficile* (toxin A/B)
- *Plesiomonas shigelloides*
- *Salmonella*
- *Yersinia enterocolitica*
- *Vibrio (parahaemolyticus, vulnificus, and cholerae)*
- *Vibrio cholera*

DIARRHEAGENIC E. COLI/SHIGELLA:
- *Enteroaggregati E. coli* (EAEC)
- *Enteropathogenic E. coli* (EPEC)
- *Enterotoxigenic E. coli* (ETEC) *lt/st*
- *Shiga-like toxin-producing E. coli* (STEC) *stx1/stx2*
- *E. coli* O157
- *Shigella/Enteroinvasive E. coli* (EIEC)

PARASITES:
- *Cryptosporidium*
- *Cyclospora cayetanensis*
- *Entamoeba histolytica*
- *Giardia lamblia*
- Microsporidia (*E. bieneusi, E. intestinalis, etc.)*
- *Cystoisospora belli*

VIRUSES:
- Adenovirus F40/41
- Astrovirus
- Norovirus GI/GII
- Rotavirus A
- Sapovirus (I, II, IV, and V)

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Question #7

- A 24-year-old male presents to the emergency room with several days of watery diarrhea, nausea, and vomiting. He returned three days prior from a weeklong trip to India.
- Vital signs are T 37.5C, BP 80/52, HR 118, O2 98%.
- Physical examination is notable for dry mucous membranes.
- Labs are notable for HCT 50, Na 144, K 3.0, HCO3 12, BUN 41, Cr 1.2

What is the most likely cause of his illness?

A. Campylobacter jejuni
B. Rotavirus
C. Vibrio cholerae
D. Shigella sonnei
E. Adenovirus Type F

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Question #8

- A 42-year-old male presents to the emergency room with fever, abdominal pain, and constipation. He returned from a business trip to India two weeks prior and was in his usual state of health until the onset of fever and fatigue 4 days prior to presentation.
- His fevers worsened and were accompanied by abdominal pain, poor appetite, and constipation.
- Blood cultures revealed a Gram-negative rod.

What is the most likely cause of his illness?

A. *Campylobacter jejuni*
B. Plasmodium falciparum
C. *Salmonella Typhi*
D. *Shigella flexneri*
E. Enteroinvasive *E. coli*

To be continued…

Key Clues And Distinguishing Clinical Features For Less Common Causes Of GI Illness In Travelers

Cholera

Exposures: travel to South/Southeast Asia > East Africa

Clinical manifestations: Rice water stools, severe dehydration

Lab findings: Hemoconcentration, azotemia, acidosis, hypokalemia

Enteric fever (*Salmonella Typhi >> Paratyphi)*

Risk factors: Absence of pre-travel vaccination (or oral typhoid vaccine not taken appropriately) + travel to South/Southeast Asia > Africa > Americas (Paratyphi)

Clinical manifestations: Fever, abdominal pain, and constipation>>diarrhea

Lab findings: Elevated liver enzymes, blood culture with GNR

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A Typical GI Pathogen Panel
(Additional Stool-based Diagnostic Needed)

BACTERIA:
- *Campylobacter (jejuni, coli, and upsaliensis)*
- *Clostridium difficile* (toxin A/B)
- *Plesiomonas shigelloides*
- *Salmonella*
- *Yersinia enterocolitica*
- *Vibrio (parahaemolyticus, vulnificus, and cholerae)*
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- *Enteropathogenic E. coli* (EPEC)
- *Enterotoxigenic E. coli* (ETEC) *lt/st*
- *Shiga-like toxin-producing E. coli* (STEC) *stx1/stx2*
- *E. coli* O157
- *Shigella/Enteroinvasive E. coli* (EIEC)

PARASITES:
- *Cryptosporidium*
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- *Entamoeba histolytica*
- *Giardia lamblia*
- Microsporidia (*E. bieneusi, E. intestinalis, etc.)*
- *Cystoisospora belli*

VIRUSES:
- Adenovirus F40/41
- Astrovirus
- Norovirus GI/GII
- Rotavirus A
- Sapovirus (I, II, IV, and V)

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Sunday, August 23, 2026

18

GI Infections
Part II

James Platts-Mills, MD

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GI Infections Part 2

James A. Platts-Mills, MD
University of Virginia

8/2/2026

Disclosures of Financial Relationships with Relevant Commercial Interests

- None

Question #1

- A 43-year-old female presents with several days of watery diarrhea and one day of gross blood in her stools.
- Two other members of her family have similar symptoms. None of the family members have had a fever and she is afebrile on exam.
- Laboratory studies are notable for a hematocrit of 28%, platelets of 80,000 per ml and creatinine 2.4 mg/dl.

In addition to stool-based diagnostics, which of the following would be the most appropriate next step in management for this patient?

A. Start IV Ceftriaxone
B. Withhold antibiotic therapy
C. Start PO Azithromycin
D. Start IV Meropenem
E. Start PO Vancomycin

WITHOLD Antibiotics for Suspected and Confirmed STEC
(IDSA Guidelines)

Recommendations:

1. Empiric treatment of bloody diarrhea should be limited to **young infants**, patients with **fever + blood with high suspicion for *Shigella***; and patients with **recent international travel + high fever or sepsis**
2. Antimicrobial therapy for confirmed STEC should be **avoided** (STEC O157 / unknown) or is **debatable** (non-O157 STEC)

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Question #2

- A 21-year-old male was admitted to the hospital with fever and abdominal pain.
- The abdominal pain, which developed over the course of 48 hours, was initially generalized and then localized to the right lower quadrant. He was febrile and had abdominal guarding.
- His white blood cell count was elevated. Abdominal ultrasound revealed a normal appendix and multiple enlarged mesenteric lymph nodes.

Which of the following exposures was most likely to be the cause of his illness?

A. Consumption of undercooked chicken
B. Recent purchase of a pet lizard
C. Consumption of shellfish
D. Consumption of undercooked pork
E. Consumption of unwashed raspberries

Common Exposure/Pathogen Associations

Exposure	Pathogen
Water	Cryptosporidium/Giardia
Custard	Staph aureus toxin
Hamburger	Shiga toxin-producing E. coli (STEC)
Leftover meat that is improperly stored and insufficiently reheated	Clostridium perfringens toxin
Undercooked chicken/Handling eggs	Campylobacter/Salmonella
Produce (esp. raspberries, lettuce)	Cyclospora
Shellfish	Vibrio/norovirus
Undercooked pork/pork intestines	Yersinia
Turtles/Lizards/Frogs	Salmonella
Unpasteurized milk/cheese, deli meats	Listeria

Question #3

- A nursing home experiences an outbreak of diarrhea with fever among long-term residents.
- Over the course of several weeks, additional residents develop illness one to three days after contact with illness cases.

Which one of the following organisms is the most likely cause?

A. *Salmonella enterica* (non Typhi)
B. *Vibrio cholerae*
C. *Shigella sonnei*
D. Enterotoxigenic *E. coli* (ETEC)
E. Toxin-producing strain of *Staph aureus*

Infectious Doses for Common Enteric Pathogens

10^{5-8}	10^{1-3}
Diarrheagenic *E. coli*	*Shigella*
V. cholerae	*Giardia lamblia*
Campylobacter	*E. histolytica*
	Cryptosporidium
	Viruses
Only from food, water, other non-human sources	...also can be spread person to person

(Salmonella is complicated, but in general *S. Typhi* and *S. Paratyphi* can be person to person, whereas non-typhoidal *Salmonella* usually are not)

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Question #4

- A 32-year-old nurse providing direct patient care in an inpatient oncology unit is diagnosed with Shigella sonnei gastroenteritis after developing fever, abdominal cramps, and bloody diarrhea.
- She is treated with a 3-day course of oral ciprofloxacin, and her symptoms completely resolve 48 hours after starting therapy.
- She completes her full antibiotic course and feels well.

Which of the following is sufficient to allow her to return to providing direct patient care?

A. Resolution of symptoms for at least 24 hours
B. Completion of the antibiotic course
C. Two negative stool cultures
D. Two consecutive negative PCR tests
E. Symptom resolution and at least 24 hours of antibiotic therapy

Return to Work Precautions for GI Infections

Public health guidance, typically at the local or state level, is provided for return to work for high-risk individuals, including **healthcare workers**, **food handlers**, **childcare staff**, **children attending daycare**, and **residents/staff in long-term care facilities**

Pathogens typically requiring a **microbiologic test of clearance** include *Shigella*, Shiga-toxin producing *E. coli*, *Salmonella* Typhi/Paratyphi, *V. cholerae*

Pathogens typically requiring **symptom resolution only** include *Campylobacter*, non-typhoidal *Salmonella*, *C. difficile*

Hepatitis A is typically cleared based on duration of symptoms alone (7 days after onset of jaundice, or 14 days after symptom onset if no jaundice)

Question #5

- An 81-year-old female was admitted to the hospital with vomiting, diarrhea, fever, and headache. She initially developed vomiting, diarrhea, and fever one week prior to presentation.
- The gastrointestinal symptoms resolved over the course of three days, but the fever continued and was accompanied by a progressive headache and dizziness. Her neurologic exam was notable for ataxia.
- A stool GI PCR panel was negative. An MRI revealed hyperintense lesions in the cerebellum on T2-weighted imaging. CSF analysis revealed a mild pleocytosis, mildly elevated protein, normal glucose, and a negative Gram stain. CSF and blood cultures are pending.

What type of organism is most likely to be isolated from CSF and/or blood cultures?

A. A Gram-positive coccus
B. A Gram-negative coccobacillus
C. A Gram-positive bacillus
D. A Gram-negative bacillus
E. A Gram-negative coccus

Listeriosis

***Exposures*: unpasteurized milk/cheese**, **deli meats**

***Risk factors for neuroinvasive disease*: extremes of age** (pregnancy is a risk factor for listeriosis and *Listeria* bacteremia, but **not** for encephalitis)

***Clinical manifestations*: Focal neurologic signs** including cranial nerve abnormalities, ataxia, tremors, hemiplegia, deafness

***Lab findings*:** CSF findings are variable but **lymphocytic pleocytosis** is distinctive among non-tuberculous bacterial CNS infections; Gram stain with **short GPRs**

***Imaging findings*:** MRI with abnormal signal intensity or enhancement in the **brainstem**, particularly the pons and medulla, as well as the **cerebellum**

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Question #6

- A 75-year-old male with a history of atherosclerosis presents with persistent fever.
- Two weeks prior to presentation, he developed watery diarrhea and fever. The diarrhea resolved but the fever persisted and was accompanied by chills, night sweats, and a headache.
- He denied bone or joint pain. No murmur was present on exam.
- Multiple sets of blood cultures yielded *Salmonella* typhimurium. Antibiotic therapy was initiated and repeat blood cultures after 48 hours remained positive.

What is the next best diagnostic test?

A. Stool GI PCR panel
B. Lumbar puncture
C. CTA Chest
D. MRI Brain
E. Bone marrow biopsy

Invasive Salmonella Infections

***Exposures*: Eggs, reptiles**

***General risk factors for invasive disease*:** Extremes of **age**, immunocompromised states including **HIV**

Most common focal complications (and specific risk factors): Endovascular infection (**valvular disease, prosthetic valves/grafts or severe atherosclerosis**), osteomyelitis/septic arthritis (**sick cell disease**)

***Clinical manifestations*:** Fever, chills, night sweats, arthritis

***Lab findings*:** Blood culture with GNRs

***Imaging findings for endovascular infection*:** TTE with evidence of endocarditis, CTA/MRA with aneurysm or soft tissue enhancement, PET/WBC scan with focal uptake

Question #7

- A 35-year-old male presents to the emergency department 30 minutes after eating grilled tuna at a seafood restaurant. He complains of facial flushing, headache, palpitations, and a burning sensation in his mouth.
- In the emergency room, he begins to have diarrhea. His vital signs are temperature 37.0ºC (98.6ºF), heart rate 108/min, blood pressure 138/84 mm Hg, and respiratory rate 18/min. On physical examination, he is diaphoretic and visibly flushed but in no acute distress. Lung examination is normal.
- His symptoms improve significantly after administration of antihistamines.

Which of the following is the most likely cause of this patient's symptoms?

A. Ciguatera toxin
B. Tetrodotoxin
C. Scombroid poisoning
D. Staphylococcal food poisoning
E. Botulism

Rapid-onset Fish Poisoning Syndromes

***Scombroid*:** histamine-related symptoms (**flushing**, **perioral burning**, **rash** on face/chest, **diarrhea**) after consumption of fish (e.g., tuna, mackerel), often with a **peppery** or **spicy** taste

***Paralytic shellfish poisoning*:** Severe syndrome of numbness, tingling, vomiting **progressing** to weakness, ataxia, and paralysis (including respiratory failure) after consumption of **shellfish**

Tetrodotoxin poisoning: Perioral paresthesias, nausea/vomiting, muscle weakness, paralysis (including respiratory failure) after consumption of **pufferfish**

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Delayed-onset Fish Poisoning = Ciguatera

Constellation of findings starting as early as **3 hours** after consumption of contaminated reef fish (e.g., barracuda, eel), including **gastrointestinal** (vomiting/diarrhea), **neurologic** (peri-oral paresthesias, metallic taste, cold/hot reversal, blurred vision), **cardiovascular** (bradycardia, heart block).

Neurologic findings can be persistent (**weeks to months**)!

Thank you!

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Sunday, August 23, 2026

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Lyme Disease

Paul Auwaerter, MD

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Lyme Disease
aka Lyme borreliosis

Paul G. Auwaerter, MD
Johns Hopkins University School of Medicine

8/6/2026

Disclosures of Financial Relationships with Relevant Commercial Interests

- Research: Pfizer (investigational Lyme disease vaccine)
- Consulting: medical-legal, Tonix Pharmaceuticals, Tarsus Pharmaceutics

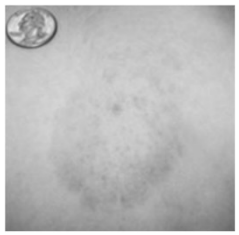
Question #1

A 56-year-old man from southern Missouri
Onset in July:

- Myalgia and malaise
- Itchy rash x 2d at tick bite site 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

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STARI
Southern Tick-associated Rash Illness

CDC

- Rash variable
  - Expansile from the site of
- Lone Star tick bite
  - Similar to erythema migrans
- Usually, a single lesion
- Multiple described
- Maybe Bull's eye-like

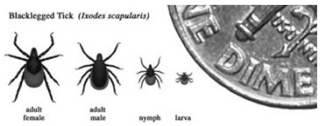
STARI

- No infection yet convincingly documented
  - *B. lonestari* (single case)
  - CDC does not support as cause of STARI
- Symptoms can include fever, headache and musculoskeletal pains
- *B. burgdorferi* tests, including serology negative
- No diagnostic test for STARI. Clinical diagnosis
- **Likely accounts for some reported Lyme disease cases in non-endemic states**
- Unclear if doxycycline is needed, typically given
- No sequelae

James AM, J Infect Dis 2001;183:1810
Wormser GW. Clin Infect Dis 2005;41:958-65
CDC, STARI (accessed 5/18/25)

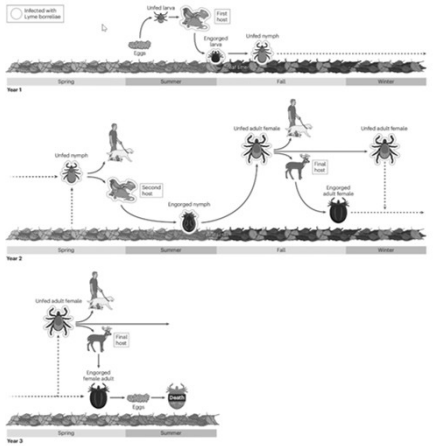
B. Burgdorferi
Vector-borne Infection

- Spirochetal infection due to *Borrelia burgdorferi* (Bb)
- Tick-borne disease
  - Ixodes species
  - In North America
    - *Ixodes scapularis* (mostly)
      - Black-legged tick
    - *Ixodes pacificus* (uncommon)
      - Western black-legged tick
- Not known as an 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



Ixodes spp.
Tick Life Cycle +/- *Borrelia burgdorferi*

Four stages over 2+ years:
Feeding:
- Larvae and nymphs → mammals, birds and lizards
- Adults → deer

Strle, Nat Rev Dis Prim 12(15) 2026

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Borrelia burgdorferi sensu lato

USA

- *Borrelia burgdorferi*
  - Geographically localized
    - 90% of cases in 15 states + DC
    - Estimates 476,000 cases/yr
    - Especially coastal, lake and river environs
      - New England
      - Mid-Atlantic
      - Upper Midwest

Europe (+ other genospecies)

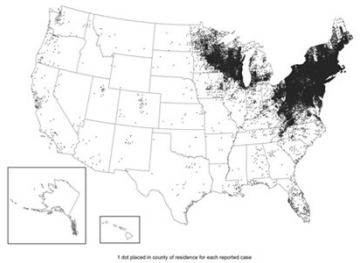
- *Borrelia afzelii* > *B. garinii* >> *Borrelia burgdorferi* sensu stricto, *B. bavariensis*
- Occasionally others
- Genus name: taxonomists prefer *Borreliella*
  (to distinguish from relapsing fever *Borrelia spp*.)

Most Common Vector-borne Infection in US: A Mostly Regional Disease

Newer States

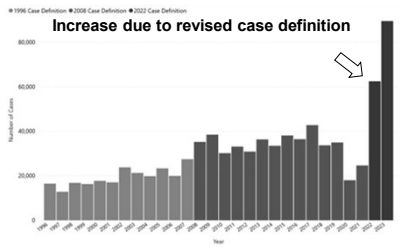
Ohio
Michigan
Indiana
Iowa
Virginia
North Carolina

Reported Cases of Lyme Disease – United States, 2023



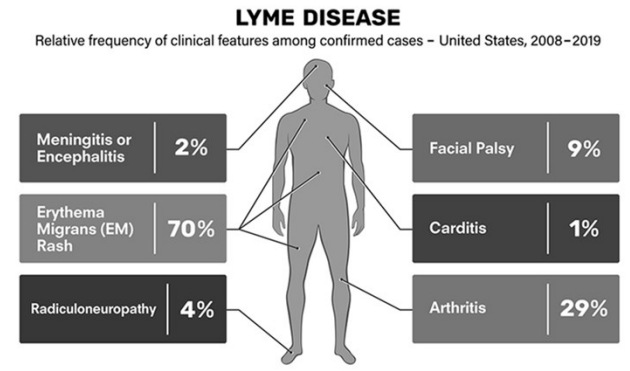
Source: CDC
Accessed 7/18/26

CDC Case Definition (Revised 2020*)



*First applied in the 2022 report. CDC graph last updated 2/11/2025
As of 2022, high-incidence jurisdictions (15): CT, DE, DC, ME, MD, MA, MN, NH, NJ, NY, PA, RI, VT, VA, WV and WI.

- 2022-3 ↑ Lyme disease cases compared to '17-'19
- High incidence states* report based on serology only (w/o clinical information)
- Low-incidence states* require clinical information



(Based on 62% of 311,561 confirmed cases reported-probably favoring later presentations, Source CDC)
http://www.cdc.gov/lyme/stats/chartstables/casesbysymptom.html

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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

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.

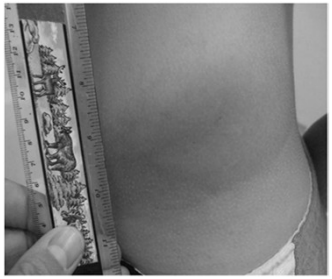
Which of the following is true?

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 standard 2-tier serology will likely confirm Lyme disease
D. Whole blood B. burgdorferi PCR is superior to serology in early infection
E. Tick should be submitted for detection of B. burgdorferi by PCR

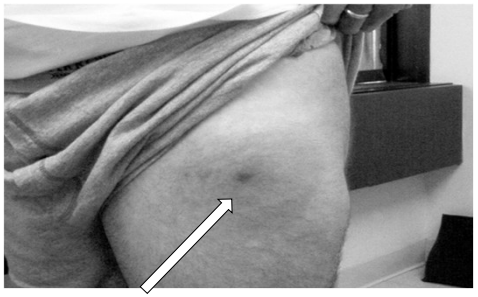
Early, Localized LD: Erythema migrans

Classic: "bull's eye"
With central clearing upon expansion

Most common: homogeneous, pink-red ovoid



Typical Erythema Migrans



Punctum:
site of bite

Lesions: occur typically below neck and above knees & elbows

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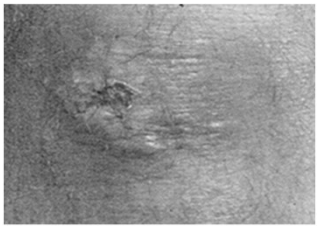
Spider Bite?

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
  - 5 cm = 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

If suspicious for Lyme disease, and serology negative, repeat in 2-4 wks

- Neuroborreliosis
  - Aseptic meningitis
    - Lymphocytic predominance
  - Cranial nerve palsy
    - CN VII (facial)
      - Most common (if isolated, no LP required)
      - Bilateral CN VII may occur
      - Other CN palsies: seen less
        - e.g., III, VI, VIII
  - Radiculoneuritis
  - Mononeuritis multiplex

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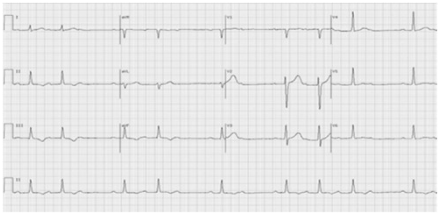
Diagnosis:
Facial Palsy

- 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 therapy2
  - 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
    - Hospitalize/telemetry for high-grade AV block or PR ≥300 ms
- 3° most commonly identified since symptomatic
  - May need temporary pacer
  - Complete heart block usually resolves within several days of antibiotic; lesser block may take weeks

Question #3

56M Long Island, NY with R knee pain and swelling x 3 weeks. Thought this was a wrenched knee from yardwork.

No fever, rash, tick bite or Lyme disease history. No prior arthritis history. (-) new sexual contacts

PMH: HTN, hyperlipidemia

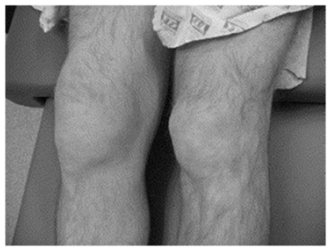
PE: afebrile, mildly warm knee, moderate effusion, reduced ROM

Labs: nl CBC

Which of the following is usually true for Lyme arthritis?

A. Knee swelling doesn't remit without arthrocentesis
B. *B. burgdorferi* PCR synovial fluid ~ 100% sensitivity
C. Synovial fluid WBCs >50,000 cells/mL
D. Synovial fluid *B. burgdorferi* culture ~100% sensitivity
E. Serum *B. burgdorferi* 2-tier testing ~100% sensitivity

Late Lyme Disease 1:
Lyme Arthritis



- Recurrent mono- or oligo-arthritis
  - Knee most common
    - Large, cool effusions
    - Baker's cysts may develop
  - Other large joints possible + TMJ
- Afflicts ~30% untreated patients (historically 50-60%)
- May remit, recur in different joints over period of wks to mos w/o abx Rx

Ann Int Med 1987; 107:725
Lantos, CID Nov 30, 2020

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Late Lyme Disease 2:
Neurologic

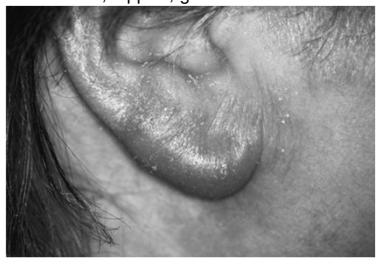
- Encephalopathy:
  - Cognitive dysfunction, objective
  - Due to systemic illness, rather than true CNS infection
- Encephalitis: rare
  - Objective neurological or cognitive dysfunction
  - White matter changes on MRI or abnormal CSF
  - CSF: (+) lymphocytic pleocytosis, Bb antibody
- Peripheral neuropathy: rare (controversial)
  - Pain or paresthesia
  - Diffuse axonal changes on EMG/NCV

Halperin JJ. Brain 2022;145(8):2635-2647
Wormser GW. Diagn Micro Biol Infect Dis 2017;87(2):163-167

Late Lyme Disease 3:
Dermatologic

Acrodermitis chronica atrophicans (Europe)
Distal extremities most commonly seen

Borrelia Lymphocytoma (Europe)
Earlobes, nipples, genitals favored sites



Question #4

- 49F complains of four years of fatigue, headache, poor sleep and joint aches since trip to London UK
  - PMH: TAH/BSO
  - Medications: hormone replacement
  - SH: Married, accountant. Lives in central Pennsylvania. Two dogs, often sleep in bed.
  - PE: normal
  - Labs: normal CBC, ESR, TSH
    - *B. burgdorferi* serology: EIA (not done), IgM WB 3/3 bands, IgG 1/10

Question #4

What is the best recommendation at this time?

A. Doxycycline 100 mg twice daily x 14 days
B. Doxycycline 100 mg twice daily x 28 days
C. Repeat Lyme serology (two tier: EIA w/ reflex WB)
D. Borrelia burgdorferi PCR (whole blood)
E. Neither additional Lyme disease testing nor treatment

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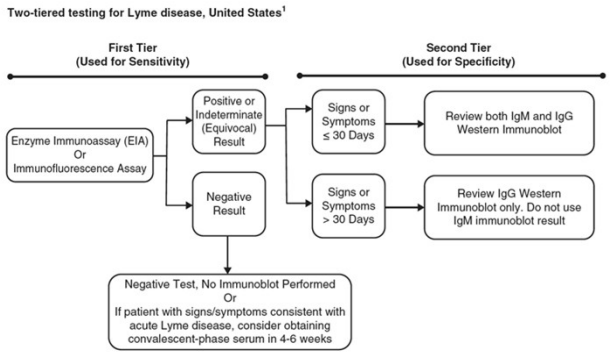
Standard Two-tier Testing (STTT)



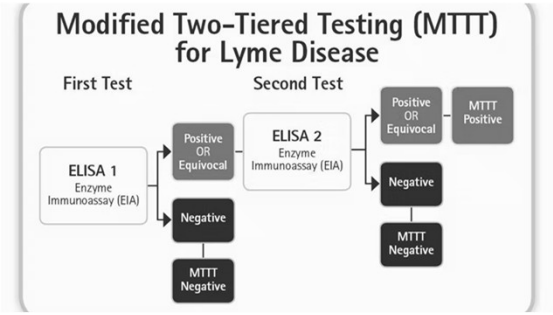
[1]Adapted from MMWR 1995

Laboratory Testing

- Standard Two tier (STTT) serology: not needed for erythema migrans
  - First: total Ab screen – ELISA or EIA (for sensitivity)
  - If positive, second tier reflexes to immunoblots (IB, for specificity)
    - IgM: ≥ 2/3 bands, use only if < 4 wks of symptoms
      - High rates false (+)
    - IgG: ≥ 5/10 bands, more reliable
      - Alternative criteria (different bands): less specific
  - Often negative in early infection (first 2-3 weeks)
  - May need acute/convalescent for confusing rashes or neuroborreliosis
  - Serology: may remain (+) for decades including IgM

MMWR 1995;44:590
Clin Infect Dis 2001;33(6):780-5

MTTT: Faster, Cheaper, Better (Early LD)



Modified Two-tier (2-EIA) vs. STTT

- Technically easy, quick
- Less cost
- Appears to provide similar sensitivity/specificity
- Better in early disease

Pooled LD USA	Standard 2-tier	Modified 2-tier	C6 only
Specificity (%)	98.3-100	98.3-100	96.5-100
Sensitivity (%) --Early LD	28-54	38-61	64-68
--Late LD	96-100	98-100	98-100

Branda et al. Clin Infec Dis 2018;66(7):1133-1139

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Diagnostics:
Lyme arthritis

- Arthrocentesis
  - Synovial fluid: inflammatory
    - 10,000-25,000 WBC average (range: 500 – 100,000)
    - PMN predominant
  - Bb PCR –non standardized
    - Sensitivity 40-96% if prior to antibiotic therapy
    - Specificity 99%
- Serology: ~100% (+) in blood
  - High titer, Bb IgG immunoblot
- Culture: rarely (+)

Arvikar, Steere: Inf Dis Clin N Am 2015;29(2):269-280

FYI: Stats on Lyme Disease Presentations and Routine Diagnostics

Table1: Sensitivity and specificity of assays for the diagnosis of Lyme disease

Assay	Specimen type	Clinical manifestation	Sensitivity (%)	Selected References	Specificity (%)	Selected References
Standard two-tiered testing	Serum	Early localized	< 40% (acute) 27% (convalescent) 61% (convalescent)	[32] [33] [97] [33] [32]	~99%	[36]
	Serum	Early disseminated	86% (carditis) 90% 42–87%	[32] [98] [99]	~99%	[98]
	Serum	Neuroborreliosis	90%	[32]	96–100%	[39]
	Serum	Late disseminated	100% (arthritis) 97–100%	[32] [99]	99–100%	[24] [39]
Modified two-tiered testing	Serum	Early localized	53% (acute) 58% (acute) 89% (convalescent) 67% (convalescent)	[37] [33] [25] [37] [33] [25]	~99% 96–100%	[36] [39]
	Serum	Early disseminated	71-86% (carditis)	[100]	96–100%	[39]
	Serum	Neuroborreliosis	98–100%	[22] [37] [100]	96–100%	[22] [37] [39]
	Serum	Late disseminated	~100% (arthritis)	[24] [100]	96–100%	[24] [39]
Polymerase chain reaction	Serum and/or skin Serum/Plasma	Early localized	64–81% 62%	[97] [101]	~100%	[102]* [103] [104]
	Serum	Early disseminated	29% (carditis)	[32]		
	CSF	Neuroborreliosis	25-38% 73%	[102]* [99]		
	Synovial fluid	Late disseminated	85% (arthritis) 83% (arthritis)	[102]* [99]		

SEE ENLARGED SLIDE FOLLOWING ENTIRE PRESENTATION

Kobayashi, Auwaerter. Inf Dis Clinics N Am Sept 2022

Common Clinical Scenarios:
Improper Use of Serology

- EIA/ELISA only, no Western blot (WB aka immunoblot)
- Ordering just WB -- w/o EIA/ELISA (total ab)
  - >50% population reactive to 1 or more antigens
- Using the IgM WB alone for symptoms > 1 month
- Serology at time of erythema migrans
- Treating tests that “stay positive [IgM or IgG]”
- Testing samples by WB other than serum
  - CSF or synovial fluid

Other Test Info

- Second-generation Ab assays: both STTT & MTTT
  - Use specific proteins, e.g., C6 or VlsE (variable major protein-like sequence expressed)
  - Offer better sensitivity and specificity than older whole-cell lysate assays
- Beware of “Lyme” specialty labs with unvalidated or poorly validated testing

Clin Infect Dis 2013;57(3):333-343.

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Lyme Disease:
Initial Regimens

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[d]	Ceftriaxone	14-21
Arthritis	Oral	Doxycycline or Amoxicillin or Cefuroxime axetil	28

[a]Further details regarding adult and pediatric dosing can be found in the 2021 Guideline.
[b]Ranges are given if available studies are insufficient to determine the optimal duration.
[c]Cefotaxime and penicillin G are alternative IV options.
[d]Parenteral therapy is used for hospitalized patients, who, with improvement, may transition to oral antibiotics to complete the treatment course.

Some key points
- 10d doxy ok for early EM
- Neuroborreliosis
  - Oral doxy = IV CTX
  - Ex. Parenchymal CNS dz
- Lyme carditis
  - Once improved → oral

Lantos et al, IDSA/AAN/ACR Lyme Guideline, CID 2021; 72(1)e1-e48

Treatment:
Late Lyme Arthritis

- Initial treatment: amoxicillin or doxycycline PO x 28d
  - If lack of response: second course orals or ceftriaxone IV x 14-28d
  - ~10% do not respond to repeated antibiotic therapy
  - Post-antibiotic Lyme arthritis
    - No viable organisms (may remain with [+] PCR)
    - Autoimmune phenomenon, associated with certain HLA DR alleles binding to OspA → strong Th1 response
  - Treatment: DMARDs, intra-articular corticosteroids, synovectomy

Lyme Disease:
Expectations Regarding Resolution

- Subjective problems, post-treatment
  - Prospective studies, treated erythema migrans

Time	Symptomatic
Erythema migrans (d0)	73%
3 months	24%
≥ 6 months	11.5% [0-40.8%]
15 years	Equivalent to general US population

Need to manage expectations

No benefit from additional antibiotics

Post-infectious syndromes not unique to LD

Wormser, et al. Ann Intern Med 2003;138:697; Wormser, et al. Clin Infect Dis 2015;61(2):244
Cerar, et al. Am J Med 2010;123:79

Randomized, Placebo-controlled Trial Scorecard for Persistent Symptoms Attributed to Lyme Disease after Initial Treatment

Longer-term abx v. placebo Subjective sx OR Encephalopathy after initial treatment	Antibiotics with Durable Effect and Clinically Significant Benefit	Antibiotics Not Effective
7 trials	0	7

Placebo effect: noted in up to 36%

No study yielded evidence of *B. burgdorferi* by culture or PCR in these patients

Klempner M, et al. NEJM 2001; 345:85 (2 studies)
Krupp LB, et al. Neurology 2003;60:1923
Oksi J, et al. Eur J Clin Micro 2007;26(8)571
Fallon BA, et al. Neurology 2008; 70:992
Sjöwall, BMC Infectious Diseases 2012; 12:186
Berende A, et al. NEJM 2016;375(13):1209-20 (PLEASE trial)

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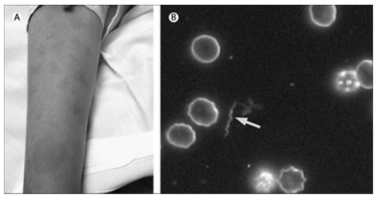
"Chronic Lyme Disease"

- 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
    - Misattributed to multiple sclerosis, ALS, Alzheimer's, autism, Parkinson's

Borrelia mayonii
Considered Part of Lyme Disease



- Ixodes scapularis transmits
- High fever may be present
- May have high spirochetemia
- Lyme serology
  - May be cross-reactive
- Dx:
  - spirochetemia
  - PCR (Mayo, ARUP)

Initial Report: 5 of 6: acute febrile illness with rash (patchy, macular)
1 of 6: 1 month knee pain/swelling
To date: seem in Minnesota, Wisconsin and New York (2025)

Pritt BS, Lancet ID 2016; 16(5):556-564
McGowan MS. OFID 2023;10(11) Oct 24
Nafiz TN, MMWR 6/4/26 75(21)271-272

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

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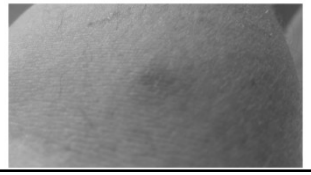
Question #6

- 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.



Which would be the best course of action?

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%)

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%]

Prophylaxis: Doxy 200 mg x 1 dose only for high-risk Ixodes *bites in an endemic area, ≥ 36 hrs attached, dose within 72 h*

JID 2001; 183:773-8; J Antimicrob Chemother 2010;65:1137-1144; N Engl J Med 2001; 345:79-84; 2020 IDSA/AAN/ACR Lyme disease Guideline

Lyme Disease: Some Pearls

- No need for serology for erythema migrans = clinical dx
- *B. burgdorferi* IgM immunoblot most common cause of misdiagnosis for patients w/ symptoms > 1 month
- Late Lyme arthritis: ~100% seropositive (IgG)
  - No evidence that seronegative Lyme exists in patients with long-term symptoms
- Lab evidence of LD essential unless hx of EM exists
- Prolonged antibiotic treatment doesn't improve resolution of subjective symptoms

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FYI: Stats on Lyme Disease Presentations and Routine Diagnostics

Table1: Sensitivity and specificity of assays for the diagnosis of Lyme disease

Assay	Specimen type	Clinical manifestation	Sensitivity (%)	Selected References	Specificity (%)	Selected References
Standard two-tiered testing	Serum	Early localized	< 40% (acute) 27% (convalescent) 61% (convalescent)	[32] [33] [97] [33] [32]	~99%	[36]
	Serum	Early disseminated	86% (carditis) 90% 42–87%	[32] [98] [99]	~99%	[98]
	Serum	Neuroborreliosis	90%	[32]	96–100%	[39]
	Serum	Late disseminated	100% (arthritis) 97–100%	[32] [99]	99–100%	[24] [39]
Modified two-tiered testing	Serum	Early localized	53% (acute) 58% (acute) 89% (convalescent) 67% (convalescent)	[37] [33] [25] [37] [33] [25]	~99% 96–100%	[36] [39]
	Serum	Early disseminated	71-86% (carditis)	[100]	96–100%	[39]
	Serum	Neuroborreliosis	98–100%	[22] [37] [100]	96–100%	[22] [37] [39]
	Serum	Late disseminated	~100% (arthritis)	[24] [100]	96–100%	[24] [39]
Polymerase chain reaction	Serum and/or skin Serum/Plasma	Early localized	64–81% 62%	[97] [101]	~100%	[102]* [103] [104]
	Serum	Early disseminated	29% (carditis)	[32]		
	CSF	Neuroborreliosis	25-38% 73%	[102]* [99]		
	Synovial fluid	Late disseminated	85% (arthritis) 83% (arthritis)	[102]* [99]		

SEE ENLARGED SLIDE FOLLOWING ENTIRE PRESENTATION

Kobayashi, Auwaerter. Inf Dis Clinics N Am Sept 2022

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Sunday, August 23, 2026

20

Fungal Diseases in Immunocompetent and Immunosuppressed Hosts

John Bennett, MD

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Fungal Diseases in Immunocompetent and Immunocompromised Hosts

John E. Bennett, MD
Bethesda, MD

8/5/2026

Disclosures of Financial Relationships with Relevant Commercial Interests

- None

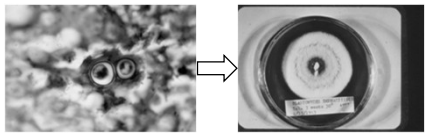
What We Are Going To Do

- I give key characteristics, you name mycosis
- Leave treatment to Dr. Alexander
- Skim over the top

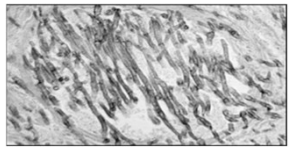
Must Know Fungal Facts
#1 Understand Dimorphism

- Fungus looks likes yeast in tissue or smear, grows like mold (dimorphic)
  - Blastomycosis
  - Histoplasmosis
  - Coccidioidomycosis
  - Paracoccidioidomycosis
  - Sporotrichosis
  - Talaromycosis
- Looks like a yeast, grows like a yeast
  - Cryptococcosis
  - Trichosporonosis
  - Candidiasis (pseudohyphae in tissue except glabrata)
- Looks like a mold, grows like a mold
  - Aspergillosis
  - Mucormycosis
  - Fusariosis
  - Scedosporiosis

Blasto Yeast and Blasto Mold



Aspergillus hyphae in a blood vessel



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Must Know Fungal Facts

#2 Location, Location, Location!
(Major Areas For Infection)

- West of the Mississippi, Mexico: Coccidioidomycosis
- Southeast Asia, South China: Talaromycosis (Penicilliosis)
- Mississippi and Ohio River valleys: Blastomycosis
- South America: Paracoccidioidomycosis

Coccidioidomycosis

Talaromycosis

Blastomycosis

Paracoccidioidomycosis

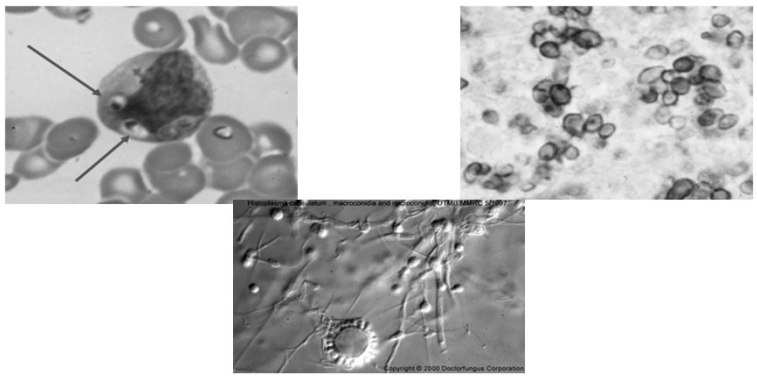
Question #1

What mycosis has these key characteristics?

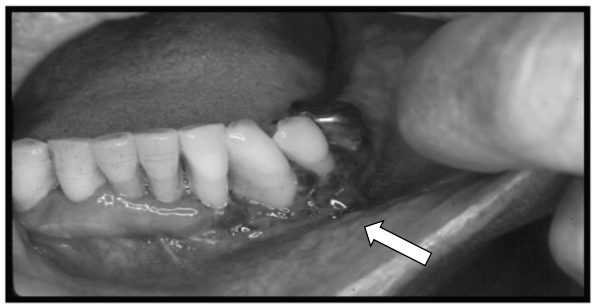
- Yeast in tissue, mold in culture
- Predispose: Anti-TNF drugs, HIV, corticosteroids
- Can have pancytopenia, abnormal LFT, miliary lung infiltrates
- Addison's disease, blood culture negative endocarditis
- Urine, serum antigen useful
- Acute pneumonia case clusters exposed to soil with bird or bat guano

A. Cryptococcus
B. Histoplasmosis
C. Coccidioidomycosis
D. Blastomycosis

Histoplasmosis



Gingival Ulcer



¼ Cases have oral lesion in disseminated histoplasmosis

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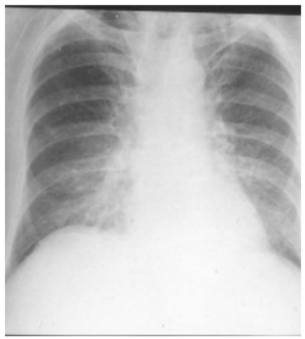
Miliary Lung Lesion in Disseminated Histoplasmosis
(Looks Like PJP on Imaging)



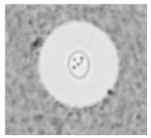
Question #2

What mycosis is this?

- Chronic meningitis: headache, altered mental state
- Predispose: HIV, corticosteroids
- Serum, CSF antigen useful
- Yeast in body and in culture

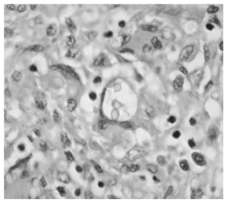
A. Cryptococcus
B. Histoplasmosis
C. Coccidioidomycosis
D. Blastomycosis
E. Paracoccidioidomycosis

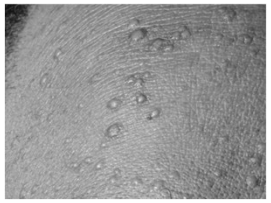
Cryptococcosis



- Cryptococcus neoformans species complex:
  - Worldwide, pigeon guano, corticosteroids, transplants, HIV , ICL
- *Cryptococcus gattii* species complex
  - Pacific coast, Australia, tropics, trees, often previously healthy
  - Serum antibody to GM-CSF
- Chronic lymphocytic meningitis
  - Headache, confusion, cranial nerve palsies, +/- fever, vision loss
  - Relieve high opening pressure (LP's, shunt)
  - HIV ARV-naïve: consider delay ARV (IRIS)
  - Skin lesions (10%) like molluscum contagiosum
- Lung: Serum antigen can be negative if just lung
- Cryptococcal antigen in CSF, serum
  - screening blood of HIV+ with low CD4

- Cryptococcal lung lesions usually asymptomatic
- Skin lesions can resemble molluscum contagiosum
- Mucicarmine often stains crypto pink





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Question #3

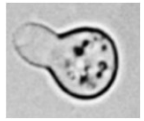
What mycosis is this?

- Broad based budding yeast, grows as mold
- Previously healthy with lung portal but skin lesions in 70%
- A few case clusters around waterways
- USA: Mississippi and Ohio River valleys

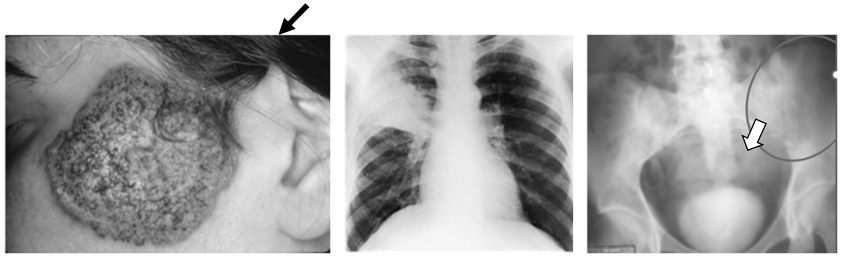
A. Cryptococcus
B. Histoplasmosis
C. Coccidioidomycosis
D. Blastomycosis
E. Paracoccidioidomycosis

Blastomyces dermatitidis, B. gilchristii

- Yeast with broad based bud, thick wall
- Acute pneumonia may self heal
- Indolent, progressive pneumonia
- Disseminates to skin, bone, male GU track
- Histo antigen often positive



Blastomycosis



Question #4

What mycosis is this?

- Dust exposure
- West of Mississippi, Mexico
- Round in tissue, mold in culture

A. Cryptococcus
B. Histoplasmosis
C. Coccidioidomycosis
D. Blastomycosis
E. Paracoccidioidomycosis

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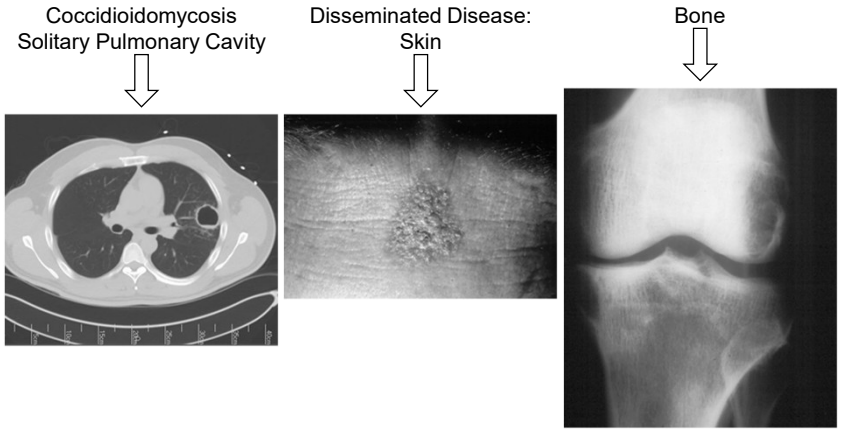
Coccidioidomycosis = Valley Fever

- Two species, one disease: C. immitis and C. posadasii
  - Both serious lab hazards
  - Southwest USA; Washington state
- Acute pneumonia 2 weeks after inhalation: arthralgias or erythema nodosum may accompany. Resolves.
- Residual nodule or thin-walled cavity may persist
- Dissemination: African Americans, HIV, SOT, TNF inhibitors
- Bone, skin, chronic meningitis
- Eosinophils in blood and CSF



Question #5

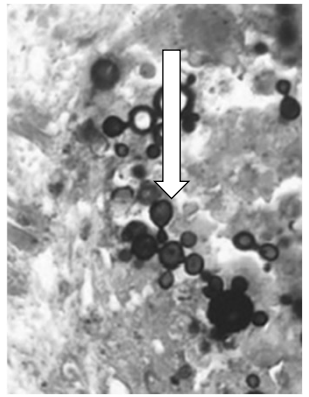
What mycosis is this?

- Worked on a farm years ago in Brazil, Columbia, Venezuela, Ecuador
- Mouth or nose lesion, asymptomatic lung lesion
- Multi-budding yeast on biopsy, mold on culture

A. Cryptococcus
B. Histoplasmosis
C. Coccidioidomycosis
D. Blastomycosis
E. Paracoccidioidomycosis

Paracoccidioidomycosis

- Rural Central and South America
- Several Species
- Starts in lung, disseminates
- May appear decades after leaving endemic area
- Multiple Buds



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Question #6

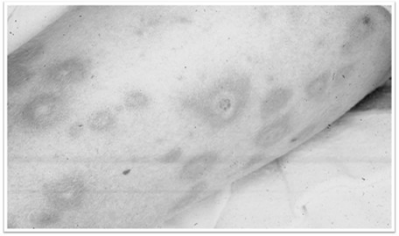
What mycosis is this?

- Grows as a mold in the body and in culture
- Multiple painful red skin lesions in half
- Routine blood cultures grow a septated mold in a third to a half
- Very, very immunosuppressed patients

A. Scedosporiosis
B. Lomentosporiosis
C. Mucormycosis
D. Fusariosis
E. Alternariosis

Fusariosis

Typical skin lesions with varying degrees of central necrosis



Fusariosis

- Severely immunocompromised patients
- Mold, looks like Aspergillus in tissue
- Red, tender skin nodules
- Routine blood culture grows mold in a third to half the patients

Question #7

What mycosis is this?

- Immunosuppressed:
  - Prolonged severe neutropenia
  - Stem cell and solid organ transplants
  - Chronic granulomatous disease
- Inhaled spores into lung or paranasal sinus
- Septate hyphae
- Halo sign or crescent sign on CT, ecthyma gangrenosa

A. Scedosporiosis
B. Aspergillosis
C. Mucormycosis
D. Lomentosporiosis

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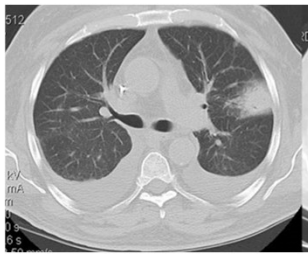
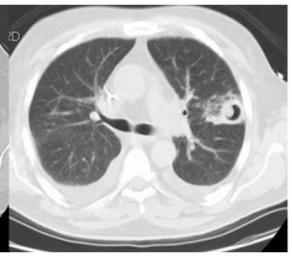
Aspergillosis

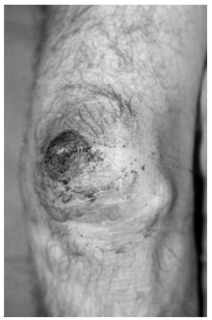
Halo Sign



Crescent Sign



Ecthyma



Question #8

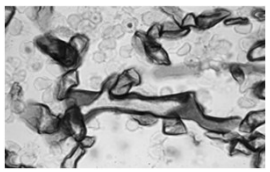
What mycosis is this?

- Mold in tissue, mold in culture. Wide, pauciseptate hyphae
- Sinusitis in poorly controlled diabetics
- Pneumonia, dissemination in immunosuppressed

A. Scedosporiosis
B. Aspergillosis
C. Fusariosis
D. Mucormycosis

Mucormycosis

- Infection acquired by inhaling spores into lung or paranasal sinus
- Rhizopus, Rhizomucor, Mucor, Cunninghamella, Apophysomyces, Saksenaea
- Broad, flexible non-septate hyphae, right angle branching
- Rhino-orbital: poorly controlled Diabetes mellitus or immunosuppression
- Pulmonary: neutropenia, immunosuppression

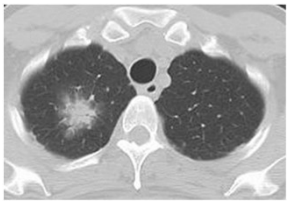


Mucormycosis

Cavity After PMN Return

Ethmoid Sinus Infection

Halo Sign in a Leukemic



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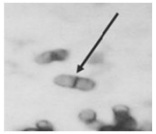
Question #9

What mycosis is this?

- Southeast Asia, Southern China, Taiwan
- Yeast in tissue, mold in culture
- Papular skin lesions
- Majority of cases PLWH

A. Lomentosporiosis
B. Scedosporiosis
C. Talaromycosis
D. Paracoccidioidomycosis
E. Pythiosis

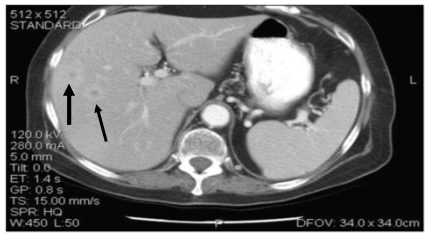
Talaromycosis



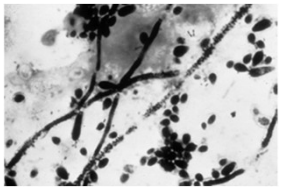
Question #10

What are these lesions in a febrile, recently neutropenic patient?

A. Babesia microti
B. Candida tropicalis
C. Fusarium oxysporum
D. Aspergillus flavus
E. Streptococcus anginosus



Candidiasis



- Fundoscopy for retinal lesions in candidemia patients
  - Intravitreal Rx may be needed
- Remove intravenous catheter with candidemia
- *Candida auris* hospital outbreaks. Spreads on hands, surfaces
  - Screening for high=risk hospital admissions
- Fluconazole resistance in C. auris, C. krusei (Pichia kudriavzevii)
  - C. glabrata (Nakaseomyces glabratus)
- Fungitell (1-3) beta-D-glucan positive in serum, CSF

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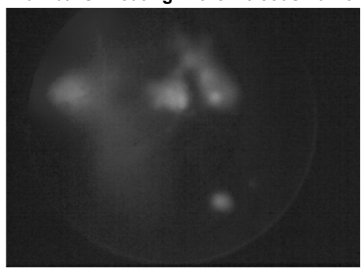
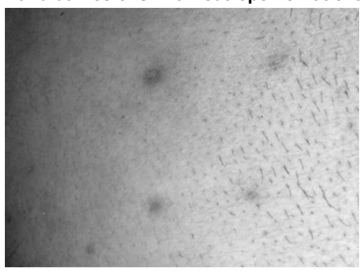
***Candida endophthalmitis*:**
"fluff balls" floating in the vitreous humor



Candida Lesions in a Neutropenic Patient

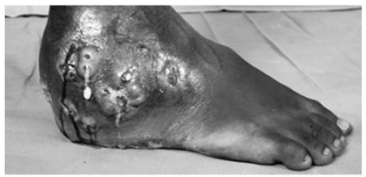


Sporotrichosis

- Sporothrix schenckii, (brasiliensis, globosa, pallida, mexicana)
- Lives on plants, inoculated by minor trauma
- Brazil and surrounding countries: >10,000 cases from infected cats
- Lymphangitic spread
- RARE: lung, disseminated
- Similar lesions: *mycobacterium marinum*, *nocardia brasiliensis*

Mycetoma (Madura Foot)

- Minor trauma to foot or hand
- Firm swelling progresses over years
- Draining sinuses



- Grains in pus
- Fungi or higher bacteria

Mycoses Worth Mentioning

- Scedosporium apiospermum: immunosuppressed host clinically resembling aspergillosis. Brain abscess after near **drowning** in polluted water. **Amphotericin b-resistant**
- Trichosporonosis: like candidiasis but **echinocandin resistant**

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If They Tell You This…Think This

- Capsule: cryptococcus
- Broad based bud: blastomycosis
- Septated mold: aspergillus, fusariosis, scedosporiosis
- Aseptate wide mold: mucormycosis
- Yeast on a blood smear: histoplasmosis
- Mold growing in routine blood culture: fusariosis

That's It!
It's all perfectly clear, isn't it?

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Sunday, August 23, 2026

21

Pneumonia

Paul Auwaerter, MD

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Pneumonia

Paul G. Auwaerter, MD
Johns Hopkins University School of Medicine

8/2/2026

Disclosures of Financial Relationships with Relevant Commercial Interests

- Research: Pfizer (investigational Lyme disease vaccine)
- Consulting: medical-legal, Tonix Pharmaceuticals, Tarsus Pharmaceutics

Community-acquired Pneumonia: Meta-analysis Traditional Culture + PCR for "Atypicals" + Viruses

Pathogen	Total (%)*
None Pathogen detected	4380 (61.3) 3279 (48.7)
Etiology Bacterial	
• S. pneumoniae	33%
• H. influenzae	8.6%
• S. aureus	4.9%
• M. catarrhalis	2.4%
• Gram negatives	6.0%
• Mycobacteria	1.8%
• Other bacteria	1.94%

Shoar and Musher, Pneumonia (2020) 12:11

- 12 Modern studies
  - 2005-2019
  - Inpatient n = 4399
  - In & outpatient = 2752
  - Outpatient = 04
- Hospital mortality: 12-15%

*Etiologic agents percentages

Community-acquired Pneumonia: Meta-analysis Traditional Culture + PCR for "Atypicals" + Viruses

Pathogen	Total (%)*
Etiology Viral & "Atypicals" And co-infections	
• Mycoplasma pneumoniae	8.9%
• Legionella pneumoniae	6.2%
• C. pneumoniae	2.9%
• Pneumocystis	0.2%
• Influenza	9.2%
• Rhinovirus	11.5%
• Parainfluenza or RSV	9.3%
• Bacterial + viral coinfection	5.9%

Shoar and Musher, Pneumonia (2020) 12:11

- 12 Modern studies
  - 2005-2019
  - Inpatient n = 4399
  - In & outpatient = 2752
  - Outpatient = 0

*Etiologic agents percentages

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Question #1

- 67M c/o fever, slightly productive cough and dyspnea x 10 days
- Received rituximab 2 mos earlier for granulomatosis with polyangiitis
- On prednisone 40 mg daily

All: sulfa (rash), azithromycin (n/v)

- **PMH:** HTN, HLD
- **SH:** Non-smoker, Baltimore resident, retired, no pets
- **Meds:** lisinopril, atorvastatin, dapsone

- T101.4°F, P 106, RR 24, 02 sat 88% RA
- No lymphadenopathy, no JVD
- Lungs: basilar crackles bilaterally
- Cor: no murmur
- Ext: no edema
- Skin: no rash

- WBC 7,800/µL 85%N 5%L 5%M 4%E 1%B
- sCr 1.0 mg/dL
- UA non-active sediment
- Methemoglobin %: normal
- Sputum: Light PMNs, no organisms
- Sputum Film array: negative

Question #1

Which of the following is the appropriate next step?

A. Begin meropenem plus doxycycline
B. Repeat sputum expectoration for dedicated *P. jirovecii PCR*
C. Obtain BAL including *P. jirovecii PCR*
D. Obtain serum galactomannan and begin voriconazole
E. Increase prednisone to 60 mg daily

PJP in Patients without HIV

- Lower organism burden in non-HIV patients
  - Scant sputum; microscopy may miss
    - Commercial film arrays don't assess for PJP
  - BAL PJP PCR ± serum β-D-glucan w/ suspicion
- May present as "CAP"
  - Include CAP pathogens, OIs
- Prophylaxis doesn't exclude PJP

References: Sarasombath PT et al. Front Microbiol. 2021;12:729193. Ramirez JA et al. Chest. 2020;158:1896–1911. Shoham S, Prono MVD. Emerging Transplant Infections. Springer; 2021:1183–1206. BIOFIRE FILMARRAY Pneumonia Panel target menu, bioMérieux.

Pneumonia Diagnostics

One commercially available PCR panel
- *Acinetobacter calcoaceticus-baumannii* complex
- *Enterobacter cloacae* complex
- *Escherichia coli*
- *Hemophilus influenzae*
- *Klebsiella aerogenes*
- *Klebsiella oxytoca*
- *Klebsiella pneumoniae* group
- *Moraxella catarrhalis*
- *Proteus* spp.
- *Pseudomonas aeruginosa*
- *Serratia marcescens*
- *Staphylococcus aureus*
- *Streptococcus agalactiae*
- *Streptococcus pneumoniae*
- *Streptococcus pyogenes*

Atypical Bacteria (Qualitative)
- *Chlamydia pneumoniae*
- *Legionella pneumophila* (only this species)
- *Mycoplasma pneumoniae*

Viruses
- Adenovirus
- Coronavirus
- Human metapneumovirus
- Human rhinovirus/enterovirus
- Influenza A virus
- Influenza B virus
- Parainfluenza virus
- Respiratory syncytial virus

- Diagnostics for severe CAP and HAP/VAP
- What can be missed on expectorated sputum?
  - Molecular panels (examples)
    - Gram negatives
      - Stenotrophomonas
      - Citrobacter spp.
      - Other rare or non-speciated Gram-negatives
    - Neisseria meningitidis
    - Atypical pathogens
      - Less sensitive
    - Tick-borne diseases and other less common causes
    - May miss polymicrobial cases
    - Fungal causes
      - Endemic fungi
      - Pneumocystis jirovecii
- Need clinical judgment to interpret both sputum culture and/or molecular tests (due to high sensitivity)

SEE ENLARGED SLIDE FOLLOWING ENTIRE PRESENTATION

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Question #2

- 35-year-old 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 #2

Which antibiotic will lead to the most rapid improvement?

A. Ceftriaxone
B. Gentamicin
C. Doxycycline
D. Trimethoprim/sulfamethoxazole

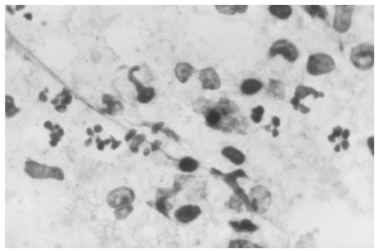
Chlamydia psittaci

- 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 appear as intracellular Gram negatives

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Chlamydia psittaci

- Range of illness:
  - Mild, bronchitic to severe/ARDS
  - **Clue**: temperature/pulse dissociation
  - Also seen with Salmonella typhi, C burnetti, Chlamydia, Dengue
- Diagnosis:
  - Molecular/PCR, sputum (best)
  - Acute/convalescent serology (microimmunofluorescence, MIF)
  - Culture: tissue culture (difficult)
- Treatment:
  - Preferred: doxycycline
  - Alternatives:
    - Macrolides
    - Fluoroquinolones

Wolff BJ et al, Diagn Microbiol Infect Dis 2018;90(3):167-170
Hogerwerf L et al, Epidemiol Infect 2017;145(15):3096-3105

Helpful Clues for "Atypical" CAP

Clinical feature	C. psittaci	C. pneumoniae	M. pneumoniae	L. pneumophila
Cough	++	+	++	+
Sputum	-	+	++	+++
Sore throat	-	++	-	-
Headache	+++	+	-	+
Confusion	+	-	-	++
CXR change	Minimal	Minimal	Worse than sx	Multifocal
Low Na^+	-	-	-	++
Doxycycline response	Rapid, < 48h	Prompt	Prompt	Slower

Adapted from Stewardson, Grayson. Inf Dis Clin N Amer 2010; 24(1):7

Question #3

- 67-year-old M 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

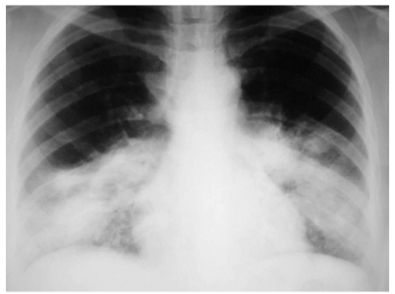
Therapy:
- Vancomycin and piperacillin/tazobactam x 3 d
- No improvement, febrile, respiratory culture negative
- ID consultation called

Question #3

You are aware of a recent *Legionella micdadei* 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 Pneumonia Plus Film Array Panel (FDA-approved)
D. Legionella direct fluorescent antigen (DFA) stain of respiratory sample
E. Paired *Legionella pneumophila* acute/convalescent serology



Pre-intubation CXR

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Legionella Pneumonia

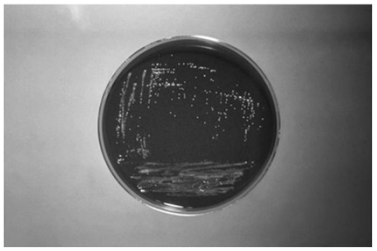
- Risks factors (and who to test)
  - Travel beyond home (e.g., hotel, hospital) last two weeks
    - May cause HAP
  - Severe pneumonia/ICU
  - Proximity to known outbreaks
  - Age > 50 yrs
  - Smoking
  - Comorbidities: diabetes, liver/renal dz, COPD, immunosuppressed
- Acquisition:
  - Aerosolization
  - Drinking water (aspiration)

1976 Bellvue Stratford Hotel, Philadelphia

Legionella

- Environmental/water pathogen
  - Ponds, lakes
  - Water systems (hot > cold), chillers, misters, A/C
  - May be a nosocomial pathogen
- Legionellosis
  - Legionnaires' disease (99%)
    - Pneumonia
    - Most typical of the atypicals
  - Pontiac Fever (1%)
    - Febrile, flu-like illness
- Microbiology: 60 species
  - *L. pneumophila* serotype 1 (most common)

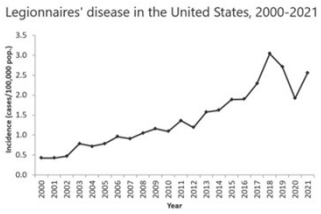
Legionella Culture



Culture media: BCYE agar
Small, pearly white colonies

Outbreaks: Known and Unknown Sources

- 8,442 cases in '21 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



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https://www.cdc.gov/legionella/php/surveillance/index.html (accessed 7/18/26)

Legionella Diagnostics

Test	Sensitivity (%)	Specificity (%)	Notes
Culture*	20-80	100	Slow, technically difficult on BCYE agar Detects all species/serotypes
Urinary Ag*	70-100	95-100	Only L. pneumophila serogroup 1, rapid, may cross-react occasionally w/ other serogroups
PCR*	95-99	99	FDA approved (2022) in some LRTI multiplex arrays, specific for L. pneumophila. Home brew/LDTs may offer broader Legionella spp. coverage
DFA	25-75	≥ 95	Technically demanding
Paired serology	80-90	> 99	Not helpful for acute care, 5-10% population with (+) titers

Source: CDC, Legionella Testing and Specimen Collection (accessed 7/18/26)
Avni, J Clin Micro. 2016;54(2):401–11; Muldyermans, Eur J Clin Microbiol Infect Dis 2019 *CDC preferred tests, obtain both in suspected patients

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	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 the organism by culture Acute/convalescent serology Dx by epidemiology/serology
Mortality	10-30%	0 %

Question #4

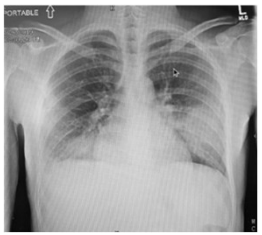
- 22-year-old M landscaper who mows lawns in Ozarks of Arkansas has 5 days of fever, chills and dry cough presenting in early July. He has run over several animal burrows with the mower.
- (+) fatigue, myalgia
- PMH: negative
- SH: Occasional MJ
- PE: Appears ill, BP 98/70, P 110
- T 39.5ºC, PaO_2 = 94%
- No lymphadenopathy
- Bronchial breath sounds lower fields with crackles bilaterally
- No murmur
- No hepatosplenomegaly, abdominal tenderness
- No rash

Question #4

Which testing approach is most likely to confirm a diagnosis?

A. Respiratory viral panel (RSV, Influenza, SARS-CoV-2)
B. Rickettsia rickettsii acute and convalescent serology
C. Whole blood Ehrlichia chaffeensis PCR
D. Francisella tularensis acute and convalescent serology
E. Blood culture yielding Yersinia pestis

WBC 18,500 88% N PLT 280K
ALT 267 U/L
CK 3280 U/L



Bilateral LL infiltrates + hilar LN

Consultant. 2020;60(11):27-29.

Francisella tularensis

CDC Tularemia reported cases 2011-2020

- Small aerobic Gram-negative pleomorphic coccobacillus
- Transmission:
  - US: biting flies (deer flies), ticks
  - Europe: mosquitoes
  - Also: aerosol, contaminated mud/water, infected carcasses, animal bites
- Risk groups:
  - Lab personnel, farmers, landscapers, vets, hunters/trappers, meat handlers
- Bioterrorism agent, Class A
- Inhaled infectious doses: ~10-50 organisms

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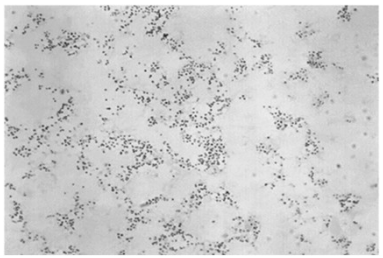
Francisella tularensis



Gram stain photomicrograph, CDC

- Small aerobic Gram-negative pleomorphic coccobacillus
- Six illness patterns
  - Ulceroglandular (most common ~200 cases/yr)
  - Glandular
  - Oculoglandular
  - Pharyngeal
  - Typhoidal
  - Pneumonic
- Routine cultures often negative or offer incorrect identification
  - Notify lab if suspicious
- Acute/convalescent serology confirms most cases

Francisella tularensis

- Differential diagnosis of pneumonic tularemia includes:
  - Plague (*Y. pestis*)
  - Anthrax (*B. anthracis*)
  - Consider bioterrorism
- Treatment recs (CDC)
  - Fluoroquinolones
  - Aminoglycosides
    - Streptomycin
    - Gentamicin
  - Tetracyclines (mild-moderate cases)
- Limited data to suggest optimal choices

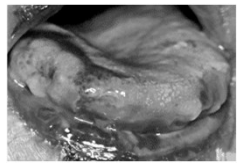
Nelson CA. CID 2024;78(S1):S15-28

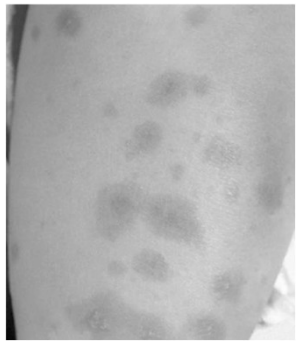
Question #5

- 18-year-old F 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

Question #5

- Azithromycin prescribed
- Following day, develops severe painful oral erosions, hemorrhagic lip crusting, and bilateral conjunctivitis with targetoid vesicles on extremities





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Question #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 the patient
- ~25% may have extra-pulmonary manifestations
  - *M. pneumoniae*-induced rash and mucositis (MIRM)
    - MIRM/RIME (reactive infectious mucocutaneous eruptions):
      - Prominent oral, ocular, or genital mucositis with sparse vesiculobullous or targetoid skin lesions; may resemble SJS/TEN.
      - Most common infectious cause (children/adolescents)
      - Male > female
      - Often ≥ 2 involved mucosal sites
  - Hemolytic anemia
  - Hepatitis
  - CNS: encephalitis, meningitis

Mycoplasma pneumoniae

Finding/Method	Pro	Con	Notes
Bullous myringitis		Description w/ experimental infection	Urban legend that is wrong or if true, rare
Molecular	High sensitivity & specificity	FDA approved, Expensive platforms needed, multiplex	New gold standard In house assays not standardized
Serology	Available commercially	Non-specific Acute/convalescent	False +'s and –'s Not timely
Culture	100% specific Antibiotic susceptibilities	Poor sensitivity Time consuming	Only reference labs Special transport media Difficult to perform
Cold agglutinin titers	Occur in 50-70%	Non-specific	Association w/ hemolysis

Question #6

- 31-year-old F fever, cough, myalgia, headache, dyspnea over 1 week ago; February
- No help w/ azithromycin x 3d
- 18 mos daughter, recent bronchitis
- PMH: not significant
- SH: ½ ppd smoker
- PE: ill
- T38.3, RR 35, BP 125/70, P 128
- Coarse breath sounds, rales bilateral and decreased L base

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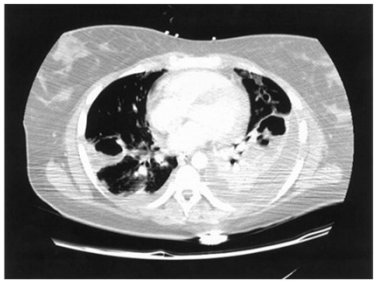
Question #6



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 (+)

Question #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

Question #7

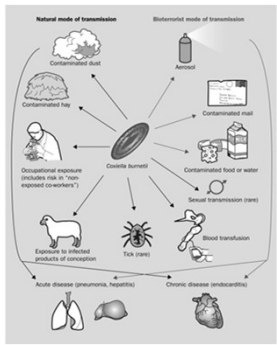
- 45-year-old M shepherd presents with 5d of dry cough, HA, fever and malaise in March
- PMH: none
- SH: Colorado, non-smoker. Helped with lambing in the past two weeks.
- PE: RR 18 T101°F P90 BP 110/70
- Non-toxic appearing
- Chest: bibasilar rales
- Labs: AST 58 ALT 89
- CXR: bilateral patchy infiltrates

What antimicrobial would be the most appropriate?

A. Amoxicillin/clavulanate
B. Fluconazole
C. Gentamicin
D. Doxycycline
E. Ceftriaxone

Acute Q Fever Pneumonia

- *Coxiella burnetii* ~175 cases in US, 80% acute
  - Intracellular pathogen
  - Primary reservoirs: cattle, sheep, goats
  - Acquire by inhaling contaminated dust from feces, urine, birth material
  - Risk factors: male, living in or near an active ranch, drinking raw milk



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Madariaga MG Lancet ID 2003;3(11):709

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Q Fever Pneumonia

Diagnosis

- Two antigenic phases produce different antibodies
  - Phase I: antibodies associated with chronic infection.
  - Phase II: antibody responses are seen in acute infection.
- Acute disease (e.g., pneumonia): seroconversion or anti-Phase II Ab > Phase I.
  - Definitive: serology + whole blood PCR.

Treatment

- First-line treatment
  - Doxycycline (IV or PO)
- Alt: macrolides + rifampin, fluoroquinolones
- Note: post-infectious fatigue >6 months in 10%

MMWR 2013;62:1-30

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

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Pneumonia Diagnostics

One commercially available PCR panel
- *Acinetobacter calcoaceticus-baumannii* complex
- *Enterobacter cloacae* complex
- *Escherichia coli*
- *Hemophilus influenzae*
- *Klebsiella aerogenes*
- *Klebsiella oxytoca*
- *Klebsiella pneumoniae* group
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- *Pseudomonas aeruginosa*
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- *Streptococcus agalactiae*
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- Respiratory syncytial virus

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      - Pneumocystis jirovecii
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- 8,442 cases in ‘21 U.S.
  - 20 Outbreaks
- 4X > cases since 2000
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- WHERE?
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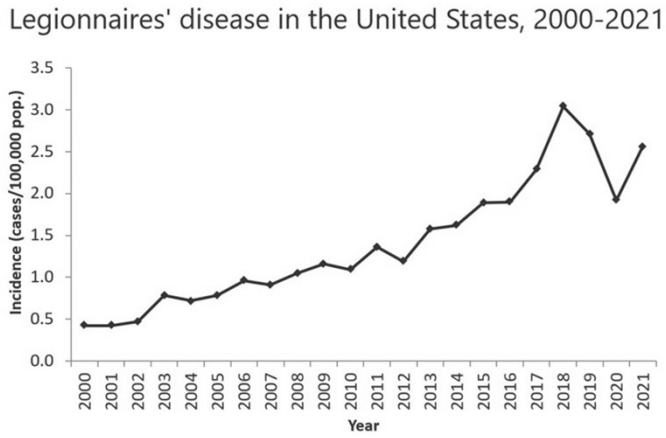
  - Long-term Care Facilities
  - Hospitals



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https://www.cdc.gov/legionella/php/surveillance/index.html (accessed 7/18/26)

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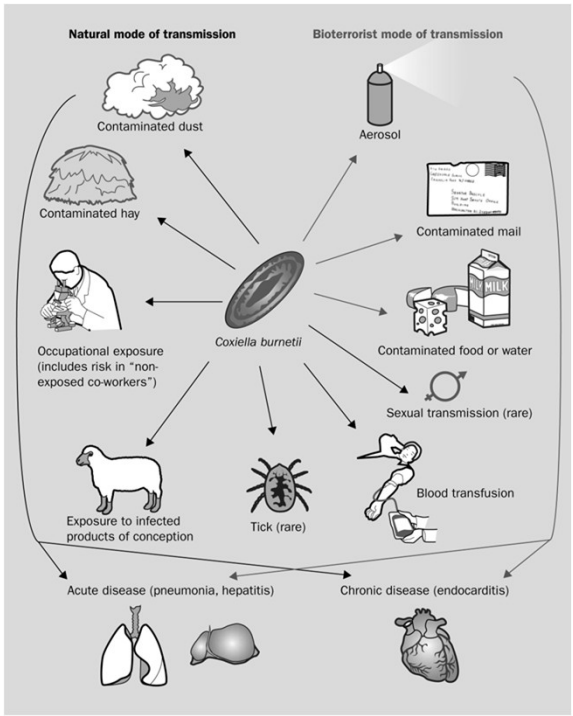
Acute Q Fever Pneumonia

- *Coxiella burnetii* ~175 cases in US, 80% acute
  - Intracellular pathogen
  - Primary reservoirs: cattle, sheep, goats
  - Acquire by inhaling contaminated dust from feces, urine, birth material
  - Risk factors: male, living in or near an active ranch, drinking raw milk



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Madariaga MG Lancet ID 2003;3(11):709

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AGENDA DAY 3: Monday, August 24, 2026

#	Start		End	Presentation	Faculty
AM Moderator: David Aronoff, MD					
22	8:00 AM	-	8:30 AM	Sexually Transmitted Infections: Genital Ulcers Diseases (GUD)	Khalil Ghanem, MD
23	8:30 AM	-	9:15 AM	Zoonoses	David Aronoff, MD
	9:15 AM	-	9:30 AM	Morning Break	
24	9:30 AM	-	10:15 AM	Nocardiosis, Actinomycosis, Rhodococcus and Melioidosis	David Aronoff, MD
25	10:15 AM	-	11:15 AM	Sexually Transmitted Infections: Other Diseases and Syndromes	Khalil Ghanem, MD
26	11:15 AM	-	12:15 PM	Core Concepts: Antibacterial Drugs II Gram Positive Organisms	Helen Boucher, MD
	12:15 PM	-	12:30 PM	Lunch Break	
BR3	**12:30 PM**	**-**	**1:15 PM**	**Board Review Day 3**	**Drs. Aronoff (Moderator), Boucher, Dhanireddy, Dorman, Ghanem, Klompas**
PM Moderator: David Aronoff, MD					
27	1:15 PM	-	2:00 PM	Skin And Soft Tissue Infections	Helen Boucher, MD
28	2:00 PM	-	2:45 PM	Helicobacter and Clostridioides	David Aronoff, MD
	2:45 PM	-	3:00 PM	Afternoon Break	
29	3:00 PM	-	3:45 PM	Immunizations: Domestic, Travel, and Occupational	Shireesha Dhanireddy, MD
	3:45 PM	-	4:00 PM	Afternoon Break	
30	4:00 PM	-	5:00 PM	Hospital Epidemiology	Michael Klompas, MD
31	5:00 PM	-	5:45 PM	Tuberculosis in Immunocompetent and Immunosuppressed Hosts	Susan Dorman, MD

Sexually Transmitted Infections: Genital Ulcers Diseases (GUD)

Khalil Ghanem, MD

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Sexually Transmitted Infections: Genital Ulcer Diseases

Khalil G. Ghanem, MD, PhD

Professor of Medicine
Division of Infectious Diseases
Johns Hopkins University School of Medicine

7/25/2026

Disclosures of Financial Relationships with Relevant Commercial Interests

- None

Note

- I have tried to use patient-first language throughout. When the terms 'women' and 'men' are used, I am referring to cis-gender women and men unless otherwise specified
  - Data on the epidemiology and management of STIs in transgender populations are very limited
- All photos are freely available from the following website unless otherwise noted: http://www.cdc.gov/std/training/clinicalslides/slides-dl.htm

Genital Ulcer Diseases (GUD)

- Syphilis (*Treponema pallidum*)
- HSV-2
- HSV-1
- Chancroid *(Haemophilus ducreyi)*
- Lymphogranuloma venereum (LGV) *(Chlamydia trachomatis)*
- Granuloma inguinale (Donovanosis) *(Klebsiella granulomatis)*
- Monkeypox

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STI Ulcer Comparison Table

STI	Ulcer characteristics	LAD	Notes
Syphilis	Single, **painless** ulcer; heaped-up borders ; clean base	Painless; bilateral	**30% may have multiple painful ulcers**
HSV	Multiple; **painful**; superficial; vesicular or ulcerative; erythematous base	Tender; bilateral	LAD less common with recurrences
Chancroid	**Painful**; indurated; "ragged" appearance	Tender; suppurative	"**kissing lesions**" on thighs-autoinoculation
Granuloma Inguinale	**Painless**; progressive/destructive ; "serpiginous" pattern; beefy red with white border; highly vascular	Absence of true LAD; **pseudo-buboes**	Progressive tissue destruction
LGV	Short-lived; **painless**	Painful; suppurative; inguinal	"**Groove sign**"; ulcer often resolves before LAD

Question #1

A 35-year-old woman presents with a painless ulcer on her vulva and one on her soft palate following unprotected vaginal and receptive oral sex 3 weeks earlier. She has no other symptoms.

Examination reveals the two ulcers with heaped-up borders and a clean base.

Which of the following diagnostic tests is inappropriate to obtain?

A. Serum RPR
B. Serum VDRL
C. Serum treponemal EIA
D. Darkfield microscopy on a specimen obtained from the oral ulcer
E. Darkfield microscopy on a specimen obtained from the vulvar ulcer

Natural History of Syphilis

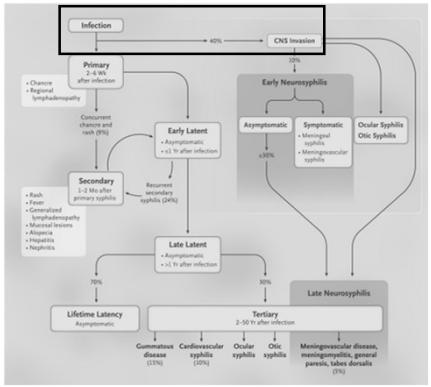
Sexual transmission (only occurs in early stages)

- Risk of infection after 1 exposure: 40%
- Index patient is most contagious during 1º and 2º stage, less so in early latent stage

Vertical transmission (may occur during any stage)

- ~80% transmission in the early stages
- ~10% transmission in the late stages

Rarely, transmission may occur through **blood transfusions** and **organ transplantations**



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N Engl J Med 2020;382:845-85

Early Syphilis: Clinical Manifestations

- Incubation ~3 weeks
- Primary: chancre; LAD; resolves 3-6 weeks
- Secondary: **Systemic symptoms:** low-grade fever, malaise, sore throat, adenopathy
  - RASHES: [1]evanescent, copper-colored, macular (dry) rash; followed by [2] a red papular eruption (involving palms and soles in 60%); mucosal lesions (gray plaques or ulcers); condyloma lata-wart-like lesions that develop in moist areas
  - Other manifestations: Patchy alopecia, hepatitis (mild elevation of aminotransferases with disproportionately high alkaline phosphatase), gastritis, periostitis, glomerulonephritis, etc.

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Neurosyphilis

Type	Timing	Characteristics
Early NS	<=12 m	Meningovascular; basilar meningitis (HA, photophobia; CN abnormalities)
Tertiary NS Meningovascular Parenchymatous Tabes Dorsalis General Paresis	> 12 m (usually 6+ years after dx)	**Meningovascular**: CVAs **Tabes dorsalis**: Shooting pains (dorsal columns), ataxia, cranial nerve abnormalities, and optic atrophy **General Paresis:** Dementia, psychosis, slurred speech, and Argyll Robertson pupil

NS= neurosyphilis; HA= headaches; CN= cranial nerves; CVA- cerebrovascular accidents; m=months

Syphilis: Eyes and Ears

Eyes

- Ocular manifestation may occur during any stage and may involve any portion of the eye; 50% bilateral
  - Uveitis most common
  - Interstitial keratitis: occurs in both congenital (typically at age 5-20; 80% bilateral) and acquired (both early and late infections)
  - **CSF examination normal in ~30% of cases of ocular syphilis**

Ears

- Sensorineural hearing loss w/vestibular complaints (sudden or fluctuating hearing loss, tinnitus or vertigo)
  - Congenital (early and late)
  - Acquired (secondary and late stages)
  - **CSF examination is normal in at least 40% of cases of otic syphilis**

***No need for a CSF examination in patients who only have ocular or otic symptoms/signs

Other Tertiary Manifestations

Cardiovascular

- 15-30 years after latency
- Men 3X> women
- Aortic aneurysm; aortic insufficiency; coronary artery stenosis; myocarditis

Late Benign Syphilis

- 'Gummas'
- Granulomatous process involving skin, cartilage, bone (less commonly in viscera, mucosa, eyes, brain)

~30% of patients with cardiovascular and gummatous syphilis will have asymptomatic neurosyphilis- perform CSF exam!

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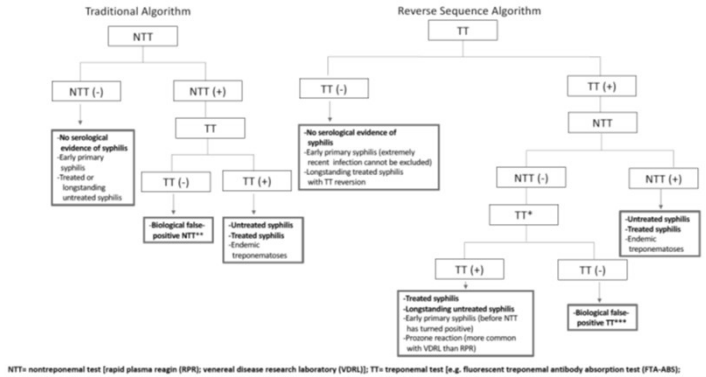
Syphilis Serological Testing

Nontreponemal Tests

- RPR (serum) or VDRL (serum or CSF)
- **False positives:** endemic treponematoses, old age, pregnancy, autoimmune disease (APS), viral infections
- **False negatives:** PROZONE effect and in early infection
- Reactive result must be confirmed with treponemal test
- Four-fold (i.e. 2-dilution) decline after treatment = CURE (**irrespective of the end-titer**)
- **Titers will decline with or without treatment**

Treponemal tests

- MHA-TP, TPPA, FTA-Abs, EIAs, CIA
- Detect IgG +/- IgM antibodies against treponemal antigens
- **False positives:** Endemic treponemal infections (e.g., yaws, pinta, bejel); Lyme disease; rarely in autoimmune conditions
- **False negatives:** Early primary syphilis
- **Once reactive, always reactive even after appropriate therapy**
  - **Exception: ~25% of persons treated early in primary syphilis may serorevert years later**



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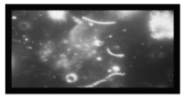
*N Engl J Med 2020;382:845-854

Syphilis: Diagnostics



- Darkfield microscopy or PCR for **genital** ulcers of primary syphilis; **sensitivity of serology in primary syphilis only~70%**
- **Sensitivity of serology for secondary or early latent syphilis ~100%**
- Over time, non-treponemal serological titers decline and may become nonreactive even in the absence of therapy while treponemal titers remain reactive for life
- Two POC and one at-home tests are now FDA cleared; all detect **treponemal antibodies**

Neurosyphilis: Diagnostics

- No single test can be used to diagnose neurosyphilis
  - CSF pleocytosis **most sensitive** marker
  - 50% of neurosyphilis cases may have negative CSF VDRL; it is **highly specific**, but **insensitive**
  - CSF treponemal tests are very sensitive but NOT specific (i.e., high false+)
    - May be used to **rule out** neurosyphilis
  - ~30% of persons with LATE neurosyphilis may have nonreactive SERUM nontreponemal tests

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A Few Important Concepts to Remember ABOUT Neurosyphilis, Ocular Syphilis, and Otic Syphilis

A normal CSF examination rules out neurosyphilis, but it does <u>not</u> rule out ocular or otic syphilis

A patient with ocular only or otic only signs and/or symptoms does <u>not</u> need a CSF examination. An immediate through clinical evaluation is warranted and if the clinical picture is consistent with ocular or otic syphilis, start antibiotic therapy

A patient with both neurological signs/symptoms and ocular or otic signs/symptoms should undergo a CSF examination. While it may not impact the <u>treatment</u> decision, it may impact <u>diagnostic</u> considerations [patients may have neurological manifestations due to something other than syphilis- you don't want to delay the diagnosis]

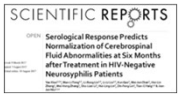
Syphilis Therapy

- Early stages (primary, secondary, early latent)
  - 2.4 MU of long-acting benzathine penicillin or doxycycline 100mg PO BID X 14 days
- Late latent/unknown duration
  - 2.4 MU of long-acting benzathine penicillin G IM X3 (over 2 weeks) [7.2 MU total] or doxycycline 100mg PO BID X 4 weeks

Syphilis Therapy (cont.)

- Neurosyphilis/Ocular/Otic syphilis
  - Aqueous penicillin 18 to 24 MU IV X 10-14 days
  - Ceftriaxone 1-2g IV/IM X 10-14 days (2nd line regimen)
  - **Follow-up CSF exams are NOT necessary if patient improves clinically, serologically, and is not immunosuppressed (PWH on ART at time of diagnosis do not need a f/u CSF exam)**

Normalization of Serum Rapid Plasma Reagin Titer Predicts Normalization of Cerebrospinal Fluid and Clinical Abnormalities after Treatment of Neurosyphilis


SCIENTIFIC REPORTS

OPEN Serological Response Predicts Normalization of Cerebrospinal Fluid Abnormalities at Six Months after Treatment in HIV-Negative Neurosyphilis Patients

- Jarisch-Herxheimer: within 6 hours (up to 24 hours) after therapy of (usually) early syphilis; antipyretics only; **<u>may induce early labor</u>**

Question #2

A 37-year-old man presents with a rash, lymphadenopathy, and low-grade fevers. A history of a condomless exposure 3 months earlier prompts the clinician to test for STIs. The following results are obtained: Treponemal EIA reactive; RPR reactive at **1:2048**. The patient is treated with a single IM dose of 2.4 MU of BPG.

- RPR titers 3 and 6 months later are 1:1024
- RPR 12 months after Rx is 1:512

The patient is doing well and denies any re-exposures

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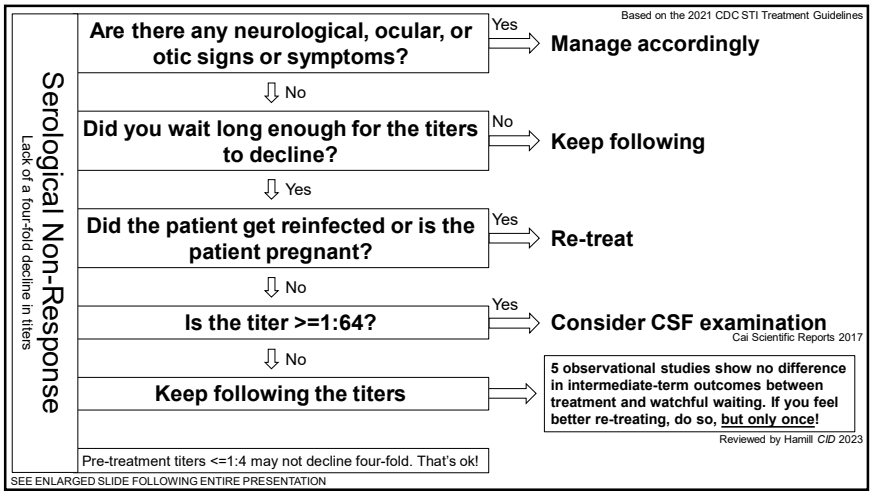
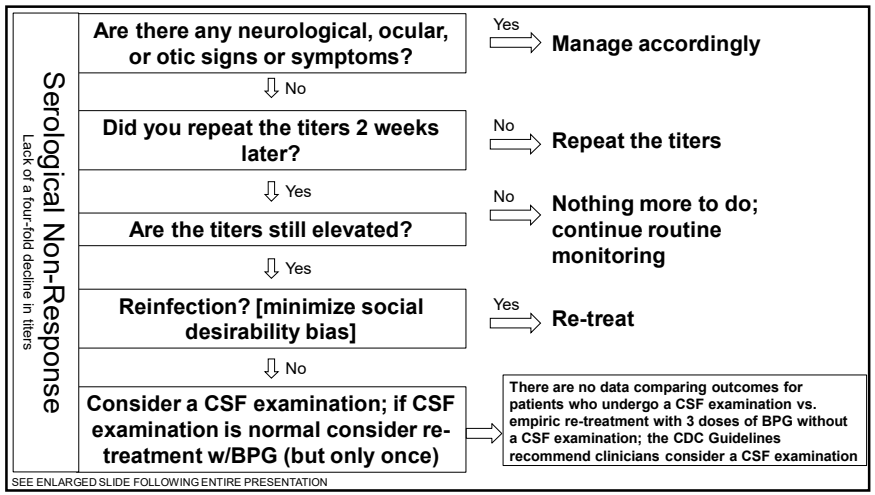
Question #2

Which of the following is the most appropriate intervention at 12 months?

A. BPG 2.4 MU IM X 1
B. BPG 2.4 MU IM X 3
C. Continue to follow
D. CSF examination





Syphilis & HIV

- Clinical manifestations similar but timeline may be compressed
  - PWH more susceptible to early neurosyphilis
- Testing and therapy similar to HIV negative
- Serological response may be slower among PWH
- Follow-up is more frequent (every 3 months)

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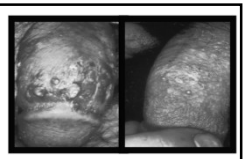
Syphilis & Pregnancy

- Screen at 1st prenatal visit, 28 weeks, and at the time of delivery (new ACOG recommendation)
- Screen all those who deliver a stillborn infant after 20 weeks' gestation
- **Pregnant penicillin-allergic patients with syphilis need to be desensitized to penicillin and treated with a penicillin-based regimen. There are NO OTHER OPTIONS (not even ceftriaxone)**

Syphilis Prevention

- Screen
- Treat
- Identify partners and treat partners
- Male condoms
- Doxy PEP (covered in the next STI lecture)

HSV



- Both HSV-1 and HSV-2 cause genital disease
- HSV-1 is now a more frequent cause of genital disease (especially in young women and MSM)
- In general, HSV-1 recurrences are less severe and less frequent and asymptomatic shedding is less frequent
- Prior infection with HSV-1 may attenuate severity of HSV-2 infection
- HSV suppressive therapy in PWH with a history of HSV and who are starting ART- but only if their CD4 <200 cells/mm^3

HSV Take-home Messages

- Both HSV-1 (particularly among young women and MSM) and 2 cause genital infections
- Most people are unaware that they are infected
- Asymptomatic shedding is the most common reason for transmission
- Condoms and antiviral suppressive therapy decrease risk of male to female transmission by 30% and 55% over time, respectively (condoms less effective from female to male)
- Currently, no formal screening recommendations
- C-section ONLY in those who have active lesions or prodromal symptoms at the time of delivery

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HSV: Diagnostics in Patients with Genital Ulcers

- Tzanck smear (40% sensitive)
- Culture (sensitivity 30-80%)
  - Mainly used for antiviral susceptibility testing
- Antigen detection (~70% sensitive)
- PCR (FDA cleared, >90% sensitive)
  - **Preferred diagnostic test when a lesion is present**

HSV: Diagnostics in Asymptomatic Patients

- Use Glycoprotein G-based type-specific EIA assays
  - If gG2 is reactive, patient has genital herpes
    - Assay has low specificity depending on EIA index value cutoff; for an EIA cutoff <3, a second confirmatory test that uses a different HSV antigen must be performed (HSV Biokit or HSV Western Blot)
  - If gG1 is reactive, patient either has oral herpes or genital herpes (assay has low sensitivity)
- Serologic testing **NOT** routinely recommended for screening
- **Never obtain IgM or try to interpret IgM results!**

HSV: Pregnancy

- Risk of vertical transmission if mom acquires FIRST episode (i.e., primary infection) of herpes at time of delivery is up to 80%
- Risk of vertical transmission if mom has RECURRENT episode of herpes at time of delivery <1%
- C-sections are recommended ONLY IF ACTIVE LESIONS OR PRODROMAL SYMPTOMS (i.e. vulvar pain/burning) PRESENT AT DELIVERY
  - ACOG: "For women with a primary or nonprimary first-episode genital HSV infection during the 3rd trimester of pregnancy, cesarean delivery MAY BE OFFERED due to the possibility of prolonged shedding". ACOG Practice Bulletin #220, May 2020
- Efficacy data on routine acyclovir use during 3rd trimester of pregnancy to prevent HSV vertical transmission are lacking.
  - ACOG: Those with a clinical history of genital herpes should be offered suppressive viral therapy at or beyond 36 weeks of gestation ACOG Practice Bulletin #220, May 2020 & Cochrane Systematic Review 2008: https://doi.org/10.1002/14651858.CD004946.pub2

Chlamydia trachomatis L1-L3: LGV

- Classical manifestation is a short-lived **painless** genital ulcer accompanied by **painful** inguinal lymphadenopathy
- Outbreaks in US and Western Europe associated with **proctitis** particularly among MSM**********
  - Rectal pain, tenesmus, rectal bleeding/discharge
  - May be mistaken for inflammatory bowel disease histologically (early syphilitic proctitis may also be mistaken for IBD on histology)

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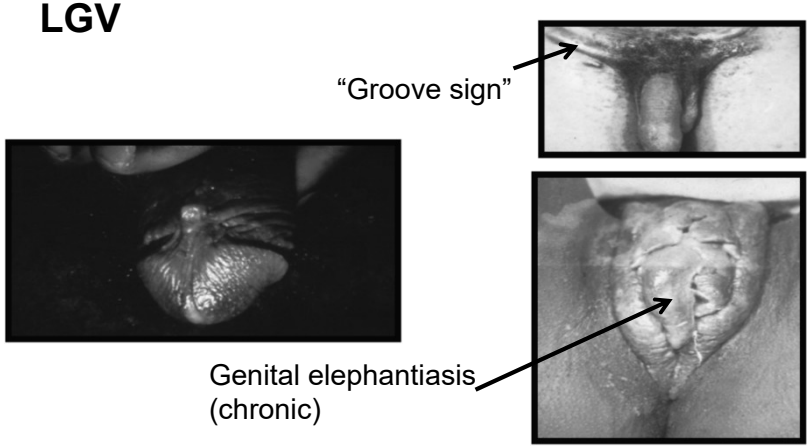
LGV



LGV Diagnosis & Therapy

- **Routine NAATs** do not distinguish between serotypes D-K and L1-L3 (LGV). **Multiplex PCR** can be performed for specific serotypes but is NOT commercially available. Serology is NOT standardized and is NOT recommended
- Therapy: **doxycycline 100mg PO BID X 3* weeks (preferred)** or azithromycin 1g PO q week X 3 weeks (alternate)
- **Patients with *C trachomatis* and a + rectal NAAT:**
  - **Mild symptoms- treat with doxycycline for 1 week**
  - **Moderate to severe symptoms- treat with doxycycline for 3 weeks**

Chancroid

- *Haemophilus ducreyi*
  - Endemic in parts of the southern US. Rates have gone down
  - Increased risk with HIV infection and commercial sex work
- Symptoms: painful, indurated, 'ragged' genital ulcers & tender suppurative inguinal adenopathy (50%); kissing lesions on thigh; 10% of patients co-infected with syphilis or HSV; bacterial superinfection not uncommon
- Dx: culture (80% sensitive) [antigen detection and PCR not widely available]
- Rx: Azithromycin 1g PO X1 OR Ceftriaxone 250mg IM X1 (erythromycin and ciprofloxacin may also be used)
- Treat all partners in preceding 60 days

Granuloma Inguinale OR Donovanosis

- *Klebsiella granulomatis (Calymmatobacterium granulomatis)*
- Not endemic in US; common in SE Asia (India), & Southern Africa (recently eradicated in Australia)
- Painless, progressive (destructive), "serpiginous" ulcerative lesions, without regional LAD (pseudobuboes occasionally); beefy red with white border & highly vascular
- Dx: tissue biopsy (no culture test; PCR not FDA cleared); demonstrating the organisms in macrophages, called **Donovan bodies**, using **Wright-Giemsa** stain (NOT Gram's stain)
- Rx: Doxycycline 100mg PO BID X 3 weeks (or until resolution) OR azithromycin 1g PO q week X3 (can also use trimethoprim/sulfa)

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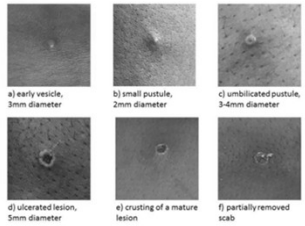
MPOX: Epidemiology

- Geographic distribution: Clades 1 (Congo basin) & 2 (West Africa); virulence varies with clade type; clades 1a [children; multiple zoonotic introductions & less efficient person-to-person] and 1b [adults; sexual transmission; more efficient transmission]; 2022-2023 Outbreak: Clade 2b; most cases in men who report sexual contact with other men Transmission via direct contact with sores or bodily fluids (likely most efficient); median duration of PCR detection in lesions is 25 days. Other routes include fomites; respiratory secretions (animal data; limited human data); vertical transmission; percutaneous.
- **Transmission most likely to occur when symptoms begin (but risk may begin up to 4 days prior to symptom onset); a person is no longer contagious when all scabs have fallen off & re-epithelialization has occurred.**

MPOX: Clinical Manifestations

- Incubation: 4 to 21 days
- Prodrome:(up to 70% of patients): Fever, chills, headache, back pain, fatigue
- Rash: (2 days before to 4 days after prodrome); **painful**; macules to papules to pseudo-pustules; traditionally lesions begin simultaneously and evolve together, but in 2022 outbreak- not all lesions were at the same stage; in 2022 outbreak lesions were mainly anogenital or perioral.
- Other manifestations: proctitis; tonsillitis; ocular (conjunctivitis, blepharitis, keratitis); neurologic (encephalitis) and other less common manifestations



UK Health Security Agency

MPOX: Treatment

- Supportive care
- Antivirals: data supporting efficacy are limited; **none FDA approved for mpox**; tecovirimat (TPOXX) for 2 weeks in patients with or at-risk for severe disease: age < 18; immunocompromised; pregnant; ocular disease (CDC-held Emergency Access Investigational New Drug Protocol); no benefit for tecovirimat in Clade I or II (N Engl J Med 2025;392:1484 N Engl J Med 2026;394:884-895) [cidofovir & brincidofovir unlikely to be on Boards]; trifluridine may be considered for ocular complications

MPOX Prevention

- Vaccines: Prior vaccinia vaccination appears to provide some protection against severe mpox disease (but not necessarily infection); 2 vaccines available: modified vaccinia Ankara (MVA; JYNNEOS)[attenuated non-replicating vaccinia virus; 2 doses]-preferred; ACAM2000 [replication-competent] associated with more side effects. Vaccinate those with risk factors: (1)Age > 18 years + MSM or (2) if traveling to an area with active spread of clade 1 with anticipated exposure or (3)occupational risks. NO routine vaccination of healthcare workers. **Vaccine may be given as PEP (within 4 days but up to 14 days) following a high-risk exposure** (e.g., sexual or intimate contact). **Monitor those exposed for 21 days**.
- Vaccinia Ig (VIG) in highly immunocompromised persons (don't use with vaccine)
- **Prevention in healthcare settings**: contact+ droplet+ airborne precautions: gowns, gloves, eye protection, and N95 (or equivalent)

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Other Causes of GUD

- **Infectious**
  - Mycobacteria (TB)
  - Fungi (candida; blastomycosis)
  - Parasites (leishmania)
- **Non-infectious**
  - **Behcet's**
  - **Granulomatosis with polyangiitis**
  - Fixed drug eruption
  - Psoriasis

GUD	Pain	Characteristics	Diagnosis	Treatment
HSV 1 & 2	Painful	Multiple, superficial, vesicular/ulcerative, erythematous base	-NAATs -Culture (sensitivity ~70%) -Serology	-Acyclovir etc. -Foscarnet (resistant HSV) -Cidofovir parenteral or topical (resistant HSV)
Syphilis (T. pallidum)	Painless	Single, well circumscribed, heaped-up borders, clean base	- Serology - PCR	-Penicillin (preferred) -Doxycycline (alternate for early and late latent)
Chancroid (H. ducreyi)	Painful	Indurated, tender suppurative inguinal LAD (50%); kissing lesions on thigh	- Culture - PCR	-Azithromycin -Ceftriaxone -Erythromycin -Ciprofloxacin
LGV (C. trachomatis)	Painless	short-lived ulcer, painful suppurative LAD, "groove sign" PROCTITIS	- NAATs - Serology - Culture (rarely)	-Doxycycline (preferred) -Azithromycin (alternate)
Granuloma Inguinale (Klebsiella granulomatis) SEE ENLARGED SLIDE FOLLOWING ENTIRE PRESENTATION	Painless	Progressive "serpiginous" without LAD; beefy red with white border & highly vascular	- Biopsy	-Doxycycline -Azithromycin -Bactrim

Thank You!

kghanem@jhmi.edu

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Natural History of Syphilis

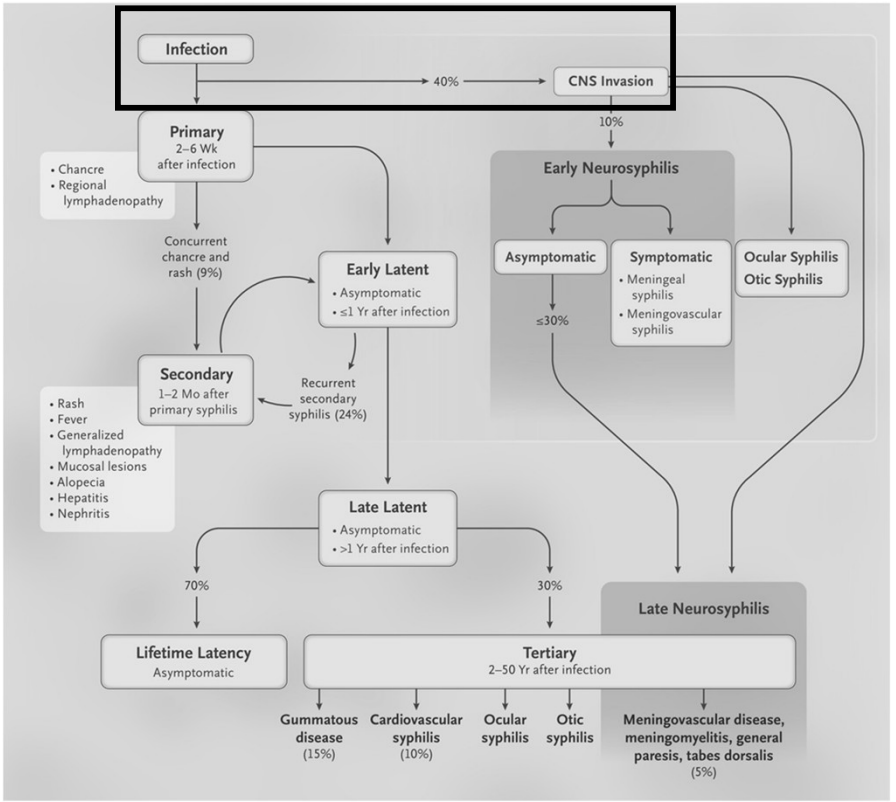
Sexual transmission (only occurs in early stages)

- Risk of infection after 1 exposure: 40%
- Index patient is most contagious during 1° and 2° stage, less so in early latent stage

Vertical transmission (may occur during any stage)

- ~80% transmission in the early stages
- ~10% transmission in the late stages

Rarely, transmission may occur through **blood transfusions** and **organ transplantations**



SEE ENLARGED SLIDE FOLLOWING ENTIRE PRESENTATION

N Engl J Med 2020;382:845-85

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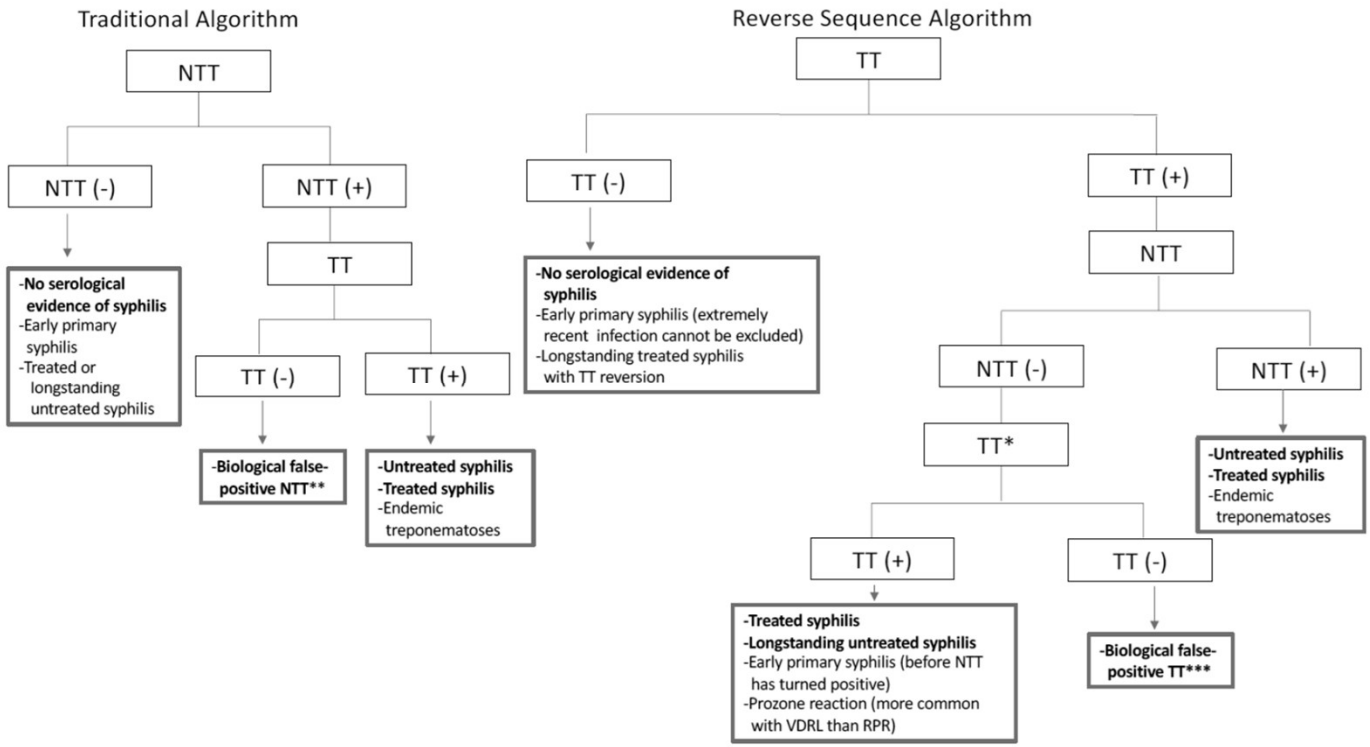

NTT= nontreponemal test [rapid plasma reagin (RPR); venereal disease research laboratory (VDRL)]; TT= treponemal test [e.g. fluorescent treponemal antibody absorption test (FTA-ABS);

SEE ENLARGED SLIDE FOLLOWING ENTIRE PRESENTATION

*N Engl J Med 2020;382:845-854

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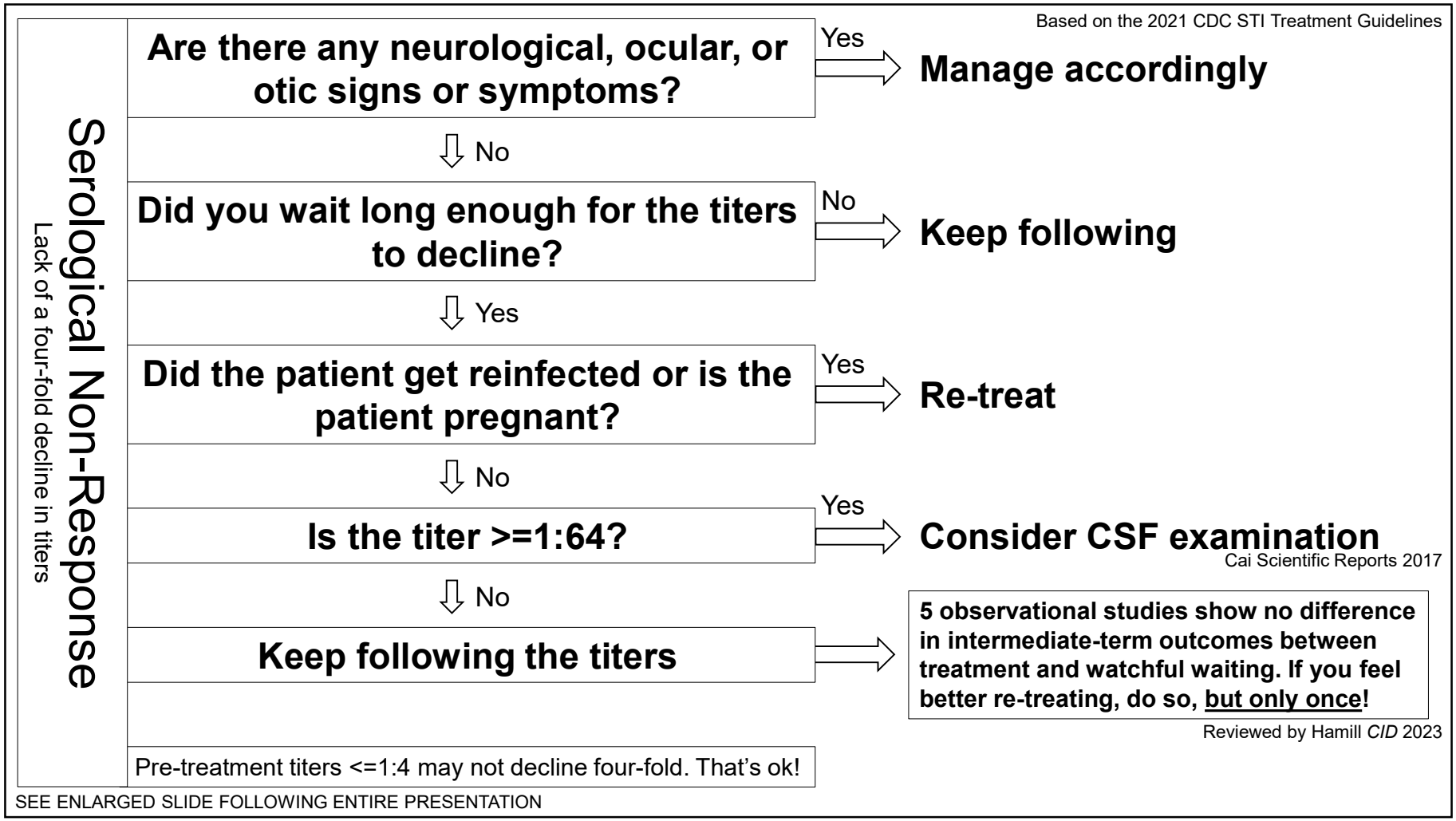

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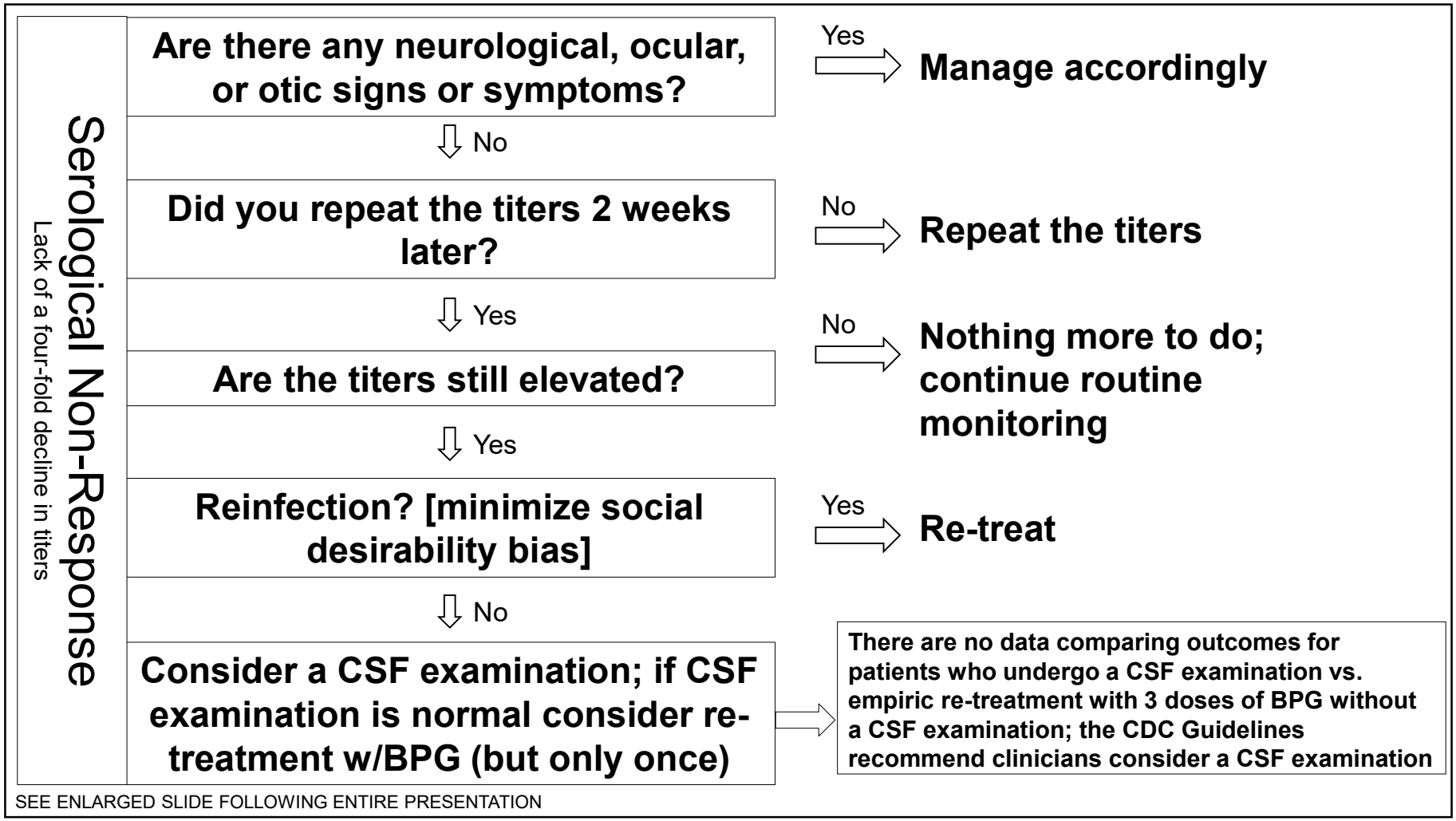

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GUD	Pain	Characteristics	Diagnosis	Treatment
HSV 1 & 2	Painful	Multiple, superficial, vesicular/ulcerative, erythematous base	-NAATs -Culture (sensitivity ~70%) -Serology	-Acyclovir etc. -Foscarnet (resistant HSV) -Cidofovir parenteral or topical (resistant HSV)
Syphilis (T. pallidum)	Painless	Single, well circumscribed, heaped-up borders, clean base	- Serology - PCR	-Penicillin (preferred) -Doxycycline (alternate for early and late latent)
Chancroid (H. ducreyi)	Painful	Indurated, tender suppurative inguinal LAD (50%); kissing lesions on thigh	- Culture - PCR	-Azithromycin -Ceftriaxone -Erythromycin -Ciprofloxacin
LGV (C. trachomatis)	Painless	short-lived ulcer, painful suppurative LAD, “groove sign” PROCTITIS	- NAATs - Serology - Culture (rarely)	-Doxycycline (preferred) -Azithromycin (alternate)
Granuloma Inguinale (Klebsiella granulomatis) SEE ENLARGED SLIDE FOLLOWING ENTIRE PRESENTATION	Painless	Progressive “serpiginous” without LAD; beefy red with white border & highly vascular	- Biopsy	-Doxycycline -Azithromycin -Bactrim

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Zoonoses

David Aronoff, MD

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Zoonoses

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7/28/2026

Disclosures of Financial Relationships with Relevant Commercial Interests

- List of disclosures or “None”

Zoonoses: Important!

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

Judson SD & Rabinowitz PM. *Curr Opin Infect Dis* 2021, 34:385–392

Question #1

- A previously healthy 42-year-old man presents to a district hospital in rural northwestern Bangladesh in late January. He developed fever, headache, & myalgias 5 days ago.
- Over the past 2 days he has become progressively confused & drowsy, & today he developed a cough & shortness of breath.
- On arrival, temperature is 39.4°C, blood pressure 138/86 mm Hg, pulse 112/min, and respiratory rate 28/min. He is somnolent & disoriented. Neurologic examination shows a depressed level of consciousness & brief, repetitive jerking movements of the limbs.
- Cerebrospinal fluid analysis reveals a lymphocyte-predominant pleocytosis with mildly elevated protein & normal glucose.
- Two other residents of his village have been hospitalized during the same period with a similar rapidly progressive febrile encephalitis.

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Question #1

Which of the following is the most likely source of this patient's infection?

A. Consuming unpasteurized dairy products
B. Drinking raw date palm sap
C. Receiving a bite from a stray dog
D. Receiving a mosquito bite
E. Swimming in a stagnant freshwater pond

Question #2

The patient's serum is positive for IgM antibodies against Nipah virus.

Which of the following is the natural reservoir of this virus?

A. Domestic pigs
B. Fruit bats of the genus Pteropus
C. Palm civets
D. Rhesus macaques
E. Rodents of the genus Rattus

Table 1. Zoonotic pathogens causing recent epidemics

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

SEE ENLARGED SLIDE FOLLOWING ENTIRE PRESENTATION

Judson SD & Rabinowitz PM. *Curr Opin Infect Dis* 2021, 34:385–392

There Are Many

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

	Causative agent(s)
Bacterial zoonoses transmitted by direct contact with animals or infected animal materials	
Anthrax	*Bacillus anthracis*
Brucellosis	*Brucella* spp.
Cat scratch disease	*Bartonella* spp.
Erysipelothrix infections	*Erysipelothrix rhusiopathiae*
Glanders and melioidosis	*Burkholderia mallei* and *Burkholderia pseudomallei*
Leptospirosis	*Leptospira interrogans* spp.
Mycobacterioses	*Mycobacteria* spp.
Q fever	*Coxiella burnetii*
Bacterial zoonoses transmitted principally by animal bites or scratches	
Pasteurellosis	*Pasteurella multocida* and other spp.
Capnocytophaga infections	*Capnocytophaga canimorsus*
Cat scratch disease	*Bartonella henselae*
Rat bite fever	*Spirillum minus* and *Streptobacillus moniliformis*
Vector-borne bacterial zoonoses	
Lyme borreliosis	*Borrelia burgdorferi* sensu lato (incl. *Borrelia garinii*, *Borrelia afzelii*)
Tick- and louse-borne relapsing fever borreliosis	*Borrelia recurrentis*, *Borrelia turicatae*, *Borrelia hermsii*, others
Plague	*Yersinia pestis*
Tularaemia	*Francisella tularensis*
Rickettsioses	Spotted fever and typhus group *Rickettsia* species
Ehrlichiosis and Anaplasmosis	*Ehrlichia chaffeensis*, *Anaplasma phagocytophilum*
Scrub typhus	*Orientia tsutsugamushi*
Foodborne bacterial zoonoses and intoxications	
Salmonellosis	*Salmonella enteritidis*
Campylobacteriosis	*Campylobacter* spp.
Listeriosis	*Listeria monocytogenes*
Escherichia coli O157:H7 infections	*Escherichia coli* STEC
Yersinia enterocolitica infections	*Yersinia enterocolitica*
Clostridium perfringens gastroenteritis	*Clostridium perfringens*
Botulism	*Clostridium botulinum*
Staphylococcal food poisoning	*Staphylococcus aureus*

SEE ENLARGED SLIDE FOLLOWING ENTIRE PRESENTATION

Chikeka & Dumler *Clin Microbiol Infect* 2015; 21: 404–415

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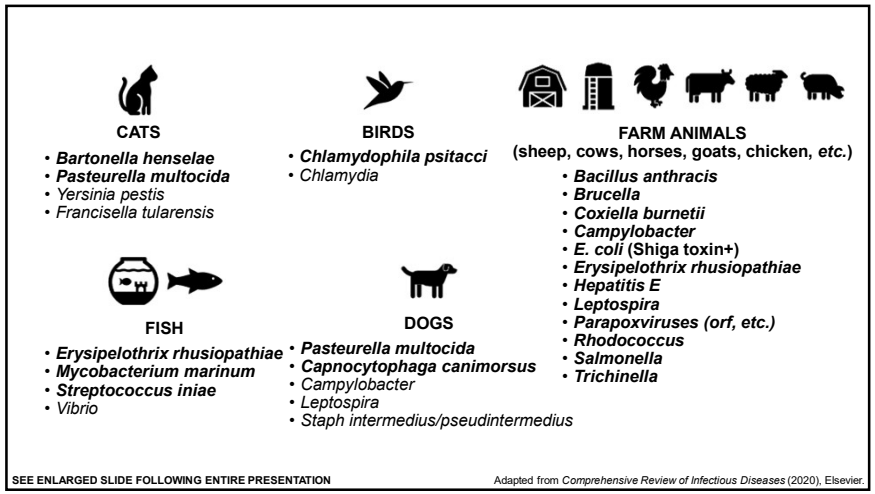

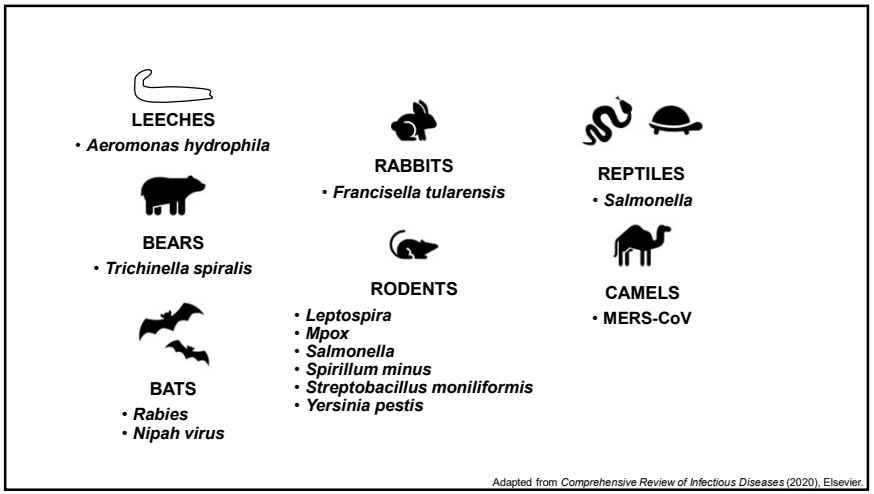

Zoonoses: Various Routes of Infection

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

Direct Contact with Animal or Animal Tissue

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Question #3

- 25-year-old male presented in July with painful right inguinal mass of one week's duration.
- He is otherwise well. Married. Monogamous. No hx penile or skin lesion.
- Fishing last week in Northern Virginia creek, hiked through wooded area. Picked ticks off legs & neck. Has kitten & dog.
- Exam: T37oC, 5 cm tender red mass in right mid-inguinal area, fixed to skin. Genitalia normal. Aspiration of soft center: 5 cc yellow pus. Gm stain neg. Cephalexin 250 mg QID.
- One week later: mass unchanged. Culture neg. Syphilis FTA & HIV neg.

Question #3

What is the most likely diagnosis?

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

Purulent Inguinal Node

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

Purulent Inguinal Node (continued)

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

Image from https://www.skinsight.com/skin-conditions/adult/lymphogranuloma-venereum-lgv

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Cat Scratch Disease

- B. henselae causes most cases
- >13,000 cases in the USA per year1
- 80% <21 yrs old
- Clinical findings:
  - Acute suppurative lymphadenitis proximal to bite, scratch, lick of young cat
  - Fever, headache, poor appetite, & exhaustion
  - Cats have chronic bacteremia but seem healthy
- Cat fleas may transmit between cats & occasionally to humans

1. Nelson CA, *at al. Emerging Infectious Diseases* 22 (2016)
Cat photo from http://www.catscratchmed.com
Cartoon from CDC.gov

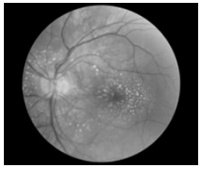
Diagnosis

- Compatible clinical syndrome
- Fastidious, slow-growing
  - Hold 21 days
- Serology (but cross reactive with other *Bartonella spp*.)
- Molecular (PCR) on tissue/nodes

Image adapted from https://my.clevelandclinic.org/health/diseases/23537-cat-scratch-fever
Diagnostic info https://www.cdc.gov/bartonella/bartonella-henselae/

Cat Scratch Disease

- Papule or pustule often at inoculation site if sought
- Often self-limited
- Encephalitis, stellate retinitis, uveitis rare



Lipid exudates forming a macular star

Photos from http://www.catscratchmed.com,
http://imagebank.asrs.org/file/1173/cat-scratch-retinitis-with-macular-lipid,
http://www.nejm.org/doi/full/10.1056/ENEJMicm010038#t=article
Encephalitis reference: Fan J & Ali H.) *Proc Bayl Univ Med Cent*. 2020 Jul; 33(3): 440–441.

Cat Scratch Disease

- Rx: 10% drain spontaneously
- If not, node aspiration improves pain & helps exclude Staph. aureus

Treatment = Azithromycin x 5 d (TMP/SMX, clarithromycin, ciprofloxacin or rifampin as alternatives)	Treat to prevent serious complications, since up to 14% of patients will have dissemination, with potential infection of the liver, spleen, eye, or CNS

Spach DH & Kaplan SL, UpToDate (2025)

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Warthin Starry Silver Stain

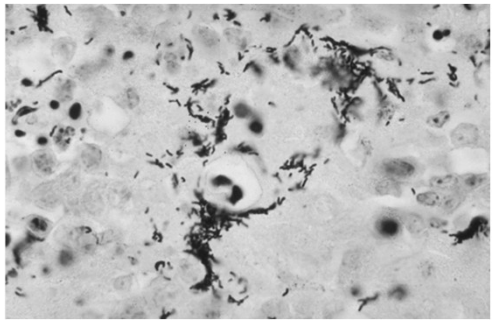
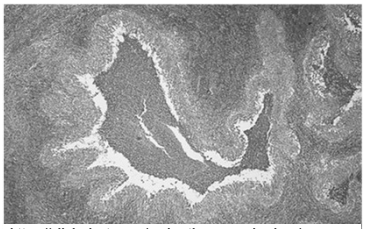


Photo by Andrew Margileth, MD.
from http://emedicine.medscape.com/article/214100-workup#c8

Cat Scratch Lymphadenopathy

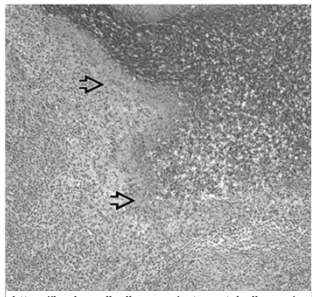
Stellate abscesses, necrotizing granulomas

Necrotic area with neutrophils surrounded by **palisading histiocytes**



https://clinicalgate.com/nodes-thymus-and-spleen/

Lymph nodes showing central abscess formation surrounded by palisaded histiocytes



https://basicmedicalkey.com/cat-scratch-disease/

Disseminated Bartonellosis

- Disseminated Bartonella henselae infection presents with a spectrum of severe manifestations, including persistent bacteremia, endocarditis, bacillary angiomatosis, peliosis hepatis, & multi-organ involvement

Treatment of *B. henselae*

- The combination of doxycycline + rifampin is a principal treatment for **disseminated** *B. henselae* infections (as is doxy + gent)
- But a recent study reported a 39% treatment failure rate

Pizzuti M, *et al. Infection* (2024) 52:1307–1314

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Anthrax

Cutaneous anthrax treated with doxycycline

At diagnosis | **6 Days Later** | **4 Weeks After Diagnosis**

Images from https://www.dermnetnz.org/topics/anthrax

Anthrax

- Bacillus anthracis: Aerobic, encapsulated, sporulating Gram-positive bacillus

- Usually infects cattle & sheep
- Human exposure may be through agriculture, or from related industry
- Those at highest risk are shepherds, farmers, & workers in facilities that use animal products, esp. contaminated goat hair, wool, or bone
- Incubation period about a week
- 2o meningitis reported in ~10% of pts hospitalized w/ cutaneous anthrax

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

Anthrax

- Skin (95%): pruritic papule on skin exposed to goat hair, animal hides. Small vesicles around an ulcer. +/- pain. Edema. Mild systemic symptoms usually
- Inhalation anthrax results from the inhalation of spores when aerosolized while working with contaminated animal products (wool, hair, hides)
- DX: Can be seen on smear, culture of vesicle fluid (alert the lab!)
- Inhalation (5%), ingestion (<1%)
- Anthrax rare in USA

https://www.pcds.org.uk/clinical-guidance/anthrax
Wilson KH, *UpToDate* (2025)

Anthrax

- Systemic anthrax:
- Pt. suspected of having inhalational, GI, injection anthrax, or anthrax meningitis should be treated urgently with intravenous antimicrobial combination therapy & antitoxin (raxibacumab, obiltoxaximab, or anthrax immunoglobulin) from CDC
- Empiric regimen = combination of 2 bactericidal agents + 1 protein-synthesis inhibitor
  - MEROPENEM + FQ (cipro/levo) + TCN (mino/doxy)
  - 2 weeks (>3 weeks for meningitis)
- Cutaneous anthrax: FQ (cipro/levo) or TCN (mino/doxy) x 7-10 days

Wilson KH, *UpToDate* (2025)

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

Edema
Vesicles
Necrotic Ulcer

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

Tularemia

Image from cdc.gov

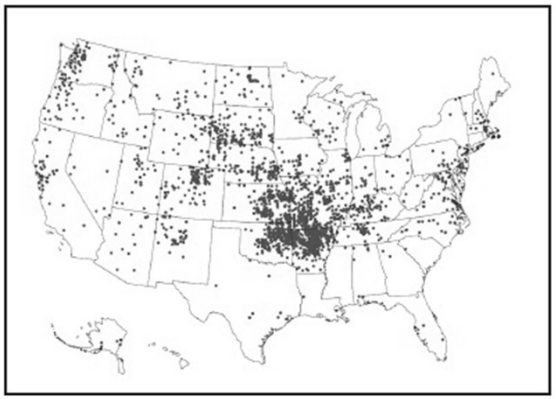
Tularemia

- Highly infectious gram-negative **coccobacillus** *Francisella tularensis*
- Teir 1 select agent with potential for misuse as bioweapon
- Vectors = **Ticks** (*Dermacentor variabilis* > *Amblyomma americanum*) & **Deerflies**
- Direct inoculation = rabbits, squirrels, muskrats, beavers, cats (bites)
- Hunters **skinning animals** (old days); farmers, veterinarians
- Red tender local lymph node inoculation site may form ulcer
- **Ulceroglandular** is the most common manifestation
- Risk of bio-weaponization

~200 cases per year in the USA

FIGURE 1. Reported tularemia cases, by county of residence* — United States, 2011–2022

Rich SN, *et al. MMWR* (2025)



* Cases are indicated randomly within county of residence.

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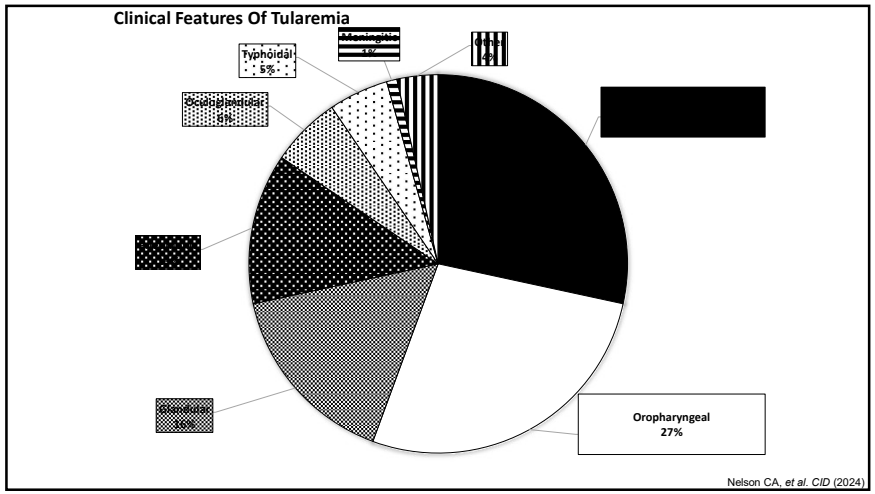
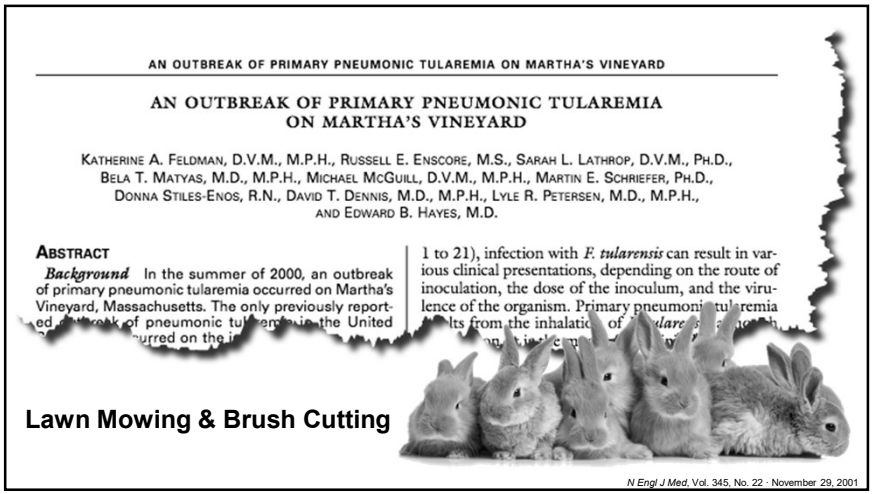


Nelson CA, *et al. CID* (2024)



N Engl J Med, Vol. 345, No. 22 · November 29, 2001

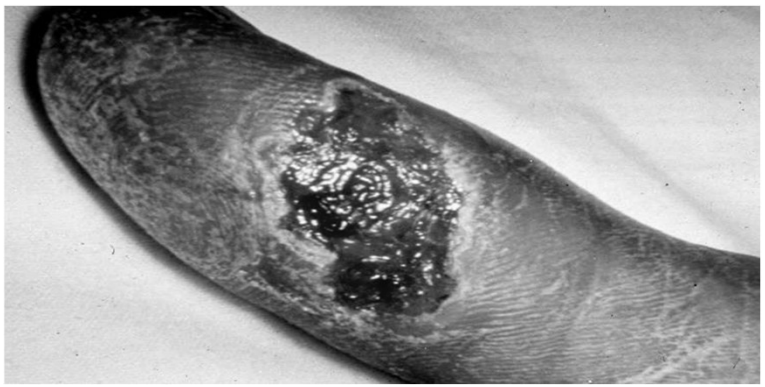
Tularemia

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

BCYE – buffered charcoal yeast extract

Maurin & Gyuranecz. *Lancet* (2016)
Nelson CA, *et al. CID* (2024)
Rich SN, *et al. MMWR* (2025)

Rabbit Skinner



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Glandular Tularemia

- 68-year-old with 1 week fever then 2-month progressive, painful swelling on R. side of neck
- Exposure to a sick cat
- Diagnosis made by + IgM (1:1280)
- Improved with 4 weeks doxycycline

Marks, Laura, & Spec. "Glandular Tularemia." *New England Journal of Medicine* 379.10 (2018): 967-967.

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

Volume 78, Issue Supplement_1
15 February 2024

Contact with Insect Vector

Plague

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Plague

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

(Michael Smith, Getty Images)

(Eye of Science/Science Source)

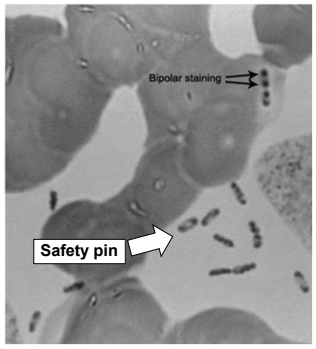
Why Madagascar & Plague?

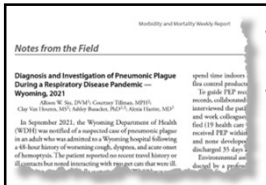
Factor	Madagascar	Other Endemic Regions (e.g., U.S. Southwest, Central Asia)
Primary Reservoirs	Black rats (*Rattus rattus*) living in close contact with humans	Wild rodents (prairie dogs, ground squirrels, gerbils) usually far from people
Main Flea Vector	*Xenopsylla cheopis* (oriental rat flea) — highly efficient at transmitting plague	Other flea species, generally less efficient or less abundant
Transmission Cycle	Domestic rat → flea → human cycle well established	Mostly sylvatic (wild animal → flea → wild animal), rare human involvement
Climate	Highland climate (mild, rainy season supports flea survival and population growth)	Often arid/desert climates, less favorable for flea proliferation
Housing & Sanitation	Many homes allow rodent entry; poverty limits rodent/flea control	Better housing quality and vector control reduce contact with rodents
Healthcare Access	Limited, especially in rural areas → delays in diagnosis and treatment	Faster access to medical care and antibiotics prevents outbreaks
Burden of Disease	Several hundred cases annually; occasional large outbreaks (e.g., 2017 urban outbreak)	Sporadic cases (dozens or fewer per year) with rare local outbreaks

SEE ENLARGED SLIDE FOLLOWING ENTIRE PRESENTATION

Plague

- Gram negative coccobacillus
- **Bipolar-staining** bacilli
- **Safety pin** appearance
  - *Yersinia pestis*: lab hazard
- Dx: PCR, Ag assay, culture
- Treatment: **Streptomycin or FQs** >> doxy




Notes from the Field

Diagnosis and Investigation of Pneumonic Plague During a Respiratory Disease Pandemic — Wyoming, 2021

Oregon's first case of human plague in 8 years likely came from a pet cat

Wyoming woman catches rare pneumonic plague from cats

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

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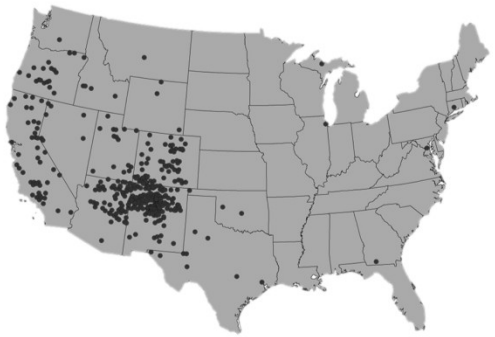
Plague Map USA



1970-2020

https://www.cdc.gov/plague/maps/index.html

Pneumonic Form

Rapid Progression of Pneumonic Plague on CXR over 13 Hours

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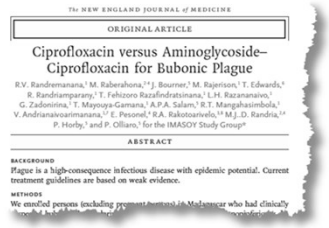
Image from Canyon, Deon V. "Environmental Change and Human Health Case Studies I." (2008).

Bubonic Form

Wikipedia image

Treatment



The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Ciprofloxacin versus Aminoglycoside–Ciprofloxacin for Bubonic Plague

R.V. Randremanana,[1] M. Raberahona,[1,2] J. Bourner,[3] M. Rajerison,[1] T. Edwards,[4] R. Randriamparany,[1] T. Fehizoro Razafindratsimana,[1] L.H. Razananaivo,[1] G. Zadonirina,[1] T. Mayouya-Gamana,[1] A.P.A. Salam,[1] R.T. Mangahasimbola,[1] V. Andrianaivoarimanana,[1,2] E. Pesonel,[1] R.A. Rakotoarivelo,[1,2] M.J..D. Randria,[1,2] P. Horby,[3] and P. Olliaro,[3] for the IMASOY Study Group*

ABSTRACT

BACKGROUND

Plague is a high-consequence infectious disease with epidemic potential. Current treatment guidelines are based on weak evidence.

METHODS

We enrolled persons (excluding pregnant women) in Madagascar who had clinically

RCT aminoglycoside (SM) x 3d -> FQ (cipro) x 7d vs FQ alone x 10 days

Cipro alone was non-inferior

Randremanana RV, *et al. NEJM* (2025)

23 Zoonoses

Speaker: David Aronoff, MD

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Intact Skin Contact with Animal Urine

Question #4

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

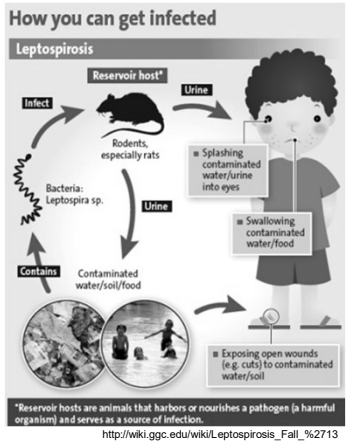
Question #4

What is the most likely diagnosis?

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

Leptospirosis

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



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

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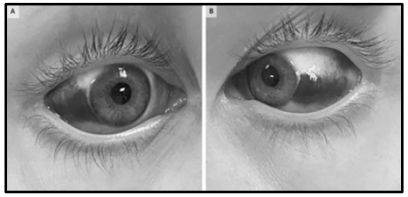
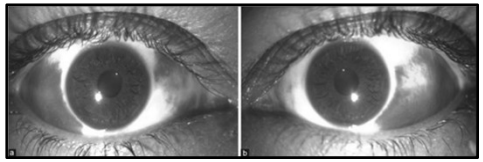
Leptospirosis

- Fever, myalgia, headache (aseptic meningitis late in course)
- **Conjunctival suffusion**, +/- rash
- In severe cases: jaundice (Weil syndrome), azotemia, pulm. hemorrhage
  - Jaundice: bilirubin is high out of proportion to transaminase elevation
- Lab: serology by agglutination test, culture urine in Fletcher's medium
  - PCR & sequencing emerging (Ciurariu E, et al. *Microorganisms* 2025)
- Rx: **doxycycline** for outpatients, IV penicillin for inpatients
  - Jarisch-Herxheimer in first 2 hr

Conjunctival Suffusion & Leptospirosis



Rijnink E, *et al. N Engl J Med* 2022;387: e71



Khurana S, *et al. Indian J Ophthalmol*. 2020 Sep; 68(9): 1971.

Ingestion of Animal Products

Question #5

- A 41-year-old car salesperson from Baltimore was admitted for a febrile illness & found to have Brucella melitensis in their blood culture. They had attended a dinner a month prior where some family members from Greece had brought food from home.
- About two weeks prior to onset of fever, they had bought some lamb & beef at a farmer's market outside Baltimore.

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Question #5

Which of the following is the most likely source of the brucellosis?

A. Home made sausage from Greece
B. Home made goat cheese from Greece
C. Cole slaw from a Baltimore delicatessen
D. Beef tartar, meat from the farmer's market
E. Lamb kabobs, meat from the farmer's market

Brucellosis

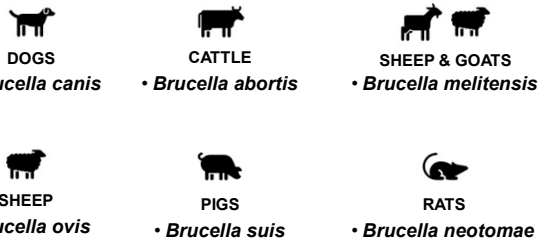
- Brucellosis is most often transmitted through the ingestion of raw or unpasteurized dairy products from infected animals, including milk & cheese (unpasteurized)
- Brucellosis can be transmitted through direct contact with infected animals or their bodily fluids, including vaginal discharges, aborted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

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

Brucellosis

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

Animal Sources of *Brucella*



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

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Brucellosis

Later onset lesions in bone, liver

Epididymo-orchitis[1], endocarditis

Sacroiliitis, tenosynovitis, meningitis

Biopsy needle

Malodorous perspiration (uncommon) "pathognomonic"[2]

1. Ip CCK, *et al. BMJ Case Rep* 2019;12:e230007. doi:10.1136/bcr-2019-230007
2. Pappas G, *et al. NEJM* (2005)

Brucellosis (cont.)

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

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

Question #6

What common cause of acute hepatitis is acquired via fecal-oral transmission or from undercooked meats, especially pig/wild boar?

It is particularly severe in pregnant patients, causing stillbirths & maternal mortality.

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

Inhalation of Animal Products

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Question #7

- A 22-year-old previously healthy male contractor returned from Afghanistan one week prior to presentation. He had a three-day history of fever, myalgia, arthralgia, mild headache & cough. He had vomited once & had mild midepigastric, non-radiating pain.
- The facility he was hired to guard was adjacent to the path that the local sheep & goat herders used on their way to market & he had purchased a wool rug from one of the locals. He remembers shaking it hard to get rid of the dust.
- He reported that some members of his guard unit also had flu-like illness from which they recovered without treatment.

Question #7

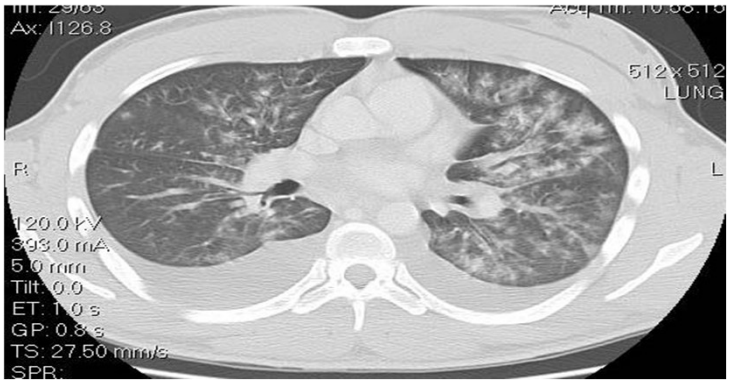
- Examination was normal except for a variable temperature up to 102°F
- WBC **3.3**K, platelets **121**K, creatinine 1.2, AST **144**, ALT **154**, alk phos 88, total bilirubin 0.6
- Admission chest X-ray was normal
- Ceftriaxone was begun but the patient remained febrile & had the chest CT shown on the next slide

Question #7

Which of the following is the most likely diagnosis?

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

Question #7



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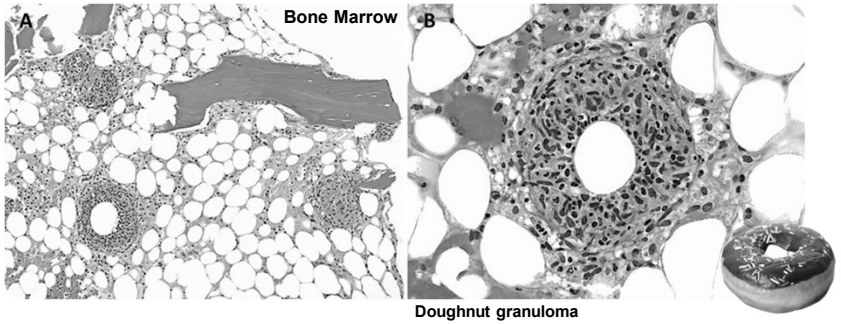
Q Fever

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

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



Doughnut granuloma

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

The End

Thank you!
aronoff@iu.edu

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

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Table 1. Zoonotic pathogens causing recent epidemics

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

SEE ENLARGED SLIDE FOLLOWING ENTIRE PRESENTATION

Judson SD & Rabinowitz PM. *Curr Opin Infect Dis* 2021, 34:385–392

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There Are Many

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

Bacterial zoonoses transmitted by direct contact with animals or infected animal materials	Causative agent(s)
Anthrax	*Bacillus anthracis*
Brucellosis	*Brucella* spp.
Cat scratch disease	*Bartonella* spp.
Erysipelothrix infections	*Erysipelothrix rhusiopathiae*
Glanders and melioidosis	*Burkholderia mallei* and *Burkholderia pseudomallei*
Leptospirosis	*Leptospira interrogans* spp.
Mycobacterioses	*Mycobacteria* spp.
Q fever	*Coxiella burnetii*
Bacterial zoonoses transmitted principally by animal bites or scratches	
Pasteurellosis	*Pasteurella multocida* and other spp.
Capnocytophaga infections	*Capnocytophaga canimorsus*
Cat scratch disease	*Bartonella henselae*
Rat bite fever	*Spinillum minus* and *Streptobacillus moniliformis*
Vector-borne bacterial zoonoses	
Lyme borreliosis	*Borrelia burgdorferi* sensu lato (incl. *Borrelia garinii*, *Borrelia afzelii*)
Tick- and louse-borne relapsing fever borreliosis	*Borrelia recurrentis*, *Borrelia turicatae*, *Borrelia hermsii*, others
Plague	*Yersinia pestis*
Tularaemia	*Francisella tularensis*
Rickettsioses	Spotted fever and typhus group *Rickettsia* species
Ehrlichiosis and Anaplasmosis	*Ehrlichia chaffeensis*, *Anaplasma phagocytophilum*
Scrub typhus	*Orientia tsutsugamushi*
Foodborne bacterial zoonoses and intoxications	
Salmonellosis	*Salmonella enteritidis*
Campylobacteriosis	*Campylobacter* spp.
Listeriosis	*Listeria monocytogenes*
Escherichia coli O157:H7 infections	*Escherichia coli* STEC
Yersinia enterocolitica infections	*Yersinia enterocolitica*
Clostridium perfringens gastroenteritis	*Clostridium perfringens*
Botulism	*Clostridium botulinum*
Staphylococcal food poisoning	*Staphylococcus aureus*

SEE ENLARGED SLIDE FOLLOWING ENTIRE PRESENTATION

Chikeka & Dumler *Clin Microbiol Infect* 2015; 21: 404–415

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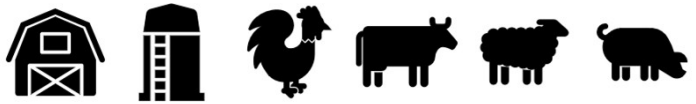
CATS

- ***Bartonella henselae***
- ***Pasteurella multocida***
- *Yersinia pestis*
- *Francisella tularensis*

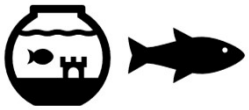
BIRDS

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



FARM ANIMALS
(sheep, cows, horses, goats, chicken, *etc.*)

- ***Bacillus anthracis***
- ***Brucella***
- ***Coxiella burnetii***
- ***Campylobacter***
- ***E. coli*** **(Shiga toxin+)**
- ***Erysipelothrix rhusiopathiae***
- ***Hepatitis E***
- ***Leptospira***
- ***Parapoxviruses (orf, etc.)***
- ***Rhodococcus***
- ***Salmonella***
- ***Trichinella***



FISH

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

DOGS

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

SEE ENLARGED SLIDE FOLLOWING ENTIRE PRESENTATION

Adapted from *Comprehensive Review of Infectious Diseases* (2020), Elsevier.

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Why Madagascar & Plague?

Factor	Madagascar	Other Endemic Regions (e.g., U.S. Southwest, Central Asia)
Primary Reservoirs	Black rats (*Rattus rattus*) living in close contact with humans	Wild rodents (prairie dogs, ground squirrels, gerbils) usually far from people
Main Flea Vector	*Xenopsylla cheopis* (oriental rat flea) — highly efficient at transmitting plague	Other flea species, generally less efficient or less abundant
Transmission Cycle	Domestic rat → flea → human cycle well established	Mostly sylvatic (wild animal → flea → wild animal), rare human involvement
Climate	Highland climate (mild, rainy season supports flea survival and population growth)	Often arid/desert climates, less favorable for flea proliferation
Housing & Sanitation	Many homes allow rodent entry; poverty limits rodent/flea control	Better housing quality and vector control reduce contact with rodents
Healthcare Access	Limited, especially in rural areas → delays in diagnosis and treatment	Faster access to medical care and antibiotics prevents outbreaks
Burden of Disease	Several hundred cases annually; occasional large outbreaks (e.g., 2017 urban outbreak)	Sporadic cases (dozens or fewer per year) with rare local outbreaks

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Monday, August 24, 2026

24

Nocardiosis, Actinomycosis, Rhodococcus and Melioidosis

David Aronoff, MD

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Nocardia, Actinomycosis, Rhodococcus, & Melioidosis

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8/8/2026

Disclosures of Financial Relationships with Relevant Commercial Interests

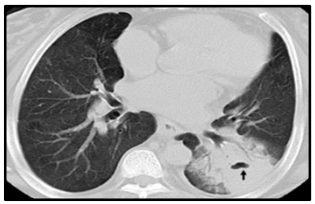
- None

Question #1

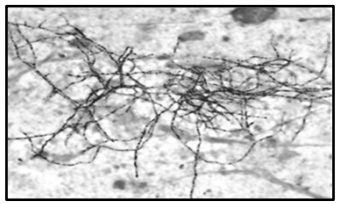
54-year-old man with 4 weeks of cough, low grade fevers, & left-sided chest pain. Received a liver transplant 11 months ago, complicated by rejection, requiring high dose steroids 4 months ago. He receives TMP/SMX three times a week. On exam, he is stable, chronically-ill appearing, febrile (101.1oF),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

Question #1

Chest CT



BAL



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

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Question #1

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

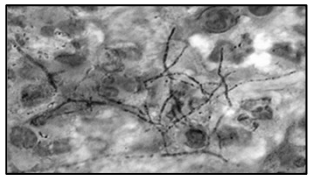
A. Cryptococcus neoformans
B. Histoplasma capsulatum
C. Actinomyces israellii
D. Nocardia farcinica
E. Aspergillus fumigatus

Question #2

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

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

Nocardia Infections

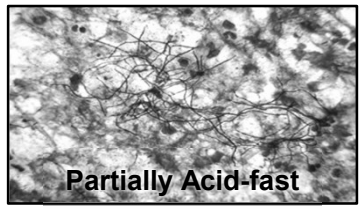


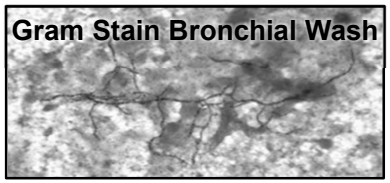
- 500-1000 cases in US/year
- Microbiology:
  - Beaded & branching gram-positive rods
  - Partially acid-fast
  - Aerobic (unlike anaerobic Actinomyces)
  - More than 80 species & >40 cause disease in humans
    - New phylogeny based on DNA sequence (formerly, N. asteroides complex): species names are lookups.
- Pathogenesis:
  - Inhalation (most common)
  - Direct inoculation through the skin

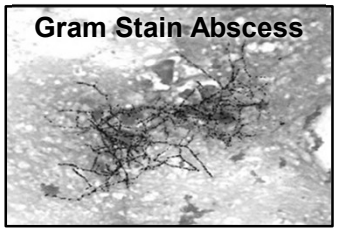
Photo: http://path.upmc.edu/cases/case226/dx.html; Good reference: Restrepo A & Clark NM. *Clinical Transplantation*. 2019;e13509.

Images of *Nocardia*

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







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

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Clinical Features of *Nocardia*

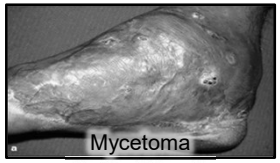
- **Immunocompromised (~60-70% of cases)**
  - **Glucocorticoid use, solid organ transplant**, hematopoietic transplant, alcoholism, diabetes, CGD, CF, autoantibodies against GM-CSF (seen in autoimmune pulmonary alveolar proteinosis), anti-TNF therapy, ectopic ACTH syndrome, AIDS (less common)
    - *PJP prophylaxis may not prevent nocardiosis* (& does not predict TMP/SMX resistance)
  - Months to years after transplantation
- **90%: slowly progressive pneumonia** with cough, dyspnea, & fever
  - *Aspergillus* similar; co-infections occur
  - Similar to cryptococcal disease & actinomycosis
  - Can disseminate to any organ (**brain** in particular: **get MRI**; can be asymptomatic!)

Margalit I, *et al. Clinical Microbiology and Infection* (2021); Liu Y, *et al. BMC Microbio.* (2024)

Clinical Features of *Nocardia*

- 10%: Skin infections from direct inoculation:
  - Immunocompetent host in tropical region (N. brasiliensis; ~80%)
  - Immunocompromised patient who gardens or walks barefoot
  - Sporotrichoid lesions
  - Mycetomas: chronic, progressive, lower limbs, draining sinuses (similar to Actinomycetes & eumycetoma).

Baradkar V P, *et al. Indian J Pathol Microbiol* 2008;51:432-4



Sharma NL, *et al. Indian J Dermatol Venereol Leprol* 2008;74:635-40

Clinical Features of *Nocardia*

- A 75-year-old woman
- 10-day history of painful lesions on the R. hand & forearm
- Nodules appeared on back of hand at site of a thorn puncture sustained while gardening
- *Reminder: tetanus booster needed*

Pipito L, *et al. N Engl J Med* 2023;388:1701

Nocardia Diagnosis

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

Odd fact: *Nocardia* can cause a false positive galactomannan test

MALDI-TOF: Liu Y, *et al. BMC Microbio.* (2024)

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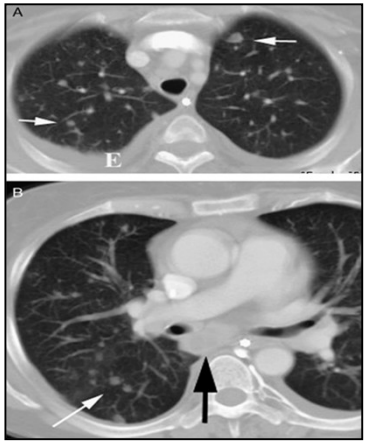
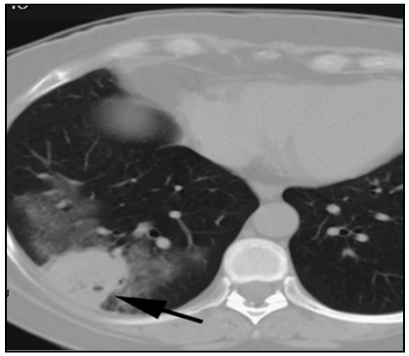
- 56-year-old woman post kidney-pancreas transplant & *N. brasilienses*
- Small lung nodules (white arrows), small right pleural effusion & subcarinal lymphadenopathy (black arrow)



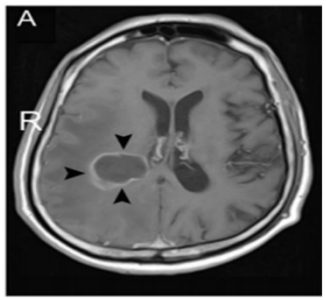
Pulmonary Nocardiosis: Computed Tomography Features at Diagnosis. Blackmon, Kevin; Ravenel, James; Gomez, Juan; Ciolino, Jody; Wray, Dannah. *Journal of Thoracic Imaging*. 26(3):224-229, August 2011. DOI: 10.1097/RTI.0b013e3181f45dd5

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



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

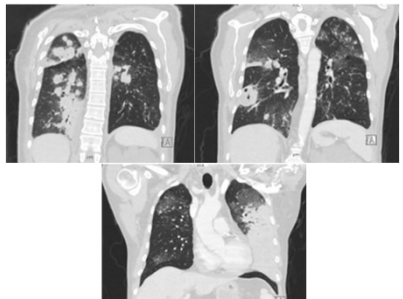
- Right frontoparietal subcortical ring lesion with a central dark signal & bright **ring enhancement** (black arrowheads) in postcontrast T1-weighted image



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

Case Study

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



Nocardia nova

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

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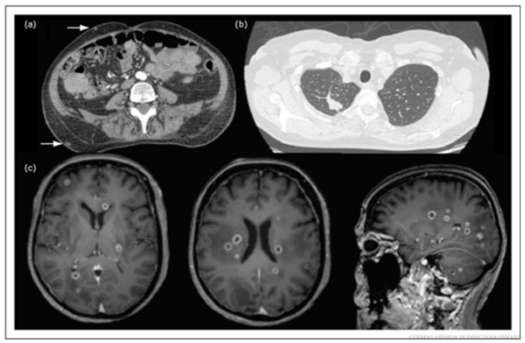
Case Study

Nocardia cerradoensis



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

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

Nocardia Treatment

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

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

Nocardia Treatment

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

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

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

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

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

Nocardia Buzzwords

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

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Rhodococcus

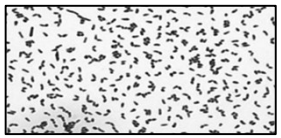

Photo: Microbe canvas

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

Rhodococcus

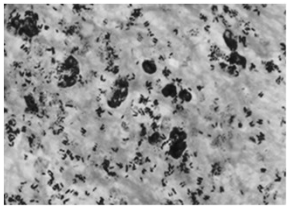

Image from W.V. Lin *et al. / Clinical Microbiology and Infection* (2019)

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

Rhodococcus

- 33-year-old male PLWHA (CD4 = 20) who lived on a cattle & horse farm
- Presented to hospital with 1 month of fever, dry cough, 13# weight loss, sweats & anorexia

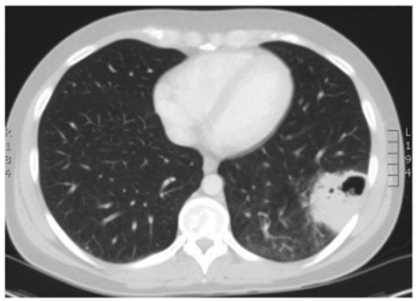

Image from Stewart A., *et al. IDCases*. (2019)

Rhodococcus

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

Zhu H, et al. Infect Drug Res (2025), Lin WV, *et al. Clin Micro Infect* (2019), Stewart A., *et al. IDCases*. (2019)
Kotton CN, *Uptodate* (2023)

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Rhodococcus Buzzwords

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

Odd fact: *Rhodococcus* can cause a false positive galactomannan test

Question #3

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

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

Question #3

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

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

Melioidosis Microbiology & Epidemiology

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

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

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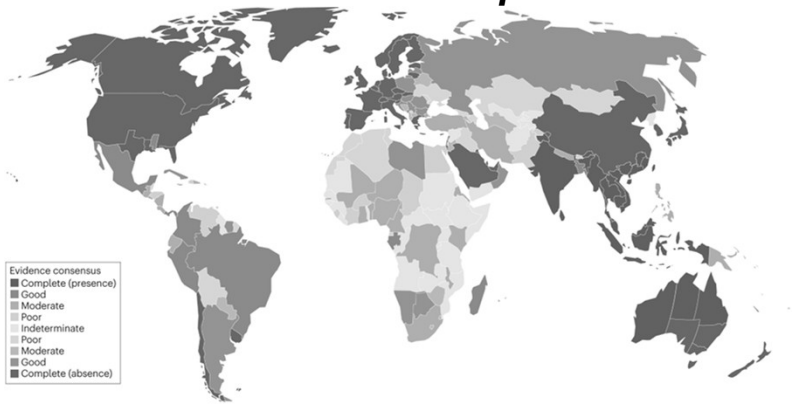
Global Distribution of *B. pseudomallei*



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

AN ASIDE:

If I Say Non-Fermenting GNR You Think of

- *Pseudomonas aeruginosa*
- *Acinetobacter baumannii*
- *Burkholderia cepacia, B. pseudomallei*
- *Stenotrophomonas maltophilia*
- *Sphingomonas paucimobilis*
- *Ralstonia pickettii*

Melioidosis Clinical Syndromes

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

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

Melioidosis Clinical Syndromes

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

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

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Melioidosis in the US

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

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

Melioidosis in the US

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

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

Bacteria with "Safety Pin" Appearance

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

Y. pestis

Melioidosis: Diagnosis & Rx

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

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

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

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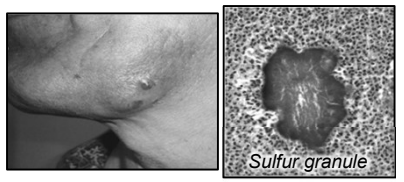
Melioidosis: Buzzwords

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

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

Actinomyces Take-Aways

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



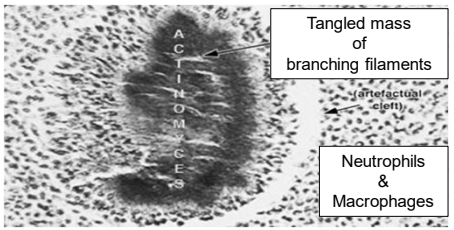
Photos: http://intranet.tdmu.edu.ua/ & webpathology.com

Actinomyces Take-Aways

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

Actinomyces: Buzzwords

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



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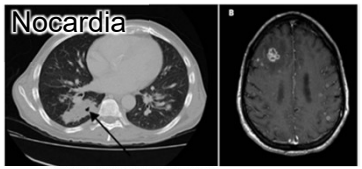
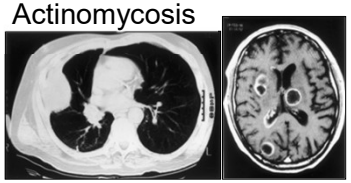
Lesions in the Lungs & Brain

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



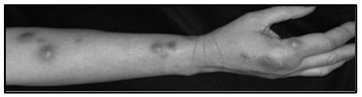
Leis JA, *et al. CMAJ*, 2011. DOI:10.1503/cmaj.100477



Colmegna I, et al. Am J Med Sci, 2003. DOI: 10.1097/00000441-200309000-00010

Causes of Sporotrichoid Lesions

Nodular lymphangitis



Organism	Exposure
Sporothrix schenckii	Gardening, soil, splinters, animal bites/scratches
Nocardia brasiliensis	Gardening, soil, splinters
Mycobacterium marinum	Aquarium, fish handling, water exposure
Cutaneous leishmaniasis	Living/traveling in endemic regions
Several others	Blasto/Cocci/Histo, Crypto, tularemia, *Erysipelothrix*, etc.

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

Thank You

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david.aronoff (Insta, Threads)

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Monday, August 24, 2026

25

Sexually Transmitted Infections: Other Diseases and Syndromes

Khalil Ghanem, MD

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Sexually Transmitted Infections: Other Diseases & Syndromes

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7/30/2026

Disclosures of Financial Relationships with Relevant Commercial Interests

- None

Of Note

- I have tried to use patient-first language throughout. When the terms 'women' and 'men' are used, I am referring to cis-gender women and men unless otherwise specified
- All photos are freely available from the following website unless otherwise noted: http://www.cdc.gov/std/training/clinicalslides/slides-dl.htm

Other STI Syndromes

- Urethritis/Cervicitis/Vaginitis
- Proctitis
- PID
- Epididymitis
- HPV
- Ectoparasites

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Urethritis/Cervicitis/Vaginitis

- *Neisseria gonorrhoeae*
- *Chlamydia trachomatis*
- *Mycoplasma genitalium*
- *Trichomonas vaginalis*
- Bacterial vaginosis

Question #1

A 32-year-old man presents complaining of a penile discharge. Gram stain of the urethral discharge reveals intracellular Gram-negative diplococci. He reports an allergy to penicillins and cephalosporins.

Which of the following regimens does the CDC recommend as the most appropriate therapy?

A. Azithromycin
B. Azithromycin plus ceftriaxone
C. Azithromycin plus gentamicin
D. Ciprofloxacin
E. Spectinomycin

Question #2

A man with persistent urethritis following doxycycline therapy is tested and found to be positive for *Mycoplasma genitalium*.

Which of the following is the most appropriate therapy (assume today is his last day of doxycycline)?

A. Azithromycin 1g orally
B. Azithromycin 500mg orally X1 followed by 250 mg daily on the subsequent 3 days
C. Doxycycline 100 mg orally twice daily for 14 days
D. Moxifloxacin 400 mg orally daily for 7 days

Chlamydia Trachomatis: Take-home Points

- Annual screening of all sexually active women aged ≤25 years is recommended for serotypes D-K, as is screening of older women with risk factors (e.g., new or multiple sex partners)
- High rate of reinfection for D-K
- Both D-K and LGV (L1-L3) cause proctitis/proctocolitis
- Longer duration of therapy (3 weeks of doxycycline) for L1-L3 serotypes **if symptomatic*****
- Association with reactive arthritis; prompt treatment reduces risk of reactive arthritis

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Chlamydia Trachomatis

- Serological classification
  - A,B, Ba, C (Trachoma)
  - D-K (Genitourinary and ocular infections)
  - L1-L3 (Lymphogranuloma venereum)

Chlamydia Trachomatis D-K

MEN

Asymptomatic
Urethritis
Epididymitis **(70% of cases in young men)**
Proctitis
Conjunctivitis
Pharyngitis (rare)
Reactive arthritis (urethritis, conjunctivitis, arthritis, skin lesions)

WOMEN

Asymptomatic
Cervicitis
Urethritis
Pelvic inflammatory disease
Bartholinitis
Proctitis
Conjunctivitis
Reactive arthritis

Chlamydia: Diagnostics

- Detection of WBCs on Gram's stain is not sensitive
- Cell culture (sensitivity 70%), direct immunofluorescence, non-amplified molecular tests (sensitivity ~85%), and NAATs (gold standard; sensitivity >95%; specificity >99%)
- FDA cleared for the detection of C. trachomatis on endocervical and urethral swab specimens, urine, vaginal swab specimens, throat and rectal swabs
- **Routine NAATs do NOT distinguish between D-K and L1-L3 serotypes. Multiplex tests do but are not commercially available.**

Chlamydia Trachomatis Treatment

- Duration of therapy depends on serotype:
  - D-K serotypes: **doxycycline 100mg PO BID X 7d is preferred**; alternate is 1 g oral azithromycin
  - L1-L3 serotypes (if moderate to severe proctitis): **Doxycycline 100 mg PO BID X3 weeks** (preferred); alternate is azithromycin 1g PO q week X 3 weeks
- Use of azithromycin is safe in pregnancy
- Test of cure (i.e., repeat testing after completion of therapy) to document chlamydial eradication approximately 4 weeks after therapy completion during pregnancy is recommended
- Screen all persons treated for chlamydia infection 3 months later (REINFECTION rates are high)

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Azithromycin vs. Doxycycline

- **Urogenital** *C. trachomatis*
  - RCT in correctional facility: azithromycin=97% vs. doxycycline=100% (noninferiority of azithromycin was **not** established) Geisler NEJM 2015
- **Rectal** *C. trachomatis*
  - 2 RCTs: Efficacy difference in favor of doxycycline of 20%

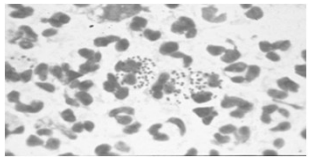
Dombrowski CID 2021; Lau NEJM 2021

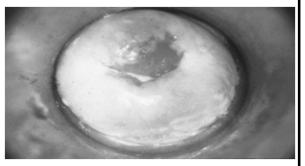
Gonorrhea: Take-home Points

- IM ceftriaxone 500 mg is the preferred regimen for uncomplicated gonorrhea
- Pharyngeal gonorrhea: ceftriaxone is the only drug that is recommended; test of cure 7-14 days after treatment
- Disseminated gonococcal infection: patients may NOT have symptoms of urethritis
- Gonococcal conjunctivitis: 1g of ceftriaxone

Neisseria Gonorrhoeae

- Clinical presentation similar to that seen with C. trachomatis.
  - No association with Reiter's
  - Responsible for 30% of cases of epididymitis in young men
  - **MOST cases (>90%) of pharyngeal and rectal gonococcal infections are ASYMPTOMATIC**





Disseminated Gonococcal Infection (DGI)

- DGI frequently results in petechial or pustular acral skin lesions (< 12 lesions), asymmetrical arthralgia, tenosynovitis, or (monoarticular) septic arthritis
- The infection is occasionally complicated by perihepatitis and rarely by endocarditis or meningitis.
- Strains of N. gonorrhoeae that cause DGI may cause minimal genital inflammation
- **Risk factor for DGI: terminal complement deficiency (acquired form often seen in SLE) and with complement inhibitors (Eculizumab)**
- Differential diagnosis: meningococcemia, RMSF, dengue, staphylococcal endocarditis, Reiter's
- Treatment: Ceftriaxone IM/IV usually 5-7 days; longer with arthritis, meningitis, or endocarditis

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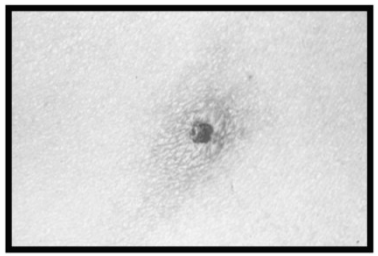
DGI



Gonorrhea Diagnostics

- A negative Gram's stain should NOT be considered sufficient for ruling out infection in **asymptomatic** men. In addition, Gram stain of endocervical specimens, pharyngeal, or rectal specimens are not sufficiently sensitive or specific to detect infection
- Sensitivity of culture ~80-90% from endocervical or urethral specimens in symptomatic persons; **<50% from throat/rectum**
- NAATs offer the widest range of testing specimen types because they are FDA-cleared for use with endocervical swabs, vaginal swabs, male urethral swabs, and female and male urine
- **In patients suspected of having DGI, perform both NAATs and culture testing at all sites: genital, throat, and rectum**

Gonorrhea Therapy (Cont.)

- First line is ceftriaxone 500 mg IM X1
- Second-line agents for **urogenital** or **rectal infections**:
  - Cefixime (800mg PO X1)
  - **Gentamicin 5mg/kg IM+ 2g azithromycin**
  - Azithromycin 2g PO X1 is no longer recommended
- **There are NO second-line recommendations for pharyngeal gonorrhea**- it's ceftriaxone or bust!
  - Gentamicin and cefixime have lower efficacy for pharyngeal infections Ross JDC, et al. Lancet 2019
  - All pharyngeal infections: must do a test of cure within 2 weeks after ceftriaxone therapy

St Cyr MMWR 2020

Gonorrhea Therapy (Cont.)

- DGI: Ceftriaxone 1g IM or IV until clinically better (can also use cefotaxime and ceftizoxime); then, can complete 7-day course of therapy with a PO cephalosporin (once results of antibiotic susceptibility testing are available)
- Gonococcal conjunctivitis: Ceftriaxone 1g IM X1

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Extragenital Gonorrhea and Chlamydia

- 90% are asymptomatic
- NAATs, now FDA cleared, are the preferred (and most sensitive)diagnostic modality
- CDC recommends screening for both GC and CT at the rectum but screening for only GC at the throat
- Sexually active MSM should be screened at all sites of exposure
  - The majority of GC cases in MSM would be missed if genital-only testing were performed
- No formal extragenital screening guidelines for women

Non-gonococcal Urethritis (NGU)

- Gram stain of urethral secretions demonstrating ≥2 WBC per oil immersion field or positive leukocyte esterase test on first-void urine or microscopic examination of sediment from a spun first-void urine demonstrating ≥10 WBC per hpf
- More common etiologies:
  - *Chlamydia trachomatis* (25% cases)
  - ***Mycoplasma genitalium*** (30% of cases)
  - *Trichomonas vaginalis* (10-25% of cases; mainly MSW not MSM)
  - *Ureaplasma urealyticum* (controversial; do NOT test for this bacterium)
  - HSV
- Less common etiologies: anaeobes; enterobacteriaceae, Haemophilus, Staphylococcus saprophyticus, adenovirus
- NGU treatment: **doxycycline 100mg PO BID X 7d is now the preferred regimen**

Non-gonococcal Urethritis (NGU) (Cont.)

- If a person with NGU fails to respond to therapy, think of 4 possibilities: (1) Reinfection (2) *M. genitalium* that did not respond to above therapy (see next slide) (3) T. vaginalis - rare in MSM (treat with metronidazole) or (4) HSV

Mycoplasma genitalium

- Strong association with non-gonococcal urethritis (NGU) [up to 30% of cases] and up to 35% of cases of persistent urethritis
- Moderate association with cervicitis and PID; weaker association with infertility
- Test men with persistent urethritis or epididymitis; consider testing women with persistent cervicitis or PID (discuss with patient); consider testing in men and women with persistent proctitis symptoms; DO NOT SCREEN (except known contacts to a person with *M genitalium*)
- Combined molecular diagnostic with molecular detection of macrolide resistance is not yet FDA cleared but is available at a commercial laboratory in the US.

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M. Genitalium Therapy

- **DUAL antibiotic therapy is recommended**
  - Start with one week of doxycycline 100 mg orally BID (will decrease bacterial load) followed by either:
    - Azithromycin 500mg orally X1 followed by 250 mg daily on the subsequent 3 days (if macrolide sensitivity is known) OR
    - Moxifloxacin 400mg PO X 7 days (if macrolide resistant or if macrolide resistance is unknown)
  - Emerging resistance to fluoroquinolones (~15% moxifloxacin resistance)
- **NOT FOR THE BOARDS**: In persons with FQ failures, you can use minocycline (100 mg PO BID X 14 d) or ? tinidazole (2 g daily for 7 days); Pristinamycin (not available in US)

Int J STD AIDS. 2019;30(5):512-514
Clin Infect Dis. 2015;60(8):1228-36
Sex Transm Dis. 2025. 1;52(2):e2-e4
https://sti.guidelines.org.au/sexually-transmissible-infections/mycoplasma-genitalium/

Summary: Urethritis Approach

- All men presenting with urethritis should be tested for both GC and CT and treated with ceftriaxone and one week of oral doxycycline
- If the GC and CT tests are negative and the patient has persistent symptoms and signs:
  - If the patient is a MSW: Test for *M genitalium* and trichomonas and treat based on results
  - If the patient is a MSM: Test for *M genitalium* and treat based on results (trichomonas is rare in MSM)

Question #3

A 22-year-old woman is diagnosed with persistent cervicitis secondary to *Mycoplasma genitalium.* She is treated with one week of doxycycline followed by one week of moxifloxacin. She reports one male sex partner in the prior two months.

Which of the following is the recommended approach to managing her sex partner?

A. The CDC does not recommend routine partner therapy for *M genitalium*
B. Test the partner for *M genitalium* only if symptomatic and, if positive, treat
C. Test the partner for *M genitalium* irrespective of symptoms and, if positive, treat
D. Treat the partner for *M genitalium* without testing using expedited partner therapy

Trichomonas Vaginalis

- May be asymptomatic in both men and women; causes vaginitis and NGU
- Diagnosis: culture and PCR; wet mount is not sensitive
- Vaginal pH usually >4.0
- Therapy: Treat all women with metronidazole 500mg PO BID X 7 days OR tinidazole 2g PO X1 [do NOT use topical gel formulations]
  - RCT: 7 days of metronidazole superior to 2g single dose Kissinger et al. Lancet Inf Dis 2019
- Therapy: Treat all men with metronidazole 2g PO X1 OR tinidazole 2g PO X1
- Resistance: ~5% of strains have low-level resistance to metronidazole; <1% have high level resistance (see next slide)
- Partners in the preceding 60 days must be treated
- No need to screen asymptomatic pregnant women for trichomonas; **screen all women with HIV annually**

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Trichomonas & Nitroimidazoles

- **Tinidazole** has a longer serum half-life and achieves higher tissue concentrations than metronidazole; MICs to tinidazole lower than to metronidazole
- Can use 2g of oral tinidazole to treat both men and women
- If patient fails Rx with metronidazole & reinfection is excluded:
  - Option 1: Tinidazole 2 g PO X1
- If patients fails option 1 above:
  - Option 2: Metronidazole 2g PO QD X 5d
  - Option 3: Tinidazole 2g PO QD X 5d

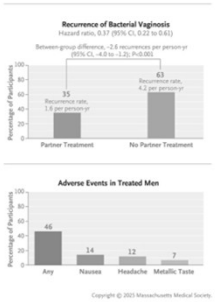
Bacterial Vaginosis

- Complex polymicrobial infection; causes vaginitis (thin, white, discharge with 'fishy' odor) and cervicitis; may increase risk of PID
- Dx: Nugent's score preferred in research settings; Amsel's clinical criteria performed in clinical settings: (1) discharge (2)pH>4.5 (3) clue cells (4) amine odor with KOH (whiff test)

Bacterial Vaginosis

- Rx: Metronidazole 500mg PO BID X 7days OR Clindamycin 300mg PO TID X 7 days OR topical metronidazole gel or clindamycin cream OR Secnidazole 2g PO X1 dose
  - *L crispatus* supplements after topical metronidazole resulted in a 34% reduction in recurrence at 3m Cohen NEJM 2020
- **Do NOT use metronidazole 2g PO X1**
- **BV during pregnancy**: associated with preterm labor, PROM, post-partum endometritis
- Treat all **symptomatic** cases of BV during pregnancy; **screening asymptomatic pregnant women for BV if high risk for pre-term delivery (e.g., history of premature delivery) is no longer recommended**

- RCT; monogamous male partners of women with BV were treated with metronidazole 400-mg tablets and 2% clindamycin cream applied to penile skin, both twice daily for 7 days
- Trial stopped early by DSMB
- 80% of men were uncircumcised
- 7 prior studies did not show benefit, but none used topical clindamycin
- No change in recommendations in the US yet (but stay tuned)



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Pelvic Inflammatory Disease (PID)

- Diagnostic criteria - only ONE of the following:
  - Cervical motion tenderness
  - Uterine tenderness
  - Adnexal tenderness
- Hospitalize
  - Pregnant
  - Tubo-ovarian abscess
  - Appendicitis cannot be excluded
  - Did not respond to PO antibiotics
  - Patient has nausea and vomiting, or high fevers/severe illness
  - Unreliable follow-up if treated as outpatient
- MOST patients with PID can be treated as outpatients (including first-episode PID and HIV positive women who do not meet above criteria)

Pelvic Inflammatory Disease (PID)

- **Therapy**
  - Ceftriaxone 500 mg IM in a single dose PLUS Doxycycline 100 mg orally twice a day for 14 days **WITH Metronidazole** 500 mg orally twice a day for 14 days
  - Cefotetan 2 g IV every 12 hours OR Cefoxitin 2 g IV every 6 hours PLUS Doxycycline 100 mg orally or IV every 12 hours
- Additional recommended regimens can be found in the 2021 CDC STI Treatment Guidelines (online at cdc.gov)
- All patients treated with PO regimens should improve within 3 days otherwise, admit for parenteral antibiotics
- Treat all sex partners in preceding 60 days

Fitzhugh-Curtis Syndrome

- Perihepatitis: RUQ pain or pleuritic pain; usually NO LFT abnormalities (or very mild)
- Complicates ~10% of PID cases
- Pathophysiology: ?Direct extension of pathogens vs. immunological mechanism
- Rx: NSAIDs (+ treat PID)

Epididymitis

- In young men:
  - *C. trachomatis* (70%)
  - *N. gonorrhoeae* (30%)
- In older men: E. coli causes majority of cases
- Therapy:
  - **Ceftriaxone 500mg IM X1 + Doxycycline 100mg PO BID X 10 days**
  - For acute epididymitis most likely caused by sexually-transmitted chlamydia and gonorrhea and enteric organisms (men who practice insertive anal sex): Ceftriaxone IM X1 + levofloxacin X 10 days
  - For acute epididymitis most likely caused by enteric organisms: Levofloxacin 500mg PO X10 days

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Question #4

A 30-year-old man with HIV presents with severe pain on defecation and bloody anal discharge. He had unprotected anal sex one week ago. He experiences pain with DRE. There are no visible anal ulcers, but a bloody mucoid anal discharge is noted. No diagnostic tests are available.

Which of the following empiric antibiotic regimens is most appropriate?

A. Ceftriaxone 500mg IM + Azithromycin 1g PO X1
B. Ceftriaxone 500mg IM + Doxycycline 100mg PO BID X 7d
C. Ceftriaxone 500mg IM + Azithromycin 1g PO weekly X 3wks
D. Ceftriaxone 500mg IM + Doxycycline 100mg PO BID X 21d
E. Ceftriaxone 500mg IM + Doxycycline 100mg PO BID X 7d + oral valacyclovir

Proctitis/Proctocolitis

COMMON

- Neisseria gonorrhoeae
- *Chlamydia trachomatis* D-K
- *Chlamydia trachomatis* L1-L3 (LGV)
- *T. pallidum*
- HSV (severe especially among HIV+)
- Mpox

OTHER CAUSES

- Campylobacter
- Shigella
- Entamoeba
- CMV
- *Giardia lamblia** (mainly enteritis; especially among MSM)

Proctitis Therapy

- **Ceftriaxone 500mg IM X1 + Doxycycline 100mg PO BID X 7-21 days <u>depending on extent of symptoms</u>**
- **Treat for 21d**: Moderate to severe symptoms - (e.g., pain, bloody discharge +/- ulcers)
- Treat for HSV: Painful perianal ulcers or mucosal ulcers are detected on anoscopy
- Azithromycin is less effective than doxycycline when treating proctitis due to *C. trachomatis*

HPV

- >30 types cause genital infections
- High risk (e.g., 16, 18) and low-risk (e.g., 6 &11)
- 16 & 18 cause ~70% of cervical cancers in addition to significant proportion of vulvar, vaginal, anal, and upper airway cancers
- Low-risk types can cause genital warts and low-grade dysplasia (CIN I)
- Low-risk types cause recurrent respiratory papillomatosis
- Single biggest risk factor for dysplasia is PERSISTENCE of infection
- Risk factors for persistence: older age; immunosuppression; smoking; concurrent infection with multiple types

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Genital Warts

- 90% of warts caused by HPV 6 & 11; concomitant infection with types 16, 18, 31, 33, and 35 increases risk of HSIL
- Genital warts may develop months or years after infection
- Up to 60% of warts will recur within 3 months after therapy. Many will clear spontaneously after 12 months
- Available therapies do not completely eradicate infectivity
- Hypopigmentation or hyperpigmentation can occur with ablative modalities (cryotherapy and electrocautery) and with immune modulating therapies (imiquimod).
- No c-section in pregnant women with visible warts
  - C-section only if the warts are obstructing the birth canal or if vaginal delivery may lead to increased risk of bleeding

HPV Vaccines

- **Nonavalent (6, 11, 16, 18, 31, 33, 45, 52, 58)**; 2-3 doses given over 6-12 months (2 doses induce good immunity if age<=14 years)
- Consists of VIRUS-LIKE PARTICLES (noninfectious; NO DNA)
- Efficacy: >97% against CIN 2/3, vulvar, and vaginal lesions; >98% against genital warts*
- Recommended for routine use in 9- to 26-year-old women (even those who have a history of abnormal Pap smears); routine use in boys ages 11-12 years, catch-up for males ages 13-21, and permissive use of the vaccine in men ages 22-26; vaccine FDA cleared for women up to age of 45 (but ACIP has not recommended it in women age>26)

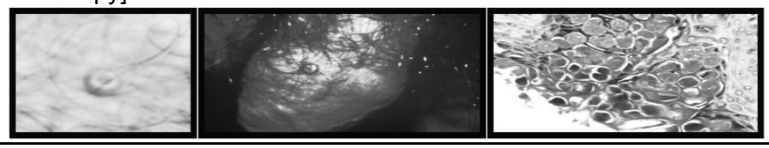
*FDA approved a supplemental biologics licensure application in 6/2020: prevention of oropharyngeal and other head and neck cancers caused by HPV types targeted by the vaccine

HPV Vaccines (Cont.)

- **Do not give during pregnancy**; no need to restart schedule for patients who don't follow-up on time: JUST PICK UP WHERE YOU LEFT OFF
- Continue routine Pap smears on all women who get the vaccine
- Side effects: vasovagal response; local reactions
- Not a therapeutic vaccine

Molluscum Contagiosum

- Poxvirus
- 1 to 5mm lesions; painless papules; CENTRAL UMBILICATION
- Not necessarily sexually transmitted
- Molluscum bodies: intracytoplasmic inclusions
- Rx: curettage; cryotherapy; topical cidofovir; cantharidin 0.7% topical solution ("beetle juice")[must be given in clinic]; berdazimer 10.3% topical gel (nitric-oxide releasing) [at-home therapy]



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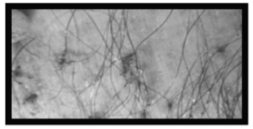
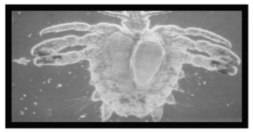
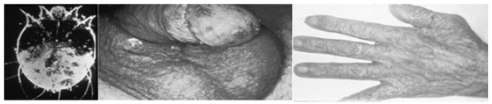
Pediculosis Pubis

- Pediculosis pubis=pubic lice=crabs (*Pthirus pubis*)
  - Nits confined to upper shaft=old infection (no need for retreatment)
  - Maculae ceruleae (blue gray macules)
  - Permethrin 1% cream OR Pyrethrins with piperonyl butoxide (topical)
  - Resistance increasing; consider malathion 0.5% lotion or Ivermectin in case of treatment failure
  - Do NOT use Lindane; toxicities include seizures and aplastic anemia
  - Treat sex partners within previous 30 days





Scabies



- *Sarcoptes scabei*
- Severe pruritus; especially at night or after bathing; burrows; the diagnosis is usually a clinical one
  - Permethrin cream 5% (wash off after 8 hours) OR
  - Ivermectin 200 mcg/kg PO day 1 and 14
  - Only use Lindane as an alternative
- **Crusted scabies or 'Norwegian scabies'**
  - Mainly occurs in immunodeficient patients (HIV)
  - May NOT cause pruritus or burrows
  - Contagious and aggressive
  - Ivermectin 250mcg/kg on days 1, 15, and 29
- Rash and pruritus of scabies may persist for up to 2 weeks after successful therapy***

Arch Dermatol. 2007;143(5):626

Prevention: Doxy-PEP

- Doxycycline 200 mg within 72 hours of a sexual exposure in MSM and transgender women with >=1 STI in prior 12 months
  - Data in cis-gender women do not yet suggest benefit (additional studies are in progress)
  - Significant protection against syphilis and chlamydia; data on gonorrhea are less clear
  - In addition to known doxycycline toxicities, data on emergence of antimicrobial resistance (in *N gonorrhoeae* and *S aureus*) and data suggesting that clinical manifestations and lipoidal titer increases may be abrogated in persons who are infected with syphilis while on DoxyPEP

MMWR Recomm Rep 2024;73(No. RR-2):1–8. DOI: http://dx.doi.org/10.15585/mmwr.rr7302a1
Clinical Infectious Diseases, 2024;, ciae062, https://doi.org/10.1093/cid/ciae062

The End

Thank you and good luck!

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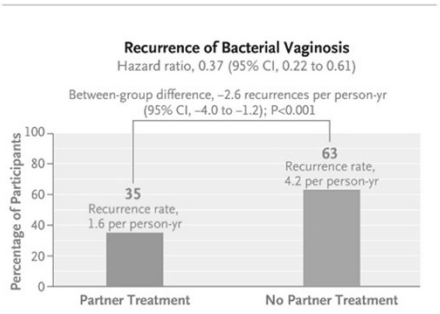
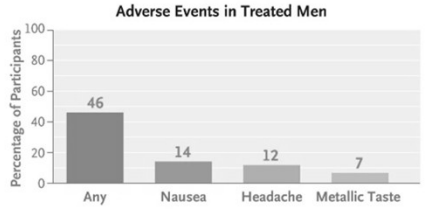
The NEW ENGLAND JOURNAL of MEDICINE

Male-Partner Treatment to Prevent Recurrence of Bacterial Vaginosis

A Research Summary based on Vodstrcil LA et al. | 10.1056/NEJMoa2405404 | Published on March 6, 2025

- RCT; monogamous male partners of women with BV were treated with metronidazole 400-mg tablets and 2% clindamycin cream applied to penile skin, both twice daily for 7 days
- Trial stopped early by DSMB
- 80% of men were uncircumcised
- 7 prior studies did not show benefit, but none used topical clindamycin
- No change in recommendations in the US yet (but stay tuned)





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Monday, August 24, 2026

26

Core Concepts: Antibacterial Drugs II
Gram Positive Organisms

Helen Boucher, MD

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Core Concepts: Antibacterial Drugs II Gram Positive Organisms

Helen W. Boucher, MD, FACP, FIDSA (Hon), FRCPI
Tufts University School of Medicine

8/5/2026

Disclosures of Financial Relationships with Relevant Commercial Interests

- Editor: ID Clinics of North America, Sanford Guide

Overview of Antibacterial Mechanisms
To Orient You: Little is Testable

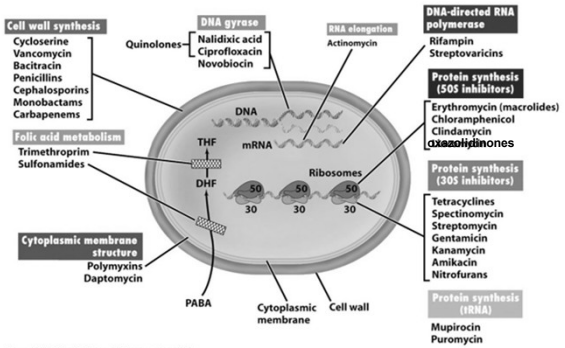

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Figure 20-14 Brock Biology of Microorganisms 11/e
© 2006 Pearson Prentice Hall, Inc.

Cell Wall Active Agents

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

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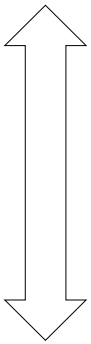
β-lactam Spectrum

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



Gram-positive

Gram-negative

β-lactam Antibiotics Share Mechanism of Action

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

β-lactam Adverse Effects

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

Question #1

What is the only cephalosporin active against MRSA?

A. Cefpodoxime
B. Cefepime
C. Ceftobiprole
D. Cefixime
E. Cefoxitin

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Cephalosporins

- Bactericidal
  - Inhibit bacterial cell wall synthesis
- Time dependent killing
- Resistance mostly due to susceptibility to β-lactamases
- Fewer allergic reactions than PCN
- CSF penetration with third generation
- Most renally excreted

Key Points About Cephalosporin Activity

- Enterococci
  - None are active
- MRSA
  - Only ceftaroline and ceftobiprole active
- Anaerobic activity
  - Only Cephamycins active
    - (e.g., cefoxitin, cefotetan)
    - Now high levels of resistance

Ceftaroline Fosamil – a Prodrug (IV and IM, Not Oral)

- Activity
  - Gram-positive including MRSA and MDR S. pneumoniae
    - Some activity vs E. faecalis; not E. faecium
  - Limited activity vs. anaerobes
    - Active vs Cutibacterium (formerly Propionobacterim) acnes, Actinomyces spp.

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

Ceftaroline Fosamil – a Prodrug (IV and IM, Not Oral)

- Activity
  - Active vs Gram-negative pathogens
    - *E. coli, Klebsiella spp., H. influenzae* (incl B-lactamase positive), *M. catarrhalis*
  - **Not Pseudomonas or ESBL+ GNB**
  - **Similar spectrum to ceftriaxone**
- Bactericidal, time dependent killing

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

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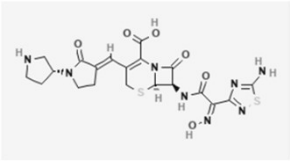
Ceftobiprole



- Advanced spectrum IV cephalosporin
- Broad spectrum (similar to ceftaroline)
  - Active vs G+ incl PRSP, MRSA, anaerobes
  - Some activity vs E. faecalis; not E. faecium
  - Active vs Enterobacteriaceae
  - Not active vs CRE, P aeruginosa

Overcash et al. CID 2021: 73: e1507; Awad SS et al. Clin Infect Dis. 2014;59(1):51–61
Holland et al. N Engl J Med 2023: 389(15):1390

Ceftobiprole

- FDA approved:
  - ABSSSI, CABP, *S. aureus* bloodstream infection/Right-sided endocarditis
- Not FDA approved for VABP
  - EU approved HAP not VAP
  - Early HABP studies failed; low ceftobiprole levels found in young ICU patients
- Dosing
  - ABSSSI and CABP:
    - 667 mg IV q 8h x 5-14 days
  - S. aureus bloodstream infection:
    - 667mg IV q 6h day 1-8 then 667 mg IV q 8h day 9+ (thru 42)

Overcash et al. CID 2021: 73: e1507; Awad SS et al. Clin Infect Dis. 2014;59(1):51–61
Holland et al. N Engl J Med 2023: 389(15):1390

Vancomycin

- Bactericidal (slowly)
  - Inhibits bacterial cell wall synthesis
- Active against:
  - Gram Positive Aerobes
    - Streptococcus
    - Staphyloccus
    - Enterococcus
  - Gram Positive Anaerobes
    - Clostridia
    - Propionibacteria
    - Peptostreptococci
    - Actinomyces

Vancomycin Resistance

- VISA
  - Thick walls, generous binding sites…
- Vancomycin resistance
  - Not in Streptococcus
  - RARE in Staphylococcus
  - Common in Enterococcus
    - Rare in *E. faecalis* (4% in 2014)
    - Common in *E. faecium* (71% in 2014)
    - Mechanism
      - Change in vancomycin binding site on peptidoglycan

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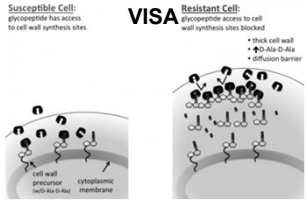
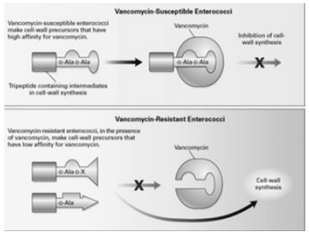
Vancomycin Resistance

- VISA thickened cell wall + xs vancomycin binding sites (D-Ala-D-Ala); result: vanco trapping with reduced cellular targets
- VRE – replacement of D-Ala-D-Ala with D-alanyl-D-lactate termini – result: decreased **vancomycin** binding affinity --- high level resistance: MIC increase x 1000





SEE ENLARGED SLIDE FOLLOWING ENTIRE PRESENTATION

Murray NEJM 2000

Vancomycin for MRSA Bloodstream Infection

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

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

Vancomycin ADRs / Interactions

Adverse Drug Reactions

- Nephrotoxicity
  - Duration > 14d
  - Dose > 4g / day
  - Trough > 20
- Ototoxicity
- Histamine Release Syndrome
- DRESS
- Immune thrombocytopenia
- Neutropenia
- IgA bullous dermatitis

Drug Interactions

- Increased nephrotoxicity when given with other nephrotoxins
  - Aminoglycosides
  - NSAIDs
  - Contrast
  - Cyclosporine
  - Tacrolimus
  - Loop Diuretics
  - ACE inhibitors
  - Pip/tazo (pseudo interaction)

Daptomycin (IV)

- Antimicrobial Class: Lipopeptide
- Broad spectrum gram + activity
  - Including MRSA
- Rapidly bactericidal
- Concentration-dependent killing
- Indications
  - cSSSI
  - *S. aureus* bloodstream infection
  - Right-sided endocarditis

Fenton C et al. *Drugs* 2004; 64: 445-55, Tedesco KL, Rybak MJ. *Pharmacother* 2004; 24:41-57, Mangili A et al. *Clin Infect Dis* 2005; 40:1058-60, Fowler VG et al. *New Engl J Med* 2006; 355:653-665

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Daptomycin for *S. aureus* Bacteremia and Right IE

- Pneumonia
  - Do not use: surfactant binding inactivates drug
- Monitoring
  - CPK twice weekly
  - Discontinue if myopathy or CPK > 5x ULN
- Toxicity
  - Eosinophilic Pneumonia
    - Rx supportive care and steroids
  - Falsely prolonged Prothrombin Time
  - Muscle inflammation
    - CPK increase, myopathy, myositis
    - Risk factors: renal failure, statins, obesity

Vancomycin and Daptomycin

Drug	Mechanism of Action	Mechanism of Resistance	Spectrum	Adverse Event
Vancomycin	Inhibits cell wall synthesis (not a beta lactam)	Change in cell wall terminus from D-ala-D-ala to D-ala-D-lactate (high level resistance)	Gram positive cocci only including MRSA	• Histamine release syndrome • Kidney toxicity
Daptomycin	Cell membrane depolarization Potassium efflux	• Decreased binding of drug to cell membrane • Altered cell membrane potential	Resistant gram-positive cocci including MRSA and VRE Inactivated by surfactant (not for pneumonia)	• Skeletal muscle toxicity

Oritavancin and Dalbavancin Long-Acting Glycopeptides

- Mechanism of Action
  - Similar to vancomycin
  - Inhibition of cell wall synthesis
- Dosing
  - Oritavancin: IV only: 1 dose (1200 mg over 3hours)
  - Dalbavancin: IV only: 1000mg, then 500mg every 7 days …OR 1500mg x 1
- Approved
  - Skin and Soft Tissue
  - Oritavancin FDA warning against use in osteomyelitis
  - Dalbavancin also used for osteomyelitis, right sided endocarditis
- Toxicity
  - Oritavancin prolongs aPTT (artificially), PT, and activated whole blood clotting time (ACT) for 5 days

Lipo/Glycopeptide Testable Toxicities

- Vancomycin: Nephrotoxicity, Histamine Release
- Daptomycin: CPK elevation, myopathy, rhabdomyolysis; eosinophilic pneumonia
- Telavancin: Nephrotoxicity
- Oritavancin: LFT elevation, false prolongation of aPTT
- Dalbavancin: LFT elevation

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Question #2

Which quinolone has activity against MRSA?

A. Ciprofloxacin
B. Moxifloxacin
C. Trovafloxacin
D. Delafloxacin
E. Levofloxacin

Antibiotics Active Intracellularly

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

Fluoroquinolone Mechanism of Action and Resistance

- Topoisomerase inhibitors
  - Inhibits DNA gyrase and topoisomerases II and IV
  - Gyrase more for gram negs, topos for gram pos
- Resistance
  - Target site mutations
  - Drug permeability mutations
  - Occurs spontaneously on therapy
  - Susceptible to drug modifying enzymes

Fluoroquinolones
Spectrum of Gram-positive Activity

	Gram-positive	**Gram-negative**	**Anaerobes**
Cipro	Poor strep Some MSSA	Best FQ for • Pseudomonas • *E coli*	Some
Levo	Good strep Some MSSA	Best for *Stenotrophomonas spp.*	Some
Moxi	Good strep Good MSSA	**Not effective** • **Don't use for UTI**	**Best**

Drs. Tamma and Gilbert will address Gram-negative activity

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Fluoroquinolone Pharmacokinetics

- High oral bioavailability
  - >95% for moxi / levo, 70-80% for cipro
  - Potential low bioavailability when taken with multivalent cations – chelation blocks absorption
- Widely distributed to tissues
  - Lower than serum but therapeutic concentration in CSF, saliva, bone, ascitic fluid and prostate gland
- Elimination
  - Levo / cipro: renal through tubular secretion
  - Moxi: >60% hepatic / biliary unchanged

Fluoroquinolone Adverse Effects

- *C. difficile*
- Arthropathy/cartilage toxicity / tendonitis
  - FDA Warning for rare tendon rupture
    - Increased risk: advanced age, poor renal function, concomitant steroids
- Altered mental status (HA, dizziness, insomnia)
- Dysglycemia-FDA warning especially for older adults and diabetics
  - Hypo- and hyperglycemia
- Aortic aneurysm and aortic dissection-FDA warning
  - Association is controversial
- QTc Prolongation:
  - Moxi > levo ? Cipro
  - Increased risk:
    - Concomitant QTc prolongers, cardiomyopathy, bradycardia, low K+ and Mg++

Delafloxacin

- Broad spectrum fluoroquinolone
- Potential advantages:
  - MRSA activity
  - Broad spectrum including Pseudomonas
- Dosing IV and oral twice daily
- Approved for skin and soft tissue infections

Saravolatz LD and Stein GE. Clin Infect Dis. 2019;68(6):1058–62

Tetracyclines: Major Clinical Uses

- Acne (minocycline)
- Respiratory tract infections
  - Atypical pneumonia
- Sexually Transmitted Diseases
  - Syphilis (*T. pallidum*) – alternative therapy
  - *Chlamydia spp*.
- Tick-Borne Illnesses
  - Lyme disease
  - Anaplasmosis
  - Ehrlichiosis
  - Rocky Mountain Spotted Fever
- Community Acquired MRSA infections

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Tetracyclines: Adverse Effects

- Gastrointestinal
  - Nausea
  - Esophageal ulceration
  - Hepatotoxicity
- Skin
  - Photosensitivity
- Children
  - Yellow brown tooth discoloration if age <8 yrs for tetracyclines
  - **Doxycycline therapy OK for ≤21 days in children of all ages**
    - Ref: Redbook 2018 and Am Academy Pediatrics
- Pregnancy
  - Tetracyclines cross the placenta; accumulate in fetal bone/teeth
  - Most tetracyclines contraindicated in pregnancy

Newer Tetracyclines

	Omadacycline	Eravacycline
FDA approval	ABSSSI, CABP	cIAI, not cUTI (failed studies)
Dosing	200 mg loading dose over 60 min day 1, 100mg IV over 30 min or 300mg orally once daily No dose adjustment for renal/hepatic impairment	1mg/kg IV q 12h (over 60 minutes) Dose adjustment with hepatic impairment
Activity	Broad spectrum: Gram-pos including MRSA, VRE; Gram-neg including ESBL, CRE (not all); anaerobes	
Issues	Limited activity vs carbapenem-resistant *K. pneumoniae*	High MIC *Pseudomonas*, *Burkholderia* spp.
Safety	GI, rash, ?heart rate	GI, rash

Question #3

What is the major advantage of tedizolid compared to linezolid?

A. Longer half life
B. Better penetration of prostate
C. Better CSF Penetration
D. Wide spectrum of activity against anaerobes
E. More effective in clinical studies for VRE

Linezolid and Tedizolid
Oxazolidinone Drug Class

- Mechanism
  - Binds 50s ribosome/prevents formation of initiation complex
- Spectrum of activity
  - Gram positive cocci including MRSA and VRE
    - Linezolid resistant *S.aureus* reported
  - Mycobacteria
- Resistance is rare; target change
- Linezolid twice daily; Tedizolid once daily
- FDA approvals for Linezolid:
  - Skin and Soft Tissue, Pneumonia, VRE
  - NOT Bloodstream infection (Black Box Warning)

Shinabarger DL et al. *Antimicrob Agents Chemother* 1997; 41: 2132-36; Swaney Sm et al. *Antimicrob Agents Chemother* 1998; 42: 3251-55; French G. *Int J Clin Pract* 2001; 55: 59-63

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Linezolid Adverse Events

- Adverse events related to mitochondrial toxicity:
  - Cytopenias
    - Monitor CBC
  - Peripheral and irreversible optic neuropathy
  - Rare:
    - Lactic acidosis, **serotonin syndrome (w SSRIs)**
- ↑ mortality in study of intravenous catheter-associated bacteremia

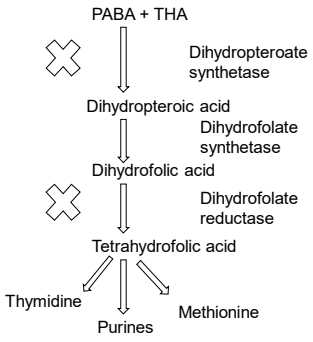
Tsiodras S et al. *Lancet* 2001;358: 207-208; Pillai SK et al. *Clin Infect Dis* 2002; 186: 1603-7; Wilson P et al. *J Antimicrob Chemother* 2003;51:186-88; Medwatch March 16, 2007

Sulfonamides & TMP/SMX

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

TMP/SMX Mechanism of Action

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



TMP/SMX Resistance Mechanisms

Sulfamethoxazole

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

Trimethoprim

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

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TMP-SMX Adverse Effects

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

HIGH PLASMA PROTEIN BINDING

- Gastrointestinal effects
- "Nephrotoxicity"
- Fever
- Drug-drug interactions
- Hyperkalemia

COMPETES FOR TUBULAR SECRETION

TMP/SMX Spectrum of Activity: Typical Bugs

- **Gram Positive**
  - Staphylococci: great
  - Streptococci: controversial
  - Enterococcus: not effective
- **Gram Negative**
  - *E. coli*: ok, increasing resistance
  - Enterobacterales: relatively effective
  - Pseudomonas / Acinetobacter: not effective
  - Stenotrophomonas: often drug of choice (2024 IDSA Guidance suggests combination with cefiderocol, minocycline or levofloxacin)

TMP/SMX Spectrum of Activity Odd Bugs

- *Stenotrophomonas maltophila*
- *Listeria monocytogenes*
- *Nocardia*
- *Moraxella catarhallis*
- *Pneumocystis jirovecii*
- *Toxoplasmosis gondii* (but not superior to pyr/sulf)
- *Chlamydia* (but enough resistance that its not used for STDs)
- Atypical *mycobacteria*

Lefamulin

- Pleuromutilin antibiotic with IV and PO formulation
  - Protein synthesis inhibitor
  - Bacteriostatic
- FDA Approved community acquired bacterial pneumonia
  - Non-inferior to moxifloxacin for CABP in two studies
    - **5 days** of po lefamulin vs. 7 days of po moxifloxacin

File CID 2019

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Macrolides (Erythro, Clarithro, Azithro)
Protein Synthesis Inhibitor Binds 50s Ribosome

Spectrum:

CABP Pathogens:

- *Streptococcus pneumoniae*
- *Haemophilus influenzae*
- *Moraxella catarrhalis*
- *Leigonella spp.*
- *C. pneumoniae*
- Streptococcus groups A, C, and G

Strep Pneumo Resistance

- Rising rates in US
  - Don't use macrolides if local rates of resistance > 25%

Macrolide Spectrum

STDs

- *Haemophilus ducreyi (chancroid)*
- *Chlamydia spp.*

GI Pathogens

- *Campylobacter spp.*
- *Helicobacter pylori*
- *Salmonella typhi*
- *Shigella spp.*

Miscellaneous Bugs

- *Arcanobacter spp.*
- *Bartonella henselae* (cat-scratch)
- *Bordetella pertussis*
- *Atypical mycobacteria*
- *Borrelia burgdorferi*
- *Babesia microti*

Macrolide Adverse Drug Reactions

- QTc Prolongation
  - Ery ≥ clarith > azith
- GI intolerance: nausea, bloating, diarrhea
  - Ery >> clarith >> azith
  - Dose related
  - Activity at motilin (peristalsis) receptors
  - Rare cholestatic hepatitis
- Pregnancy risk

Clindamycin Adverse Events

- Allergic reactions:
  - Rash, fever, erythema multiforme, anaphylaxis
- Elevated AST/ALT
  - Rare progression to severe liver injury
- Diarrhea
  - Can cause severe *C. difficile* toxin-mediated colitis
- Reversible neutropenia, thrombocytopenia, and eosinophilia
- Taste disturbance

Sanford Guide, Brit J Clin Pharmacol 64:542, 2007; Clin Med Insights Case Rep 2019 Dec 25;12:1-4

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Thank You!

- Henry Masur
- Sue Cammarata
- G. Ralph Corey
- Sara Cosgrove
- Mike Dudley
- Mike Dunne
- David Gilbert
- Susan Hadley
- Teena Kohli
- Kenneth Lawrence
- Evan Loh
- Paul McGovern
- Federico Perez
- Debra Poutsiaka
- George H. Talbot

Our patients and their families

Questions, Comments?

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Overview of Antibacterial Mechanisms
To Orient You: Little is Testable

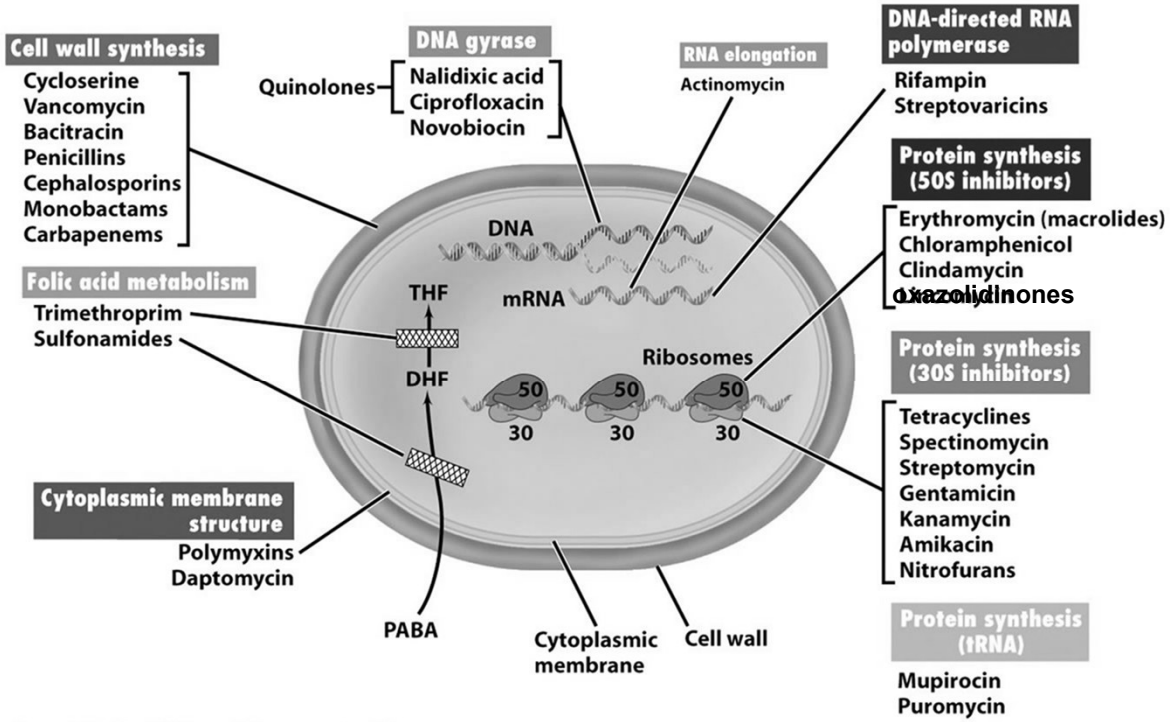

Figure 20-14 Brock Biology of Microorganisms 11/e
© 2006 Pearson Prentice Hall, Inc.

SEE ENLARGED SLIDE FOLLOWING ENTIRE PRESENTATION

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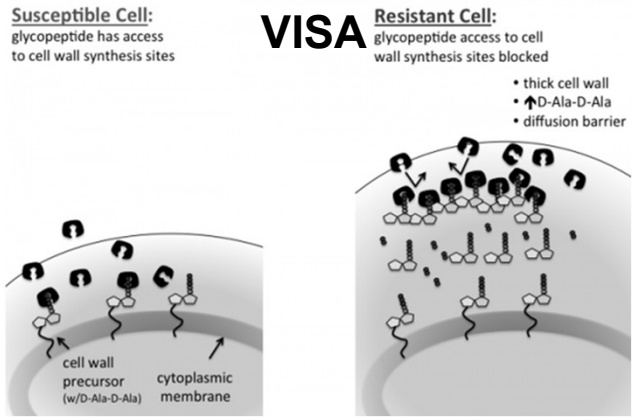
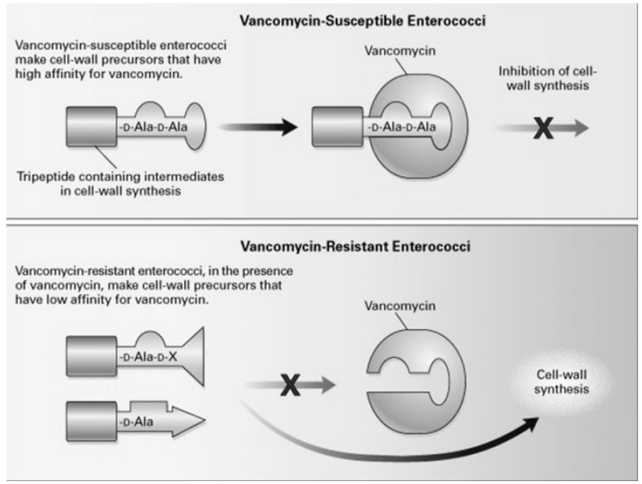
Vancomycin Resistance

- VISA thickened cell wall + xs vancomycin binding sites (D-Ala-D-Ala); result: vanco trapping with reduced cellular targets
- VRE – replacement of D-Ala-D-Ala with D-alanyl-D-lactate termini – result: decreased **vancomycin** binding affinity --- high level resistance: MIC increase x 1000





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Murray NEJM 2000

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Monday, August 24, 2026

BR3

Board Review Day 3

Drs. Aronoff (Moderator), Boucher, Dhanireddy, Dorman, Ghanem, and Klompas

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Board Review: Day 3

Moderator: David Aronoff, MD

Faculty: Drs. Boucher, Dhanireddy, Dorman, Ghanem, and Klompas

7/28/2026

BOARD REVIEW DAY 3

#31 **A 58-year-old man with a history of alcohol use disorder presents to the emergency department with fever, hypotension, and diffuse purpura fulminans involving both lower extremities.**

His partner reports that three days ago he was bitten on his forearm by his neighbor's German shepherd while trying to separate the dogs during a fight. The bite wound was cleaned and bandaged at an urgent care clinic and was not sutured.

On examination, he is febrile (40.1°C), hypotensive (BP 82/48 mm Hg), and tachycardic.

1 of 4

BOARD REVIEW DAY 3

#31 **The bite wound on his forearm appears only mildly erythematous, but his lower legs and feet have extensive dark purple, nonblanching lesions.**

Laboratory testing reveals thrombocytopenia (platelets 28,000/μL), elevated INR and PTT, and elevated D-dimer consistent with disseminated intravascular coagulation (DIC).

Blood cultures are pending. He is started on broad-spectrum empiric antibiotics.

2 of 4

BOARD REVIEW DAY 3

#31 **Which of the following organisms is most likely to be identified on blood culture?**

A. ***Pasteurella multocida***
B. ***Streptococcus canis***
C. ***Capnocytophaga canimorsus***
D. ***Clostridium perfringens***
E. ***Neisseria meningitidis***

3 of 4

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#32 **A 58-year-old man with poorly controlled type 2 diabetes mellitus is admitted for fever.**

He was most recently admitted 6 weeks ago for hyperosmolar coma.

That hospitalization was complicated by a central-line associated MRSA bacteremia for which he was treated with vancomycin for 14 days.

#32 **Two of two blood cultures obtained at this admission are again positive for MRSA with the following MIC results:**

- **Linezolid 2 mg/ml (susceptible)**
- **Vancomycin 4 mg/ml (intermediate)**
- **Daptomycin 2 mg/ml (non-susceptible)**
- **Ceftaroline 1mg/ml (susceptible)**
- **Ceftobiprole 2 mg/ml (susceptible)**
- **Rifampin 0.25 mg/ml (susceptible)**
- **Gentamicin 1 mcg/ml (no breakpoint established)**

#32 **Which antibiotic regimen would you recommend for this patient?**

A. Linezolid
B. Vancomycin + rifampin
C. Daptomycin + gentamicin
D. Ceftobiprole

#33 **A 35-year-old agricultural consultant in good health is returning to India for 3 months where she will inspect crops in rural areas.**

There is known to be Japanese encephalitis in the area.

Three years ago, when she had visited the same area, she was vaccinated for Japanese B encephalitis with the standard two dose regimen.

BR3 Board Review - Day 3
Moderator - David Aronoff, MD

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#33 **What advice should you give her for protection against Japanese B encephalitis?**

A. **Immunization is ineffective and therefore no immunization was needed 3 years ago or is needed now**

B. **Immunization is associated with a substantial risk for encephalitis and therefore should not be given**

C. **Since she was immunized three years ago, she should receive a booster dose**

D. **She should receive a booster only if titers demonstrate no measurable IgG antibodies against JE**

#34 **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.**

PPD was negative when he departed.

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

Baseline laboratory values, including liver function tests, are normal.

He has been vaccinated for HBV and HAV and is HCV seronegative.

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

He returns after 4 weeks of taking isoniazid and pyridoxine. He is asymptomatic and reports taking his drugs daily and missing very few doses.

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

#34 **What is the best option for management at this point?**

A. **Continue the current regimen with the patient told to report any symptoms immediately and recheck enzymes in 2-4 weeks**

B. **Continue the current regimen but measure the patient's acetylation rate to determine safety of continuation**

C. **Double the dose of pyridoxine**

D. **Perform an interferon-gamma release assay (IGRA) to determine if prophylaxis is really needed**

E. **Abandon plan to treatment of latent tuberculosis infection (LTBI); monitor the patient closely for symptoms and obtain a chest x-ray every 6 months for 3 years**

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BOARD REVIEW DAY 3

#35 **A 38-year-old marine sergeant reports to sick bay a week after shore leave with acute onset of fever, malaise and five pustular skin lesions, including the one shown here.**

He appears acutely ill, but his vital signs (other than temperature) are normal.

He has pain on flexion and slight swelling in the right wrist; his wrist flexor tendons are quite tender. His left ankle was tender the day before but is now asymptomatic.

BOARD REVIEW DAY 3

#35 **While on shore leave in a port city in Mexico, he had sex with a commercial sex worker, consumed alcohol and passed out in an alley infested with rats and mice.**

On hospital day 3 the lab reports a positive blood culture.

Which of the following would be the most likely organism?

A. Spirochete

B. Gram negative bacillus

C. Gram negative coccus

D. Gram positive bacillus

E. Endemic mycosis

BOARD REVIEW DAY 3

#36 **A 69-year-old woman requires a hip replacement after fracturing her greater trochanter.**

She has a history of recurrent urinary tract infections typically treated with nitrofurantoin or fosfomycin, but is otherwise healthy.

To reduce the likelihood of an infection involving her surgical site, what antibiotics do you recommend for preoperative prophylaxis?

A. Cefazolin

B. Vancomycin

C. Vancomycin plus cefazolin

D. Ceftriaxone

E. Cefepime

BOARD REVIEW DAY 3

#37 **A 34-year-old woman presents to her physician with a 10-day history of nonproductive cough, fever, headache, and myalgias. She has no history of recent travel, and has been otherwise healthy.**

She works as a clerk at a pet supply store. Two weeks ago, she began helping to care for a recently purchased flock of parakeets after a previous employee became ill with a similar respiratory illness.

On examination, her temperature is 39.1°C, heart rate is 72 beats per minute, and she has diffuse crackles on auscultation.

A chest X-ray reveals patchy bilateral infiltrates. Routine sputum cultures are negative.

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BOARD REVIEW DAY 3

#37 **A 34-year-old woman presents to her physician with a 10-day history of nonproductive cough, fever, headache, and myalgias. She has no history of recent travel, and has been otherwise healthy.**

She works as a clerk at a pet supply store. Two weeks ago, she began helping to care for a recently purchased flock of parakeets after a previous employee became ill with a similar respiratory illness.

On examination, her temperature is 39.1°C, heart rate is 72 beats per minute, and she has diffuse crackles on auscultation.

A chest X-ray reveals patchy bilateral infiltrates. Routine sputum cultures are negative.

BOARD REVIEW DAY 3

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

A. Legionnaires disease
B. *Mycoplasma pneumoniae*
C. Psittacosis
D. Q fever
E. Influenza

BOARD REVIEW DAY 3

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

A transesophageal echocardiogram shows a 6 mm mobile mass on the mitral valve. MRI of the spine shows evidence of discitis between the 3rd and 4th lumbar vertebrae.

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

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

BOARD REVIEW DAY 3

#38 **Follow-up blood cultures from hospital days 4 and 5 are negative.**

The white blood cell count is 18,000/mm^3 with 90% neutrophils on admission; on hospital day 20, the white blood cell count is 3,000/mm^3 with 30% neutrophils.

Renal function is normal.

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BOARD REVIEW DAY 3

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

A. Cefazolin 2 gm IV every 8 hours
B. Ceftriaxone 2 gm IV every 12 hours
C. Linezolid 600 mg IV every 12 hours
D. Nafcillin 1 gm IV every 4 hours
E. Vancomycin 1 gm IV every 12 hours

3 of 4

BOARD REVIEW DAY 3

#39 **A 70-year-old woman in good health had an episode of zoster 20 years ago which was diagnosed clinically and resolved uneventfully with acyclovir treatment.**

When she went to a new internist 15 years ago, that internist recommended Zostavax-- Zoster Vaccine Live (ZVL) -- which the patient received.

She now wants to know if she should receive Shingrix (recombinant zoster vaccine-RZV)). She remains in good health.

1 of 3

BOARD REVIEW DAY 3

#39 **What would you advise her?**

A. Since she had a clinical case of zoster, she did not need Zostavax 15 years ago and does not need Shingrix (recombinant zoster vaccine) now
B. Since she had Zostavax, she does not need Shingrix
C. She should only get Shingrix if her IgG titers against zoster are below the level of detection
D. She should receive Shingrix (recombinant zoster vaccine)

2 of 3

BOARD REVIEW DAY 3

#40 **You are treating a 66-year-old man for pulmonary disease due to *Mycobacterium abscessus* complex that is resistant to macrolides.**

He completed 8 weeks of IV imipenem, IV amikacin, and oral omadacycline and one week ago he was transitioned to oral omadacycline, oral linezolid, and inhaled amikacin.

He also has COPD, hypertension, and depression, and takes an inhaled combination beta agonist and muscarinic antagonist, lisinopril, and sertraline.

1 of 4

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#40 This morning his wife called reporting that over the past few days he has had increasing agitation, and this morning is confused, with fever, sweating, loose stools, and tremors.

On exam in the emergency department, he is agitated; his temperature is 101°F, pulse 110/minute and regular, there is marked diaphoresis, and there is muscle clonus in the lower extremities.

Lab testing shows normal WBC and creatinine.

#40 Which of the following best explains this situation?

A. *Clostridioides difficile* colitis
B. Monoamine oxidase inhibition by linezolid
C. Sertraline-mediated inhibition of linezolid metabolism
D. Side effect of inhaled liposomal amikacin

#41 A 17-year-old adolescent cis-gender woman presented for care because of a ten-day history of increasing abdominal pain, accompanied by low grade fever the past two days.

The pain was mostly in the right upper quadrant, worse on deep breathing. On deep inspiration, the pain was felt in her right shoulder. She also reported abnormal yellow vaginal discharge. Her menses have been normal. No dysuria was reported.

She reported condomless vaginal intercourse with a several male partners.

#41 On exam, her vital signs were normal except for a temperature of 38.5°C.

She had marked tenderness in the right upper quadrant and some dull tenderness over the lower abdomen bilaterally.

Her WBC was 11,800/mm^3 with normal liver chemistries. Abdominal ultrasound showed no evidence of cholecystitis or liver abscess.

A urine pregnancy test was negative.

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BOARD REVIEW DAY 3

#41 **Which test is most likely to establish the correct diagnosis?**

A. CT of abdomen and pelvis with oral and IV contrast
B. Laparoscopy
C. Cervical NAAT for herpes simplex virus
D. Liver biopsy
E. Cervical NAAT for *Chlamydia trachomatis*

3 of 4

BOARD REVIEW DAY 3

#42 **A 68-year-old man with a history of schizophrenia presents to the emergency department with paranoid delusions. He is currently undomiciled and has not been taking his antipsychotics.**

He says that he feels like he has tiny worms crawling all over him that are making his skin dry and flaky.

Exam is notable for a cachectic, disheveled man in dirty clothing. He has thick hyperkeratotic plaques and warty skin crusts in a patchy distribution over the entire body which are particularly pronounced on the hands, feet, and elbows.

1 of 3

BOARD REVIEW DAY 3

#42 **Which of the following care providers require post-exposure prophylaxis?**

A. The psychiatrist who interviewed him for 120 minutes while sitting in a chair next to his bed in a regular hospital room
B. The patient who was in an adjacent bed in the same room for 14 hours
C. The intern not wearing PPE who did a complete physical exam
D. The nurse in gown & gloves but no mask who helped him into a hospital gown
E. The registration clerk whose pen he used to sign his admission paperwork

2 of 3

BOARD REVIEW DAY 3

#43 **A 22-year-old patient with HIV infection (CD4 count 350 cells/ μL, viral load <50 copies/ml on dolutegravir/lamivudine) lives with his parents in an apartment.**

His mother, who works as a correctional officer, is healthy but was recently diagnosed with pulmonary tuberculosis when she developed a cough, radiologic evidence consistent with tuberculosis, and has a sputum that was smear positive and NAAT (Cepheid Xpert MTB/Rif) positive for rifampin-susceptible *Mycobacterium tuberculosis*.

1 of 4

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#43 The patient has no symptoms consistent with TB and has an unremarkable physical examination.

Laboratory results are consistent with prior visits. Chest x-ray is normal.

The patient had a negative PPD in clinic 2 years ago when he was first evaluated for HIV infection.

#43 What would you recommend for this patient?

A. Withhold decision until results of repeat PPD or IGRA are available from current clinic visit
B. Withhold decision until results of chest CT and PPD or IGRA are available from current clinic visit
C. If initial PPD and IGRA are negative, repeat PPD or IGRA at 3, 6 and 12 months and initiate treatment only if PPD or IGRA are positive
D. Initiate treatment for latent TB regardless of PPD or IGRA result

#44 A 28-year-old woman presents with her fourth episode of symptomatic bacterial vaginosis (BV) within the past year.

She is in a mutually monogamous relationship with her male partner.

She has previously responded to standard BV therapy but experiences frequent recurrences.

#44 In addition to standard treatment with metronidazole in this patient, what additional intervention may be considered in her male partner?

A. No treatment for the male partner; advise condom use only
B. Single 2 g dose of oral metronidazole for the male partner
C. Oral metronidazole 500 mg twice daily for 7 days plus 2% topical clindamycin cream applied to the penile glans/coronal sulcus twice daily for 7 days
D. Topical metronidazole gel applied to the penis once daily for 5 days
E. Doxycycline 100 mg twice daily for 7 days

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BOARD REVIEW DAY 3

#45 **A previously unvaccinated immigrant from Bangladesh was seen in the emergency department for pharyngitis two days after arrival in the United States.**

The patient required an emergency tracheostomy and while the differential diagnosis was extensive, the patient received broad spectrum antibiotics plus steroids.

The patient was found to have an oropharyngeal culture positive for *Corynebacterium diphtheriae*, presumably acquired in Bangladesh.

1 of 4

BOARD REVIEW DAY 3

#45 **The patient was treated appropriately with penicillin and horse origin antitoxin obtained from CDC.**

The emergency department team that had close contact with the patient during examination and tracheostomy inquires about prophylaxis, although they have all been immunized.

2 of 4

BOARD REVIEW DAY 3

#45 **What should you recommend?**

A. A single dose of intramuscular benzathine penicillin G or a 7- to 10-day course of oral erythromycin; if last dose of toxoid was ≥5 years ago add a single dose of diphtheria toxoid

B. Single dose of ciprofloxacin plus a single dose of diphtheria toxoid if last dose of toxoid was 5 or more years ago

C. Four doses of rifampin plus a single dose of diphtheria toxoid if last dose was 5 or more years ago

D. No therapy unless the healthcare worker's oropharyngeal culture is positive

E. No therapy regardless of culture since they have been vaccinated

3 of 4

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Monday, August 24, 2026

27

Skin And Soft Tissue Infections

Helen Boucher, MD

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Skin and Soft Tissue Infections

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8/2/2026

Disclosures of Financial Relationships with Relevant Commercial Interests

- Editor: ID Clinics of North America, Sanford Guide

Question #1

A 25-year-old female suffers a cat bite on the forearm.
She presents one hour later for care.

If no antibacterial is administered, what is the percentage of such patients that get infected?

A. 0-10 %
B. 10-30 %
C. 30-70 %
D. 70-100 %

Management of Animal Bites

- Wound care: irrigation, debridement
- Image for fracture or as baseline for osteomyelitis or to detect foreign body?
- Wound closure: NO
- Anticipatory (prophylactic) antibiotics
- Vaccines (tetanus and rabies)

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Cat Bites

- 30-50% cat bites become infected with bacteria
- Wound types: puncture
- Microbiology: 63% polymicrobial
- Infection type:
  - Nonpurulent wound with cellulitis, lymphangitis, or both (42%)
  - Purulent wound without abscess (39%)
  - Abscesses (19%)

Bacterial genus	Frequency (%)
Aerobic organisms	
Pasteurella	75
Streptococcus	46
Staphylococcus	35
Neisseria [b]	35
Moraxella	35
Corynebacterium	28
Enterococcus	12
Bacillus	11
Anaerobic organisms	
Fusobacterium	33
Porphyromonas	30
Bacteroides	28

Abrahamian FM1, Goldstein EJ. Microbiology of animal bite wound infections. Clin Microbiol Rev. 2011 Apr;24(2):231-46. doi: 10.1128/CMR.00041-10; *NEJM 1999; 340: 85-92.*

Pasteurella multocida

- In saliva of > 90% of cats and over 50% of wounds get infected
- Different species, *Pasteurella canis*, in saliva of 50% of dogs and only 2-10% get infected
- Small aerobic gram-negative bacillus
- Hard to remember antibiotic susceptibility profile, but amoxicillin sensitive; alternatives can be tricky

Six Pathogens That Can Cause Infection After Cat Bites

- *Pasteurella species*
- Anaerobic bacteria: e.g., *Fusobacteria*
- *Bartonella henselae* (Cat Scratch disease)
- Rabies virus
- *S. aureus*
- Streptococcal species

Question #2

A 50-year-old female with alcohol substance use disorder suffered a provoked dog bite

- Bite was cleansed, tetanus toxoid given, and the dog placed under observation
- **Patient is post-elective splenectomy for ITP; she received pneumococcal vaccine one year ago**
- One day later, the patient is admitted to the ICU in septic shock with severe DIC and peripheral symmetric gangrene of the tips of her fingers/toes

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Question #2

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

A. Pasteurella canis
B. Capnocytophaga canimorsus
C. Fusobacterium spp.
D. Bartonella henselae

Dog Bites and Splenectomy

- Only 2-10% of dog bites get infected
- Potential pathogens from
  - Dog's mouth:
    - *Pasteurella canis, Capnocytophaga canimorsus*
  - Human skin: *S. aureus, S. pyogenes*
- *Capnocytophaga* is an important cause of overwhelming sepsis in splenectomized patients
- *Capnocytophaga spp.*
  - Susceptible to: amox/clav, pip/tazo, penicillin G, and clindamycin
  - Resistant to: TMP/SMX and maybe vancomycin

Question #3

A 45-year-old USA male experiencing homelessness presents with fever and severe polymyalgia

- On physical exam, **animal bite marks found around his left ankle. A faint rash is visible on his extremities.**
- Within 24 hours, blood cultures are positive for pleomorphic gram-negative bacilli.

Which one of the following is the most likely diagnosis?

A. Pasteurella multocida
B. Haemophilus parainfluenza
C. Spirillum minus
D. Streptobacillus moniliformis

Rat Bite Fever

- USA: *Streptobacillus moniliformis*
- Asia: *Spirillium minus*
- Bites or contaminated food/water
- *S. moniliformis*:
  - Fever, extremity rash
    - Macular/papular, pustular, petechial, purpuric
  - Symmetrical polyarthralgia
- Treatment: penicillin or doxycycline

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Question #4

A 35-year-old male suffers a clenched fist injury in a barroom brawl.

- He presents 18 hours later with fever and a tender, red, warm fist wound
- Gram stain of bloody exudate shows a small gram-negative rod with some coccobacillary forms
- The aerobic culture is positive for viridans streptococci

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

A. Viridans streptococci
B. Eikenella corrodens
C. Peptostreptococcus
D. Fusobacterium species

Talan, D. CID 2003; 37: 1481

Eikenella corrodens

- Anaerobic small gram-negative bacillus
- Susceptible to:
  - Penicillins, fluoroquinolones, doxycycline, and extended spectrum cephalosporins (ceftriaxone, ceftazidime)
- Resistant to:
  - Cephalexin/cefazolin, clindamycin, erythromycin, diclox/oxacillin, metronidazole, and TMP/SMX

Question #5 Extra Credit

Medicinal leeches are applied to a non-healing leg ulcer.

Which one of the following pathogens is found in the "mouth" of the leech?

A. Alcaligenes xylosoxidans
B. Aeromonas hydrophila
C. Acinetobacter baumannii
D. Arcanobacterium haemolyticum

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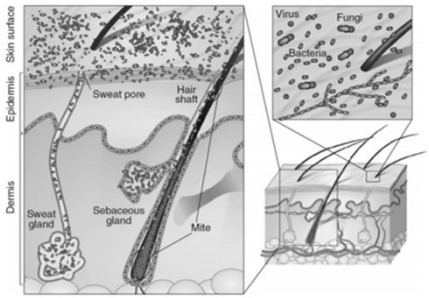
Aeromonas spp.

- *Aeromonas spp*. - aerobic gram-negative bacilli
  - *Aeromonas hydrophila* (most common)
  - *Aeromonas veronii*
  - *Aeromonas shubertii*
- Cause gastroenteritis (most common), wound infection (following trauma/exposure to leeches) or bacteremia after exposure to Aeromonas species in fresh, brackish, or marine water
- Variable antimicrobial susceptibility; need culture and susceptibility testing of infected wound, stool, and blood
  - Resistance to beta-lactams and fluoroquinolones in selected areas of the world
  - **Uniformly resistant to ampicillin, penicillin, and cefazolin**

The Skin: Local Invasion by Structure



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

Skin Infections: Predisposing Factors

- Trauma to normal skin
- Immune deficiency
- Disrupted venous or lymphatic drainage
- Local inflammatory disorder
- Presence of foreign body
- Vascular insufficiency
- Obesity; poor hygiene

S. aureus Skin Infection
Predisposing Factors

Risk Factors Associated with MRSA SSTI

- Ethnicity (African American, Hispanic compared with Caucasian)
- Socioeconomic lower quintile
- Previous colonization or *S. aureus* infection
- Exposure: hospital, long-term care facility, household contacts
- Contact activities - daycare children, contact sports, military
- Comorbidities: diabetes, peripheral vascular disease, cardiovascular disease, chronic wounds
- Chronic kidney disease, dialysis dependence, intravenous drug use
- Pre-existing skin lesions (burns, eczematous dermatitis, etc.)
- Hereditary or iatrogenic neutrophil disorders

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

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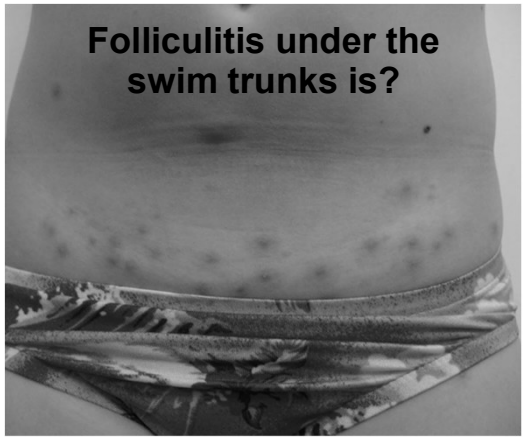
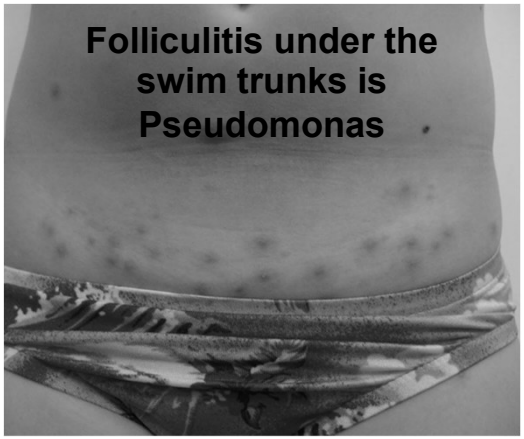
What Is This?

Superficial Folliculitis

- **Purulence (sometimes mixed with blood) where hair follicles exit skin**
- Etiology:
  - *S. aureus*
  - *P. aeruginosa* (hot tub)
  - *C. albicans* (esp. in obese patient)
  - *Malassezia furfur* - lipophilic yeast (former *Pityrosporum sp*)
  - Idiopathic eosinophilic pustular folliculitis in AIDS patients





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Microbial Etiology?

Streptococcal Infection of the Epidermis Name of the Clinical Syndrome?

- Infection of outer layers of epidermis with production of "honey-crust" scales
- Prevalent in warm, humid environments – esp. in children.
- Microbial etiology
  - Streptococci: Groups A, B, C, G
- **Name?**
  - **Streptococcal impetigo**

Fragile Superficial Bullae

Fragile Bullae in Epidermis

Diagnosis?
- Bullous impetigo

Etiology?
- S. aureus

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Impetigo ("To Attack")

- Bullous impetigo: *S. aureus*
- Non-bullous impetigo: *S. pyogenes*, group A
- So, empiric therapy aimed at *S. aureus* as could be MRSA
- Topical: topical antibiotic ointment (TAO), mupirocin, retapamulin
- **Oral rarely needed**
  - e.g., clindamycin, doxycycline

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

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

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- Acute onset of painful, rapidly spreading red plaque of inflammation involving epidermis, dermis, and subcutaneous fat
- NO PURULENCE

Diagnosis?

- Acute onset of painful, rapidly spreading red plaque of inflammation involving epidermis, dermis, and subcutaneous fat
- NO PURULENCE

Diagnosis:

- **Erysipelas: Non-purulent cellulitis**

- Acute onset of painful, rapidly spreading red plaque of inflammation involving epidermis, dermis, and subcutaneous fat
- NO PURULENCE

Diagnosis:

- Erysipelas: Non-purulent cellulitis

Etiology?

- Acute onset of painful, rapidly spreading red plaque of inflammation involving epidermis, dermis, and subcutaneous fat
- NO PURULENCE

Diagnosis:

- Erysipelas: Non-purulent cellulitis

Etiology:

- **Hemolytic Streptococci: Group A**
  - **Now less common than groups C and G**
- **If on the face, could be *S. aureus***

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Erysipelas ("Red Skin")

- Acute onset of painful skin, rapid progression +/- lymphangitis
- Inflamed skin elevated, red, and demarcated
- Etiology: Streptococci--Groups A,B,C, & G (*S. pyogenes, S. agalactiae, S. dysgalactiae subsp. equisimilis*)
- Predisposition:
  - Lymphatic disruption, venous stasis

Erysipelas and Cultures

- Most often, no culture necessary
- Can isolate *S. pyogenes* from fungal-infected skin between toes
- Low density of organisms
  - Punch biopsy positive in only 20-30%
- Blood cultures positive in </= 5%
- Confused with stasis dermatitis

Stasis Dermatitis

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Stasis Dermatitis

- Looks like erysipelas; more frequent in obese individuals
- **No fever**
- Chronic, often **bilateral**, dependent edema
- Goes away with elevation
- **Does not respond to antimicrobials**
- **Cadexomer iodine (IODOSORB) response rate 21% vs 5% for usual care**

Treatment of Erysipelas (Non-purulent "cellulitis")

- Elevation
- Topical antifungals between toes if tinea pedis present
- Penicillin, cephalosporins, clindamycin, TMP/SMX
- Avoid macrolides due to frequency of resistance

Cellulitis

Without localization or preceding macro or micro trauma:
usually Beta Strep. (usually GAS), extremities > face, elsewhere
With localization (cut, pustule, etc.) or preceding trauma: *S. aureus*

Severe Cellulitis

Microbiology: Streptococci (group A>B,C,G); less often *S. aureus*; rarely GNR

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Recurrent Cellulitis

- Frequently non-group A streptococci (esp. B, G)
- Relapse > recurrence
- Prophylaxis:
  - Benzathine penicillin IM
  - Oral penicillin; other systemic antibiotics
  - Decolonization (nasal, elsewhere)

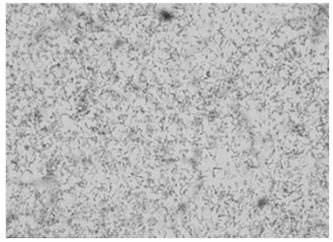
Risk Factors for Recurrent Erysipelas

- Lower Extremity
  - Post-bypass venectomy
  - Chronic lymphedema
  - Pelvic surgery
  - Lymphadenectomy
  - Pelvic irradiation
  - Chronic dermatophytosis
- Upper Extremity
  - Post-mastectomy/node dissection
- Breast
  - Post-breast conservation surgery, biopsy

Erysipelothrix (Gram + Rod)

- On finger after cut/abrasion exposure to infected animal (swine) or fish
- **Subacute erysipelas (erysipeloid)**
- Severe throbbing pain
- **Diagnosis: Culture of deep dermis (aspirate or biopsy)**
- Treatment: Penicillin, cephalosporins, clindamycin, fluoroquinolone

Erysipelothrix rhusiopathiae Infection



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

Resolving cellulitis caused by *Erysipelothrix rhusiopathiae*

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Question #6

A 53-year-old male construction worker has sudden onset of pain in his left calf.

- Within hours the skin and subcutaneous tissue of the calf are red, edematous and tender. Red “streaks” are seen spreading proximally
- A short time later, patient is brought to the ER confused, vomiting, and hypotensive
- Temp 40C, diffuse erythema of the skin. Oxygen sat. 88% RA
- WBC 3000 with 25% polys and 50% band forms; platelet count is 60,000; creatinine 3.2mg/dl

Question #6

Which one of the following is the most likely complication of the erysipelas?

A. Bacteremic shock due to *S. pyogenes*
B. Toxic shock due to *S. pyogenes*
C. Bacteremic shock due to *S. aureus*
D. Toxic shock due to *S. aureus*

Toxic Shock Syn. (TSS): Staph vs Strep

Feature	Staphylococcal	Streptococcal
Predisposition	Tampon, surgery; colonization	Cuts, Burns, Varicella, erysipelas
Focal Pain	No	Yes
Tissue necrosis/inflammation	Rare	Common
N/V, renal failure/DIC	Yes	Yes
Erythroderma	Very common	Less Common
Bacteremia	Very rare (5%)	60%
Mortality	<6%	30-70%

Sore Throat and Skin Rash

- 20-year-old male with 3 days of sore throat, fever, chills, and skin rash
- Rash is nonpruritic and involves abdomen, chest, back, arms, and legs
- Exam: exudative tonsillitis, strawberry tongue, rash, and tender cervical lymph nodes

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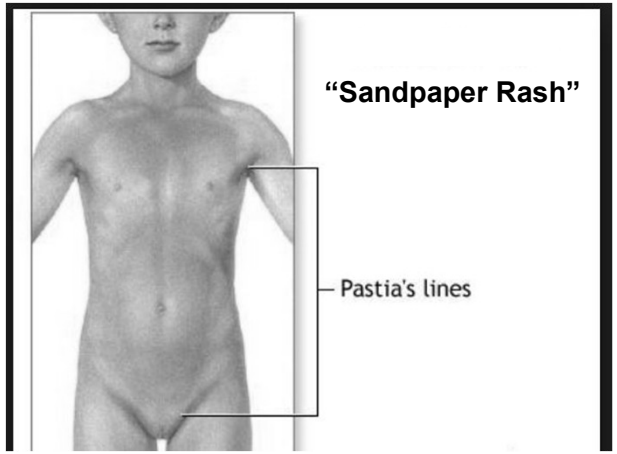

Case Study

Which is the most likely diagnosis?

A. Infectious mononucleosis
B. Coxsackie hand, foot and mouth disease
C. Scarlet fever
D. Arcanobacterium hemolyticum

Question #7

- 18-year-old male taking anti-seizure meds for idiopathic epilepsy develops fluctuant tender furuncle on right arm
- He develops fever and generalized erythroderma
- Wherever he is touched, a bullous lesion develops
- **Skin biopsy shows intra-epidermal split in the skin**

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Question #7

Which one of the following is the likely etiology of the skin bullae?

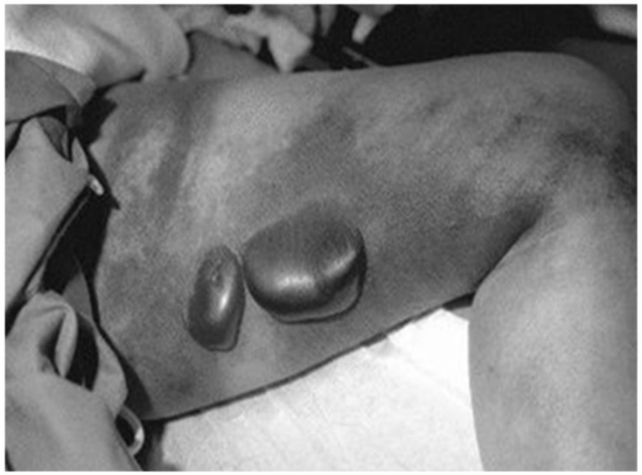
A. S. aureus scalded skin syndrome
B. Bullous pemphigus
C. Drug-induced Toxic epidermal necrolysis (TEN)
D. S. pyogenes necrotizing fasciitis

Nikolsky sign

Exfoliative Toxins cause Epidermal split
- Stratum granulosum

The Skin and Toxins of *S. aureus* and *S. pyogenes*

Organism	Toxin	Clinical Diagnosis
S. aureus colonization	TSST	TSS & Erythroderma
S. aureus colonization	Exfoliative toxin	Impetigo; scalded skin syndrome
Strep. pyogenes invasion	TSST	TSS; Erythroderma (not always)
Strep. pyogenes	Pyrogenic exotoxin	Pharyngitis; Scarlet Fever (sandpaper rash)



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Case Study

Erysipelas with Loss of Pain, Hemorrhagic Bullae, Rapid Progression…

Necrotizing fasciitis is due to which one?

- Streptococcal fasciitis
- Staphylococcal fasciitis
- Clostridial infection
- Synergy between aerobe (*S. aureus*, *E. coli*) plus anaerobe (anaerobic strep, *Bacteroides sp*) equals Meleney's, Fournier's

Lancet ID 2015;15:109

Necrotizing Fasciitis: At The Bedside

- Sudden onset excruciating pain & systemic toxicity
- Note swelling of leg & 2 small purple bullae on anterior shin
- Pressures in the anterior/lateral compartments (blood at needle entry)
- elevated; surgical exploration performed

Treatment of Necrotizing Fasciitis

- Think of it
  - Pain out of proportion to exam
  - Abnormal vital signs
  - Rapid spread
  - Tense edema
  - Ecchymoses
  - Crepitus
  - Loss of sensation
- Therapy = Surgical debridement: sometimes several times needed to achieve source control
- Watch out: imaging can be negative/misleading, patient may appear nontoxic at presentation (espec if young, otherwise healthy)
- Appropriate antimicrobial therapy – *B*-lactam + clindamycin or linezolid (IDSA Guideline Update pending)

Table 1. Signs and Symptoms of Necrotizing Soft Tissue Infection

Sign	Percentage of patients at presentation
Classic	
Bullae	25.6
Skin necrosis	24.1
Crepitus	20.3
Gas on radiographic evaluation	24.8
Nonspecific	
Swelling	80.8
Pain or tenderness	79
Erythema	70.7
Warmth	44
Fever >37.5 °C	40
Hypotension	21.1

McDermott et al. JAMA Surgery November 2024; Vol 159 (11): 1308

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Table 2. Differential Diagnoses and Distinguishing Features From NSTI

Differential diagnosis	Distinguishing features from NSTI
Cellulitis	• Often not associated with hemodynamic instability, shock, or severe pain • Less associated with violaceous skin changes
Pyoderma gangrenosum	• Not associated with sepsis, fever • Associated with inflammatory bowel disease • Progresses slower than NSTI • Violaceous ulcer edges • Resistant to blunt dissection • Typically has negative blood and tissue cultures
Pyomyositis	• Characterized by abscess formation in muscles • Imaging shows focal muscle swelling and well-demarcated areas of fluid
Deep vein thrombosis	• Pain is less severe than that of NSTI • Fever may be present, though less common than in NSTI
Erysipelas	• Raised, sharply demarcated borders

Abbreviation: NSTI, necrotizing soft tissue infection.

McDermott et al. JAMA Surgery November 2024; Vol 159 (11): 1308

Table 3. Laboratory Risk Indicator for Necrotizing Fasciitis (LRINEC) Score

Variable	Value	Score
White blood cell count (×10 000/μL)	<15	0
	15-25	+1
	>25	+2
Hemoglobin, g/dL	>13.5	0
	11-13.5	+1
	<11	+2
Sodium, mEq/L	≥135	0
	<135	+2
Glucose, mg/dL	≤180	0
	>180	+1
Creatinine, mg/dL	≤1.6	0
	>1.6	+2
C-reactive protein	<15 mg/dL	0
	≥15 mg/dL	+4

SI conversion factors: To convert creatinine to μmol/L, multiply by 88.4; glucose to mmol/L, multiply by 0.0555.

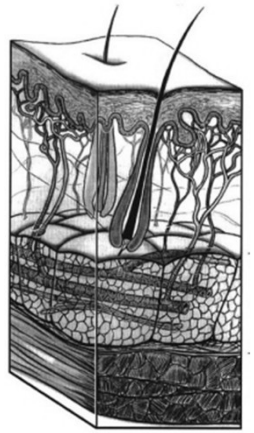
McDermott et al. JAMA Surgery November 2024; Vol 159 (11): 1308

Table 4. Empirical Antibiotics for Necrotizing Soft Tissue Infections in Patients With Normal Kidney Function

Patient status	Antibiotic combination
Stable	One of the following antibiotics: • Amoxicillin/clavulanate, 1.2/2.2 g every 8 h • Ceftriaxone, 2 g every 24 h + metronidazole, 500 mg every 8 h • Cefotaxime, 2 g every 8 h + metronidazole, 500 mg every 8 h
	Plus • Clindamycin, 600-900 mg every 8 h or Linezolid
Unstable	One of the following antibiotics: • Piperacillin/tazobactam, 4.5 g every 6 h • Meropenem, 1 g every 8 h • Imipenem/cilastatin, 500 mg every 6 h
	Plus One of the following antibiotics: • Linezolid, 600 mg every 12 h • Tedizolid, 200 mg every 24 h
	Or One of the following antibiotics: • Vancomycin, 25-30 mg/kg loading dose, then 15-20 mg/kg dose every 8 h • Daptomycin, 6-8 mg/kg every 24 h • Telavancin, 10 mg/kg every 24 h
	Plus • Clindamycin, 600-900 mg every 8 h

Linezolid not inferior to Clindamycin as adjunctive anti-toxin therapy

McDermott et al. JAMA Surgery November 2024; Vol 159 (11): 1308
*Babiker et al. Lancet 2025; Vol 25: 265



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

27 Skin And Soft Tissue Infections

Speaker: Helen Boucher, MD

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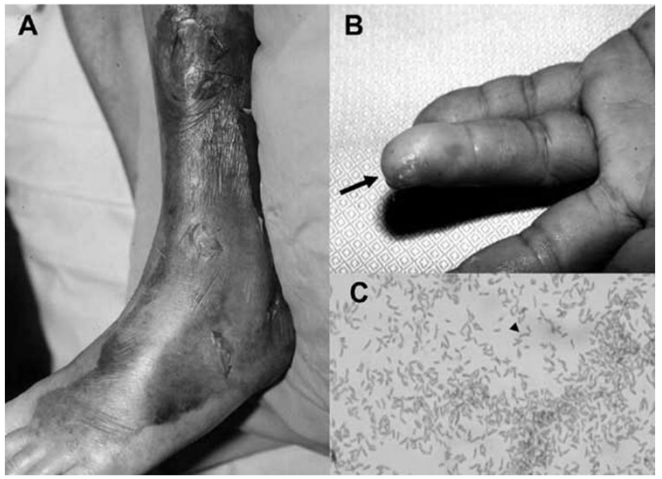
Question #8

- A 50-year-old African American male fisherman with known cirrhosis suffers an abrasion of his leg while harvesting oysters
- Within hours, the skin is red, painful, and hemorrhagic bullae appear

Which one of the following conditions predisposes to this infection?

A. G6PD Deficiency
B. Hemochromatosis
C. Sickle cell disease
D. Achlorhydria



Vibrio vulnificus

- Leading cause of shellfish (e.g., oysters) associated deaths in USA
- Portal of entry: skin abrasions or GI tract
- Liver disease, **hemochromatosis**, and exposure to estuaries are major risk factors
- **Infected wounds manifest as bullae in 75%; primary bacteremia also occurs**
- Treatment (look up): doxycycline plus ceftriaxone (alternative is a fluoroquinolone)

Organisms Whose Growth is Stimulated by Excess Iron

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

Definition: "The sails of a ship"

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Thank You!

- David Gilbert
- Paul Auwaerter

Our patients and their families

Questions, Comments?

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Helicobacter and Clostridioides

David Aronoff, MD

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Helicobacter & Clostridioides difficile

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7/28/2026

Disclosures of Financial Relationships with Relevant Commercial Interests

- None

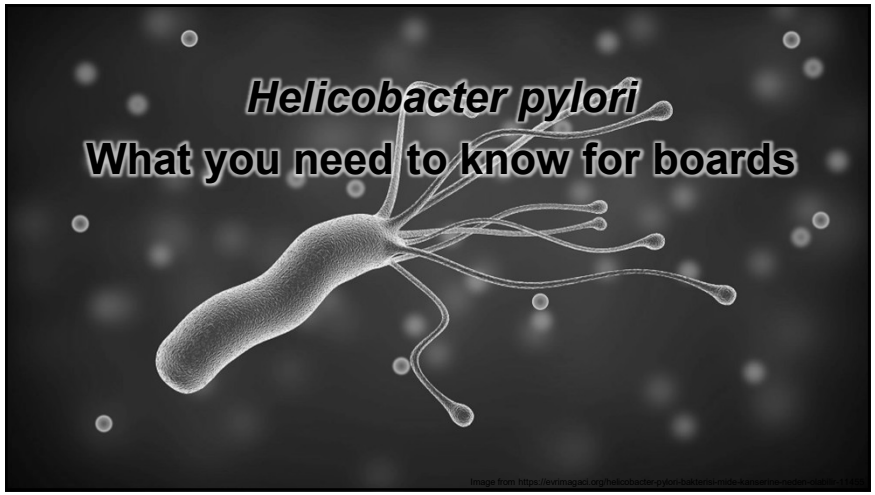

Image from https://evrimagaci.org/helicobacter-pylori-bakterisi-mide-kanserine-neden-olabilir-1102

Helicobacter pylori Microbiology

- The most prevalent chronic bacterial infection
- Spiral-shaped, Gram-negative rod
- Flagellated
- Non-invasive
- Catalase +, oxidase +
- Grows best at pH 6-8

Urease + → Survival, Colonization, Diagnosis

Urea → CO_2 + NH_3 → ↑**pH**

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

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Helicobacter pylori: Take Home Points

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

Helicobacter pylori: Take Home Points

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

Alarm Symptoms

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

Helicobacter pylori: Take Home Points

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

Helicobacter pylori: Take Home Points

- **Test of cure** to confirm eradication must be performed in all patients treated for Hp at least 4 weeks after treatment
  - PPI therapy should be withheld for 2 weeks before testing because of suppressive effects of PPI on Hp urease & some concerns about antibacterial actions of PPI

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

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Question #1

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

What are the biopsies are most likely to show?

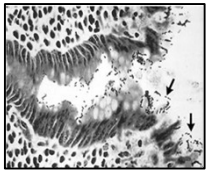
A. Hp organisms, but no gastric or esophageal inflammation
B. Hp organisms plus gastric inflammation (gastritis)
C. Hp organisms plus esophagitis
D. Neither Hp organisms, nor inflammation because the urease test is often false positive with a normal endoscopy

Question #2

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

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

Helicobacter pylori



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

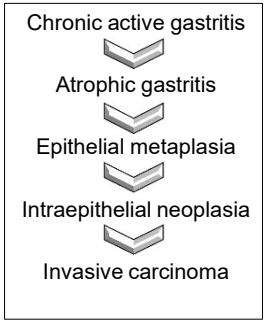
*At greater risk: indigenous Americans, Black/AA, Hispanic, & immigrants from high-cancer-risk countries like Japan, Korea, Taiwan & China

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

Helicobacter pylori and Cancer

Hp is a carcinogen that causes an inflammation-driven cancer

- **The leading cause** of infection-associated cancer worldwide
- 1-3% of infected individuals will develop cancer
- Hp causes 15% of the total cancer burden globally
- Up to 89% of all gastric cancer is attributable to Hp



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

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Transmission of *H. pylori*

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

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

Disease Paths for *Helicobacter pylori* Infection

• Asymptomatic gastritis	80%+
• Peptic ulcer (DU, GU)	10-15%
• Gastric cancer	<3%
• MALT lymphoma	<0.1%

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

Shah S, *et al. UpToDate* (2025)
Lee Y, *et al. Annu Rev Med* (2022)
NEJM 347: 1175, 2002
Gut 66:6, 2017

H. pylori: Disease Associations

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

Hp causal

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

- Iron deficiency anemia, B12 deficiency, ITP
- Eradication of Hp neither causes nor exacerbates GERD
- Hp poss. **reduces** risk for Barrett's esophagus/esophageal CA

HP is classified by WHO as a Class 1 carcinogen.
MALT = mucosal-associated lymphoid tissue

Shah S, *et al. UpToDate* (2025)
Maastricht V. Gut (2017)
Kasahun GG, Infect Drug Resist (2020)
Shah S, et al. Gastroenterology (2021)

Question #3

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

What is the best approach to the diagnosis of H. pylori infection in this patient?

A. Immediate Hp serology
B. Immediate Hp stool antigen EIA
C. Endoscopy with rapid urease test (RUT)
D. Immediate 13C Urea Breath Test
E. D/C PPI for 2 weeks then Hp stool antigen EIA

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Who Should Be Tested for Hp?

Patients with:

Do Not Test for GERD Symptoms

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

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

Diagnosis of Hp Infection

NO:

Noninvasive (global)	Sensitivity	Specificity	
Urea Breath Test UBT (^{13}C)	> 90 – 95%	> 90 – 95%	Live Hp
Stool Antigen (monoclonal)	> 90 – 95%	> 90 – 95%	Live & dead Hp
Serology	85%	79%	Detects exposure

Biopsy-based (sampling error)	Sensitivity	Specificity	
Rapid urease test	90%	95%	2-5 bx recommended
Histology	90 – 95%	95 – 98%	
Culture	73%	100%	Difficult

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

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

Testing Limitations for Hp

PPI
Antibiotics
Bismuth
Bleeding
} Interfere with Hp tests *

False negatives due to decreased Hp burden

Recommend delay diagnostic testing until:

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

**PPIs suppress urease activity; more likely to impact UBT than SAT*

Lee Y, et al. Annu Rev Med (2022)
Crowe SE, UpToDate (2018)
Crowe SE, NEJM 380:1158-65 (2019)
Kajihara Y, et al. Helicobacter (2023)

Initial Diagnosis of *H. pylori* with Dyspepsia

- MOST = NONINVASIVE
- Stool antigen test (SAT)
- Urea Breath Test (UBT)

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

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

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Question #4

Which of the following is the most appropriate next step for evaluating a 29-year-old previously healthy but overweight male patient with typical retrosternal heartburn symptoms?

A. Stool antigen test for *H. pylori*
B. Urea breath test for *H. pylori*
C. No testing for *H. pylori*
D. Serological testing for *H. pylori*
E. Empiric therapy for *H. pylori* regardless of testing

Dyspepsia vs. GERD

Feature	Dyspepsia	GERD
Primary symptoms	Epigastric pain, burning, fullness, early satiety	Heartburn, acid regurgitation
Location	Epigastric (upper abdomen)	Retrosternal (chest, throat)
Meal relation	Worse with or after meals	Worse after meals, lying down, or at night
Quality	Pain/discomfort	Burning/regurgitation
Alarm features to watch	Weight loss, persistent vomiting, anemia, dysphagia	Dysphagia, odynophagia, GI bleeding, weight loss
Main complications	Peptic ulcer, *H. pylori* gastritis	Esophagitis, Barrett's esophagus, stricture, adenocarcinoma

Question #5

A 23-year-old woman presents with persistent epigastric discomfort diagnosed as Hp+ gastritis by endoscopy. Fecal Hp antigen is also positive. Last year she was treated with azithromycin for a respiratory tract infection. As a child, she was treated repeatedly with PCN/amoxicillin for recurrent tonsillitis.

What do you recommend for therapy?

A. Clarithromycin + amoxicillin + PPI
B. Metronidazole + erythromycin + PPI
C. Bismuth subsalicylate + TCN + metronidazole + PPI
D. Metronidazole + amoxicillin + PPI
E. PPI therapy alone given her age

Who Should be Treated for H. Pylori Infection?

CLINICAL GUIDELINES

ACG Clinical Guideline: Treatment of *Helicobacter pylori* Infection

William D. Chey, MD, FACG[1], Colin W. Howden, MD, FACG[2], Steven F. Moss, MD, FACG[3], Douglas R. Morgan, MD, MPH, FACG[4], Katarina B. Greer, MD, MSEp[5], Shilpa Grover, MD, MPH[6] and Shailja C. Shah, MD, MPH[7]

ABSTRACT *Helicobacter pylori* is a prevalent, global infectious disease that causes dyspepsia, peptic ulcer disease, and gastric can...

- All patients with active *H pylorí* infection should be treated
- Infection causes chronic progressive damage to the gastric mucosa
- 20%–25% of individuals will get life-threatening problems such as peptic ulcer or gastric cancer

Chey, WD, *et al*. ACG Clinical Guideline: Treatment of *Helicobacter pylori* Infection. *Am J Gastroenterol* 119(9):p 1730-1753, September 2024

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H. Pylori Antibiotic Resistance Rates in the US

a

Antibiotic(s)	% Resistant (N=2669 strains)
Clarithromycin	31.5
Levofloxacin	37.6
Metronidazole	42.1
Tetracycline	0.9
Amoxicillin	2.6
Rifabutin	0.2
Dual Metronidazole /Clarithromycin	11.7

Antibiotic susceptibility testing performed on 2669 strains from the US between 2011-2021

Ho J et al, Am J Gastroenterol 2022;117:1221

b

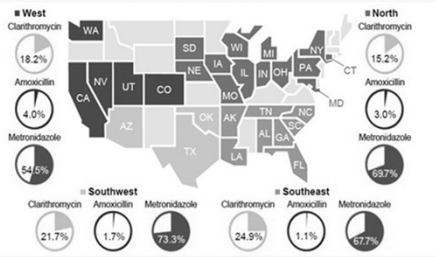
Overall resistance rates:

Clarithromycin 22.2%

Amoxicillin 1.2%

Metronidazole 69.2%

US resistance rates by subregion:



381 patients with *H. pylori* from the US underwent antibiotic sensitivity testing between 12/2019-1/2021

Megraud et al. Am J Gastroenterol 2023;118:269–275

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***In vitro* metronidazole resistance is not associated with eradication failure in patients receiving optimized BQT.**

Chey WD, *et al. Am J Gastroenterol* (2024)

Treatment of Hp

- Cure rates of most Hp therapies are relatively low (<80%)
- Antibiotic resistance is a HUGE challenge, provoking quadruple therapies
- AVOID CLARITHROMYIN & FLUOROQUINOLONES
- Discuss the critical importance of adherence to treatment
- Use high dose PPI (BID dose; increase gastric pH>4-5)
  - Hp grows optimally at pH 6-8 & low pH hinders stability & activity of macrolides, amoxicillin
  - Vonoprazan: new potassium-competitive acid blocker (PCAB) that is more potent than PPIs appears promising (Vono BID + amox TID)

Lee YC, Annu Rev Med (2022), Chey WD, *et al. Am J Gastroenterol* (2024), Shah SC, *et al. UpToDate* (2025)

Treatment of Hp

- Triple therapy with a PPI, clarithromycin, & amoxicillin or metronidazole is **not favored** due to increased prevalence of macrolide resistance (but might still be an option on boards!)
  - Clarithromycin resistance in the US now ≥ 15%
- Use a bismuth-based **quadruple therapy for 14 days** as 1st-line therapy:
  - Bismuth subsalicylate or subcitrate
  - Tetracycline (**not** doxycycline: results are inferior)
  - Metronidazole
  - PPI

Shah SC, *et al. Gastroenterology* 2021;160:1831–1841
Cho J, *et al. Gastroenterol Clin N Am* 50 (2021) 261–282
Hulten KG, *et al. Gastroenterology* 2021
Lee YC, *Annu Rev Med:* 2022

Treatment of Hp Continued…

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

Lee YC, Annu Rev Med (2022)

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ACG Clinical Practice Guideline

Treatment of *H. pylori* Infection in North America

	Treatment Naïve	Treatment-Experienced (Salvage)		Penicillin Allergy
Regimen		Empiric	Proven antibiotic sensitivity	
Optimized Bismuth Quadruple	☑☑☑	☑☑	☑☑	☑☑☑ *
Rifabutin Triple	☑☑	☑☑	☑☑	
Vonoprazan Dual	☑☑	?	?	
Vonoprazan Triple			☑☑	
Levofloxacin Triple			☑☑	

☑☑☑ Recommended ☑☑ Suggested ? May be considered when other treatments are not options

* When Bismuth Quadruple Therapy not an option, consider referral for formal penicillin allergy testing and/or desensitization

Chey et al. *Am J Gastroenterol.* 2024. doi:10.14309/ajg.0000000000002968
All icons above are from Microsoft Powerpoint.

AJG The American Journal of GASTROENTEROLOGY
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Table 5. Recommended regimens for treatment-naive patients with *H. pylori* infection

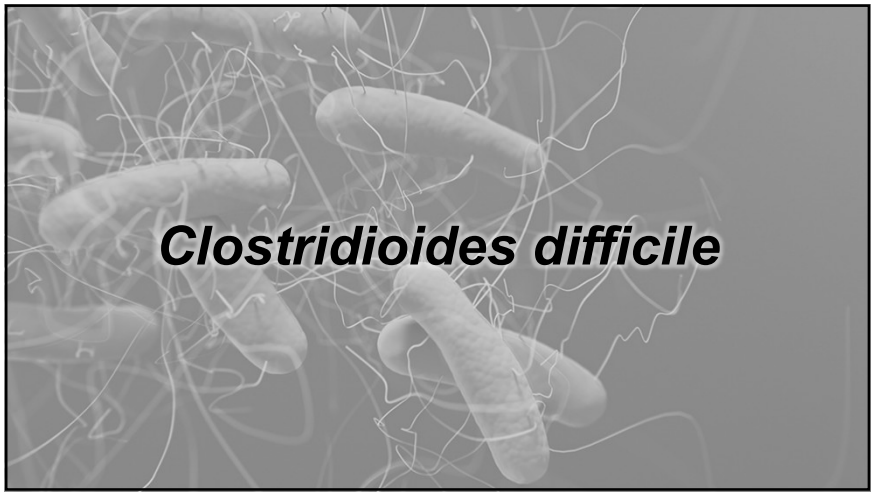
Regimen	Drugs (doses)	Dosing frequency	FDA approval	Recommendation
Optimized bismuth quadruple[a]	PPI (standard dose)[b] Bismuth subcitrate (120–300 mg) or subsalicylate (300 mg)[d] Tetracycline (500 mg)[e] Metronidazole (500 mg)	b.i.d. q.i.d. q.i.d. t.i.d. or q.i.d.	No[c]	Strong (moderate quality of evidence)
Rifabutin triple (Talicia)[f]	Omeprazole (10 mg)[b] Amoxicillin (250 mg) Rifabutin (12.5 mg)	4 capsules t.i.d.	Yes	Conditional (low quality of evidence)
PCAB dual (Voquezna DualPak)[g]	Vonoprazan (20 mg) Amoxicillin (1,000 mg)	b.i.d. t.i.d.	Yes	Conditional (moderate quality of evidence)
PCAB triple (Voquezna TriplePak)[h]	Vonoprazan (20 mg) Clarithromycin (500 mg) Amoxicillin (1,000 mg)	b.i.d.	Yes	Conditional (moderate quality of evidence)

Chey WD, *et al. Am J Gastroenterol* (2024)

Question #6

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

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



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Clostridioides difficile: Take Home Points

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

Clostridioides difficile: Take Home Points

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

Facts about *C. difficile* infection (CDI)

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

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

Pathogenesis of CDI

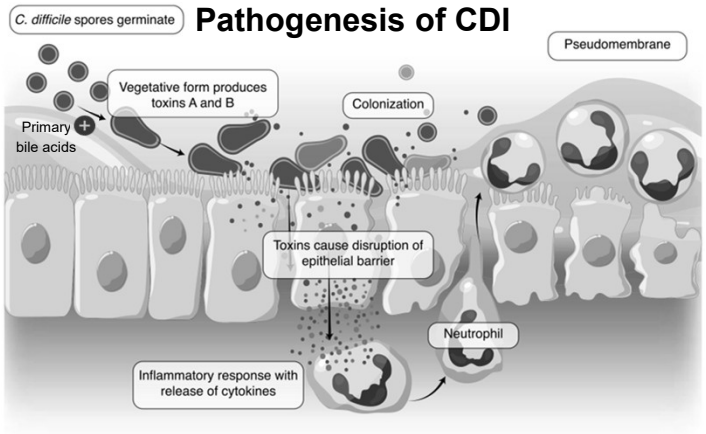

Figure adapted from Seekatz AM, *et al. Therapeutic Advances in Gastroenterology* (2022)

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Common Clinical Manifestations

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

http://year9diseases.wikispaces.com/

CDI Severity

- **Leukocytosis**
- **AKI**
- **Sepsis/shock**
- **Megacolon**

Stool frequency is not part of severity assessment

Clinical Definition	Supportive Clinical Data
Non-severe	Leukocytosis with a WBC count of ≤ 12,000 cells/mL and a serum creatinine level < 1.5 mg/dL
Severe	Leukocytosis with a WBC count of ≥ 15,000 cells/mL or a serum creatinine level > 1.5 mg/dL
Fulminant	Hypotension or shock, ileus, megacolon

Table from Wilcox M, *IDSE* (2018)
McDonald LC, *et al. Clin Infect Dis.* 2018 Mar 19;66(7):987-994

C. difficile Diagnostic Testing

Whom to test?

- Appropriate epidemiology/ill with diarrhea/endoscopic findings
  - No laxatives within last 48 hrs (board exam vs. real world caveat)
  - Chemotherapy, enteral tube feeds, IBD flare should make you think twice
- Test diarrheal stools (unless ileus). Test only one stool sample.
  - >3 liquid stools over 24h
- Only test specimens if patient > 1 year old

McDonald LC, *et al. Clin Infect Dis.* 2018 Mar 19;66(7):987-994
L'Huillier JC, *et al. J Trauma Acute Care Surg* 2024

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C. difficile Diagnostic Testing

Simplified approach:

Diarrhea* + **Toxigenic *C. difficile* &/or toxin in stool** ⇨ **TREAT**

***No other obvious causes**

C. difficile Diagnostic Testing

Nucleic acid amplification test (NAAT; PCR):

Detects the gene for toxin B

Advantages	Disadvantages
• High sensitivity • Rapid • Relatively inexpensive	• Does not detect actual toxin • Can't differentiate colonization *vs* infection

Patient selection is critical

C. difficile Diagnostic Testing

Glutamate dehydrogenase (GDH) antigen EIA:

Detects C. difficile bacteria by secreted antigen

Advantages	Disadvantages
• High sensitivity • Rapid • Relatively inexpensive	• Does not detect actual toxin • Detect NON-toxigenic strains too • Cannot differentiate colonization from infection

Must be combined to test for toxin (EIA)

C. difficile Diagnostic Testing

Toxin A/B detection by EIA:

Detects C. difficile toxin(s) directly

Advantages	Disadvantages
• Good specificity • Rapid • Relatively inexpensive	• Relatively poor sensitivity • False positives possible

Usually used in a 2-step protocol with NAAT or GDH

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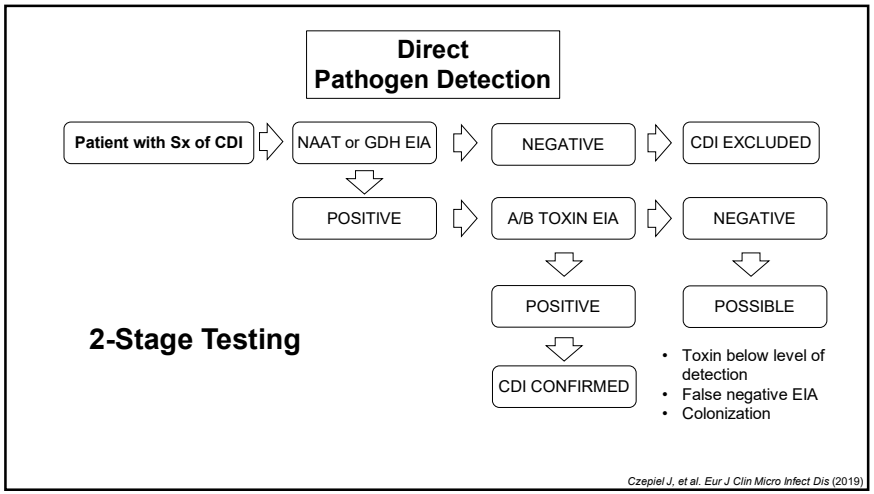

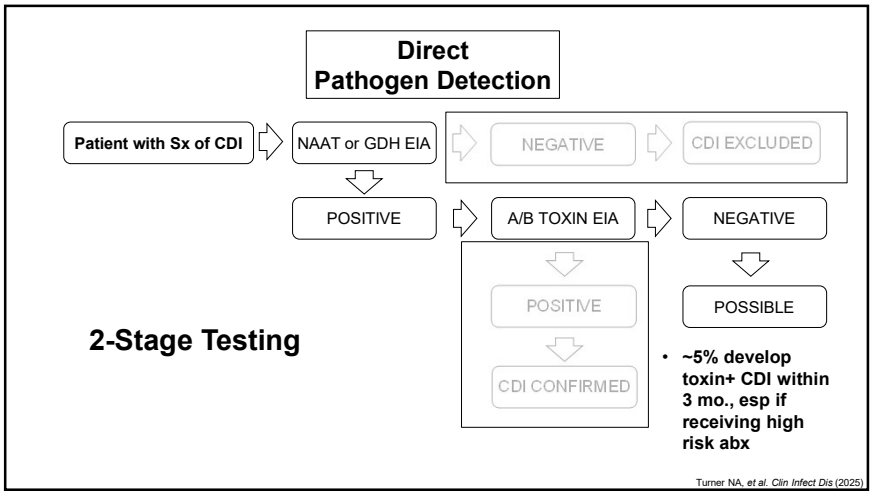

Question #7

67-year-old woman develops diarrhea while hospitalized for community acquired pneumonia. She is afebrile, WBC count is 12,000/ml, creatinine is 1.2 mg/dl (baseline 1.0 mg/dL) and she is experiencing 12 small loose stools daily with abdominal cramping. Stool PCR is positive for C. difficile toxin B.

Which of the following therapies is recommended?

A. Metronidazole 500 mg po TID x 10 days
B. Vancomycin 500 mg PO QID x 10 days
C. Fidaxomicin 200 mg PO BID x 10 days
D. Bezlotoxumab + vancomycin x 10 days
E. Fidaxomicin 200 mg PO BID + metronidazole 500 mg PO TID x 10 days

Table 1. Treatment Strategies for CDI.

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

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

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Recurrent CDI

Treatment	Contents	Dose/route	Recurrence rate (active treatment)	Recurrence rate (placebo)	Absolute risk reduction	FDA Approval	Ref.
Bezlotoxumab (ZINPLAVA®)	Monoclonal Ab	10 mg/kg IV x 1	15.7-17.[illegible] **DISCONTINUED** [illegible][a]		10.0-10.2%	YES	(1)
SER-109 (VOWST®)	Stool spores	4 caps QD PO x 3 d	12.4%[b]	39.8%[b]	**27.4%**	YES	(2)
RBX2660 (REBYOTA®)	Feces	150 mL PR enema x 1	29.4%[b]	42.5%[b]	**13.1%**	YES	(3)
VE303	8 Clostridia strains	10 caps QD x 14 d	13.8%[b]	45.5%[b]	**31.7%**	NO	(4)*
FMT#	Feces	Various	32.3%	56.6%	**23.3%**	With pt. consent	(5)

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

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

Therapy of CDI With Drug Doses

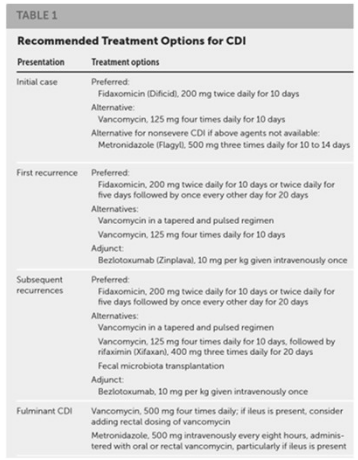

TABLE 1

Recommended Treatment Options for CDI

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

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

Therapy of CDI

TABLE 1

Recommended Treatment Options for CDI

Presentation	Treatment options	Additional information
Initial case	Preferred: Fidaxomicin (Dificid), 200 mg twice daily for 10 days Alternative: Vancomycin, 125 mg four times daily for 10 days Alternative for nonsevere CDI if above agents not available: Metronidazole (Flagyl), 500 mg three times daily for 10 to 14 days	Fidaxomicin: Caution for use in patients with congestive heart failure Diagnosis of nonsevere cases supported by: White blood cell count < 15,000 cells per µL (15×10^9 per L) Serum creatinine < 1.5 mg per dL (132.6 µmol per L)

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

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

Therapy of CDI

TABLE 1

Recommended Treatment Options for CDI

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

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

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Therapy of CDI

TABLE 1

Recommended Treatment Options for CDI

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

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

Therapy of CDI

TABLE 1

Recommended Treatment Options for CDI

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

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

Thank You

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

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Monday, August 24, 2026

29

Immunizations: Domestic, Travel, and Occupational

Shireesha Dhanireddy, MD

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Immunizations: Domestic, Travel, and Occupational

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Professor, Allergy & Infectious Diseases
University of Washington

8/5/2026

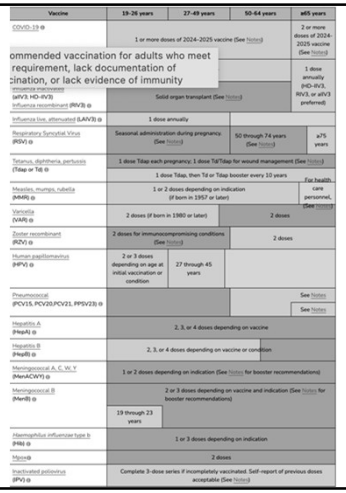
Disclosures of Financial Relationships with Relevant Commercial Interests

None

Objectives

- Review vaccine guideline resources
- Review recommendations for routine immunizations
- Discuss travel immunizations
- Review vaccines in special populations

Key Sources



SEE ENLARGED SLIDE FOLLOWING ENTIRE PRESENTATION

Source: https://www.cdc.gov/vaccines/hcp/imz-schedules/adult-age.html

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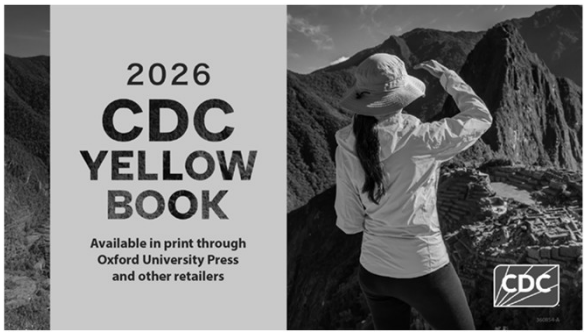
Key Sources



Source: https://wwwnc.cdc.gov/travel/page/yellowbook-home

Question #1

22-year-old man with h/o egg allergy and no prior influenza vaccine presents for routine visit. He states he has had hives after eating eggs. No h/o anaphylaxis.

Which of the following is recommended?

A. Defer vaccination and refer to an allergist for testing
B. Vaccinate with any inactivated influenza vaccine without additional monitoring
C. Vaccinate and monitor for 30 minutes after receiving any inactivated influenza vaccine
D. Vaccinate with only live attenuated influenza vaccine

Egg Allergy - ACIP Recommendations

- Egg allergy
  - 1.3% of children
  - 0.2% of adults
- Ok to get influenza vaccine if the following:
  - No reaction with cooked eggs
  - Only hives after exposure
- If have anaphylaxis, angioedema, respiratory distress or required epinephrine
  - CAN STILL RECEIVE VACCINE – but should be given by a provider who can recognize allergic reactions
  - 33 cases of anaphylaxis out of 25.1 million doses
  - 8/33 had symptoms within 30 min

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Question #2

71-year-old man underwent unrelated HSCT for MDS AML 12 years ago which was relatively uncomplicated without GVHD, and he has been off immunosuppression for 2 years. His primary care provider checks a rubeola serology as there is an outbreak in the community and patient is concerned regarding risk. The serology is negative.

Which of the following do you recommend?

A. Vaccine is not recommended as it is live and there is risk of vaccine related disease
B. One dose of MMR vaccine recommended
C. Two doses of MMR vaccine recommended

Measles in 2026

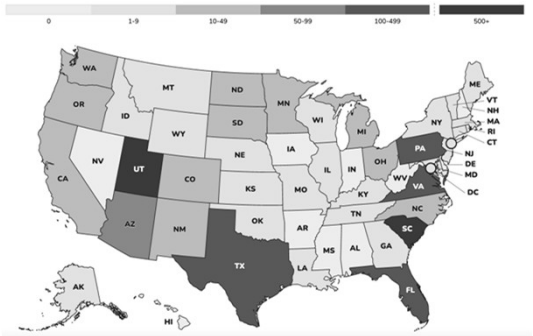
	2026 To date	2025 Full year
Total Cases	**2,231**	**2,289**
Age		
Under 5 years	446 (20%)	584 (26%)
5-19 years	1,122 (50%)	1,017 (44%)
20+ years	657 (29%)	675 (29%)
Age unknown	6 (less than 1%)	13 (1%)
Vaccination Status		
Unvaccinated or Unknown	93%	93%
One MMR dose	4%	3%
Two MMR doses	4%	4%

	2026	2025
Total Hospitalized	**6%** (140 of 2,231 cases)	**11%** (243 of 2,289 cases)
Percent of Age Group Hospitalized		
Under 5 years	10% (43 of 446)	18% (106 of 584)
5-19 years	3% (36 of 1,122)	6% (58 of 1,017)
20+ years	9% (61 of 657)	12% (79 of 675)
Age unknown	0% (0 of 6)	0% (0 of 13)

	2026	2025
Total Deaths	**0**	**3**

Source: https://www.cdc.gov/measles/data-research/index.html#cdc_data_surveillance_section_10-measles-cases-in-2026; accessed 7/13/2026

Measles in 2026



Source: https://www.cdc.gov/measles/data-research/index.html#cdc_data_surveillance_section_10-measles-cases-in-2026; accessed 7/13/2026

SEE ENLARGED SLIDE FOLLOWING ENTIRE PRESENTATION

Measles Vaccine & Prevention

- Between 1/1/25 and 4/17/25, 800 cases with 85 (11%) hospitalizations
- Among hospitalized patients, 66% unvaccinated, 33% unknown vaccine status, 1 patient had received 1 dose of vaccine
- Vaccine very effective!
  - 93% effective after 1 dose
  - 97% effective after 2 doses
  - Immunity is felt to be lifelong*
  - Post-exposure prophylaxis:
  - Immune globulin – 76-100% effective
  - Vaccine – 83-100% effective

Mathis AD et al. MMWR 2025
Montroy J et al. Vaccine 2025

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Measles Vaccine

- Evidence of presumptive immunity
  - Written documentation of adequate vaccination
    - 1+ doses of vaccine at ≥12mos
      - Pre-school age
      - Adults not at high risk
    - 2 doses
      - School age children
      - College students
      - Healthcare personnel
      - International travelers
  - Lab evidence of immunity
  - Lab confirmation of measles disease
  - Birth prior to 1957

Measles Vaccine

Who doesn't need vaccine:

- Adults born before 1957 (except HCW – should receive during an outbreak)
- Those with laboratory evidence of immunity

Who needs 1 dose:

- Adults born after 1957 considered low risk without documented vaccine and no lab evidence of immunity or prior infection

Who needs 2 doses:

- Healthcare workers
- International travelers born in 1957 or later
- Persons attending colleges or post-high school educational institutions

Measles Vaccine

Measles vaccine may be administered post-transplant if:

- 2 years post transplant
- No active GVHD
- At least 1 year off immunosuppressive medication

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Question #3

A 24-year-old healthy male presents for routine clinic visit. He is not on any medications. He smokes cigarettes. He is sexually active with both men and women and uses condoms consistently.

Which of the following is correct regarding HPV vaccine?

A. He should receive 2 doses of HPV-9 spaced 6 months apart
B. He should receive 3 doses of HPV-9 at 0, 1, and 6 months
C. He does not need HPV vaccine as he is already sexually active
D. HPV vaccination is only recommended in males through age 21

HPV Vaccine Recommendations

- Routine vaccination at age 11 or 12 years*
- Recommended for everyone through age 26 if not previously vaccinated
- **Vaccine not routinely recommended for everyone older than 26 years**

BUT

- **May consider for ages 27 through 45 through shared decision making**

*Vaccination series may be started at 9 years of age

Nonavalent:

- Types 6, 11, 16, 18, 31, 33, 45, 52, 58
- FDA-approved for females and males **9-45*** yrs

MMWR 2019;68:698-702

2 Doses Adequate in Some Populations

For boys and girls age 9-14:

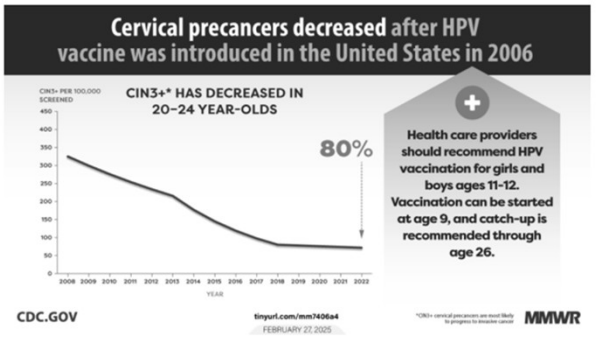
- 2 dose schedule: 0, 6-12 months

For those who are >14 or immunocompromised:

- 3 dose schedule: 0, 1-2, 6 months
- 2 dose schedule not yet tested in this group, stay tuned

Meites et al, MMWR 2016: 65(49); 1405-1408.
Iversen et al, JAMA 2016: 316(22); 2411-2421.

Impact of HPV Vaccination in the US



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Gargano et al. MMWR 2025

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Single-Dose HPV

- In US, recommendation remains 2 doses for individuals < 15 years of age
- Many other countries have adopted single dose strategy to increase uptake and decrease cost
- Efficacy equivalent for 1 dose (age 10-18 at 15-year follow-up)
- WHO recommends 1 or 2 doses

Malvi SG et al. JNCI Monographs 2024

Question #4

A 37-year-old man recently diagnosed with HIV presents to clinic for routine care after starting antiretroviral therapy 3months ago. He has not received pneumococcal vaccination.

Which of the following is most accurate?

A. He does not need pneumococcal vaccination as he is under 65
B. He needs a PCV20 alone
C. He needs a PCV20 followed 1 year later by a PPSV23
D. He needs a PCV15 followed by PPSV23 1 year later and again in5 years

Pneumococcal Disease

Age (years)	Disease Incidence Cases/100,000 (number of cases)	Death Rate Deaths/100,000 (number of deaths)
<1	17.7 (702)	0.20 (8)
1	12.6 (500)	0.20 (8)
2–4	5.07 (606)	0.13 (16)
5–17	1.23. (659)	0.00 (0)
18–34	2.33 (1,757)	0.08 (60)
35–49	6.48 (3,982)	0.46 (284)
50–64	14.8 (9,326)	1.47 (932)
65–74	18.0 (4,952)	2.17 (597)
75–84	29.0 (4,042)	4.53 (631)
≥85	45.4 (2,856)	11.4 (718)
Total	9.14 (29,382)	1.01 (3,254)

Gierke R et al. CDC Vaccine Preventable Diseases Surveillance Manual

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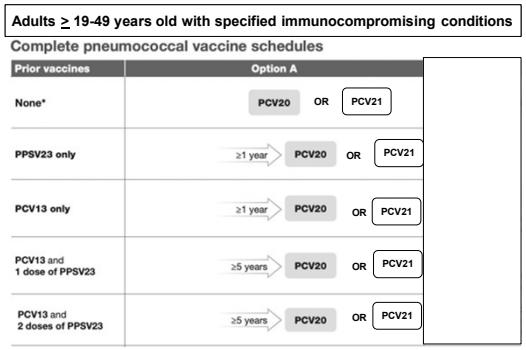
ACIP Pneumococcal Vaccine Guidelines

- CDC ACIP recommends single dose of PCV for all adults aged > 50 who have not received PCV before or if unknown
- For people at higher risk for invasive disease, give a single dose of PCV 19-49 years (unchanged recommendation)

Pneumococcal Vaccine in Adults Who is at Risk?

- Persons > 50 years of age
- Persons age 19-49 with:
  - Chronic lung disease (asthma or COPD)
  - Chronic heart disease (except HTN)
  - Chronic liver disease
  - CSF leak
  - Smokers
  - Diabetes
  - Alcoholism
  - Functional or anatomic asplenia
  - Immunocompromising conditions

Pneumococcal Vaccine



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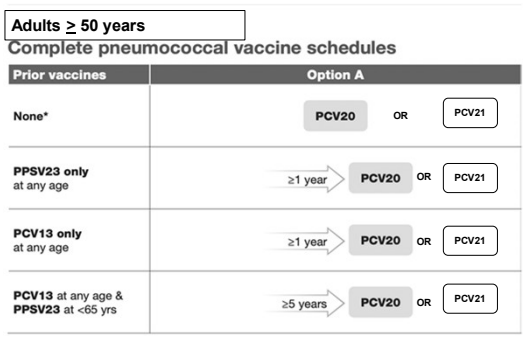
Pneumococcal Vaccine



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PCV20 vs PCV21

- PCV20 favored when proportion of serotype 4 disease is ≥ 30%

Proportion of serotype 4 IPD 2017-2023

Age group (years)	Region	State	2017	2018	2019	2020	2021	2022	2023
50-64	East	CT	0	0	1	0	0	0	0
		GA	0	0	1	0	1	0	1
		MD	0	0	0	0	0	0	0
		NY	0	0	0	4	0	0	0
		TN	0	0	0	0	0	0	3
	West	AK[1]	0	2	10	48	66	56	41
		CA	16	12	6	15	0	11	18
		CO	13	12	16	23	20	22	14
		MN	0	0	1	1	2	2	12
		NM	0	7	13	18	22	21	15
		OR	0	0	0	0	3	19	43

Age group (years)	Region	State	2017	2018	2019	2020	2021	2022	2023
50-64	East	CT	0	0	1	0	0	0	0
		GA	0	0	1	0	1	0	1
		MD	0	0	0	0	0	0	0
		NY	0	0	0	4	0	0	0
		TN	0	0	0	0	0	0	3
	West	AK[1]	0	2	10	48	66	56	41
		CA	16	12	6	15	0	11	18
		CO	13	12	16	23	20	22	14
		MN	0	0	1	1	2	2	12
		NM	0	7	13	18	22	21	15
		OR	0	0	0	0	3	19	43

SEE ENLARGED SLIDE FOLLOWING ENTIRE PRESENTATION

Question #5

A 40-year-old software engineer presents to establish care. She has no medical problems. She is in a mutually monogamous relationship with a cis-male partner. She denies any upcoming foreign travel. She reports she has not received Hep B vaccine in the past.

Which of the following is most accurate regarding Hep B vaccination?

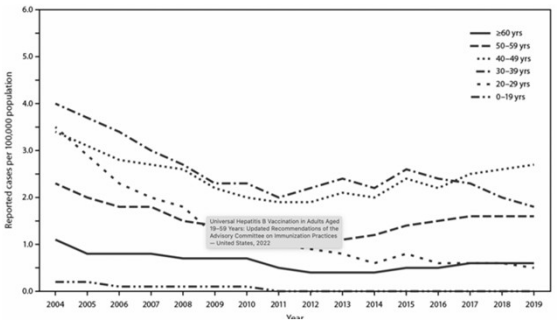
A. She should start the series today

B. She should only receive if she has risk factors for Hep B

C. Hep B vaccine is not recommended in individuals her age

Hepatitis B

Rates of reported acute hepatitis B virus infection, by age group – United States, 2004-2019



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Hepatitis B Vaccine: Current Recommendations

- All infants
- All persons < 19 years
- All adults 19-59 years
- Adults > 60 years with risk factors for Hep B
- Adults > 60 without known risk factors may receive vaccine

Hepatitis B Vaccine

- Sexual exposure
  - Partners with Hep B
  - More than 1 sex partner in last 6 months
  - Getting STI testing or treatment
  - MSM
- Percutaneous exposure (IDU, household contacts, healthcare, public safety, patients on HD or those working with HD patients)
- International travelers
- People with HIV
- Incarceration
- Chronic liver disease (including HCV)

Question #6

A 62-year-old woman with a self-reported history of shingles 10 years ago and type II diabetes presents to clinic.

What do you recommend regarding the zoster vaccine?

A. Vaccine not indicated given her history of zoster

B. Check VZV titer to confirm history. If negative, proceed with vaccination

C. Recommend recombinant zoster vaccine

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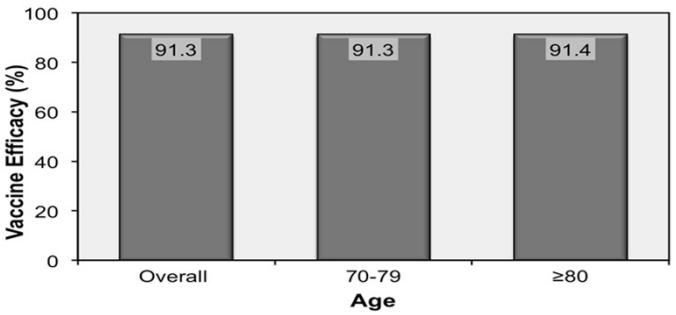
RZV Efficacy Against First Episode of Zoster in Immunocompetent Patients ≥50



Cunningham AL, et al. N Eng J Med. 2016;375:1019-32.

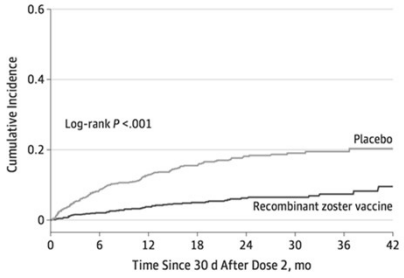
ACIP Recommendations for Zoster Vaccine

- RZV is the only vaccine available
- Healthy adults > 50 years
  - Regardless of prior h/o HZ
  - No need to wait any specific period of time after HZ to give RZV(just not during acute episode)
- 2 doses, 2-6 months apart

ACIP Recommendations for Zoster Vaccine In Immunocompromised Persons

- RZV recommended for all IC adults 18+
- 2 doses – 2-6 months apart
  - May give 2nd dose early (1-2months) if anticipating more immunosuppression
  - If second dose early, then repeat dose given at least 4weeks later
- For those without h/o VZV,RZV not indicated

Efficacy of RZV in Preventing Incident Herpes Zoster in Patients Who Had Undergone HSCT



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Source: Bastidas et al. JAMA 2019.

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Question #7

44-year-old woman hospitalized with anemia and thrombocytopenia diagnosed with complement-mediated HUS. Treatment with eculizumab is being considered. She is told she will need vaccine(s) prior to initiation of therapy.

What should you give?

A. Give meningococcal quadrivalent conjugate vaccine
B. Give meningococcal B vaccine only
C. Give both quadrivalent conjugate and meningococcal B vaccines

Meningococcal Vaccines

MenACWY vaccines	• **4 serogroups**: A, C, W, and Y
MenB vaccines	• **1 serogroup**: B
MenABCWY vaccines	• **5 serogroups**: A, B, C, W, and Y

Meningococcal Quadrivalent Vaccines:
Serogroups Included in Vaccine: A, C, Y, W-135

Menveo (MenACWY-CRM)
- Conjugate vaccine
- Approved for ages 2 to 55 years
- 2-dose series, 8 weeks apart

MenQuadFi (MenACWY-TT)
- Polysaccharide tetanus toxoid conjugate vaccine
- Approved for ages 2 to 55 years
- Single dose for 2 years or older, booster may be given at least 3 years later if age 13 or older with ongoing risk

Meningococcal Group B Vaccines:
Serogroup Included in Vaccine: B

- **MenB-4C *(Bexsero)***
  - Recombinant vaccine
  - For ages 10 to 25 years
  - 2 dose series ≥1 month apart
- **MenB-FHbp *(Trumenba)***
  - Recombinant vaccine
  - For ages 10 to 25 years
  - Healthy adolescents and young adults: 2 doses at 0, 6 months
  - Adults at risk for meningococcal disease: 3 doses at 0, 1-2, 6 months
  - Vaccinated during serogroup B meningococcal disease outbreaks: 3 doses at 0, 1-2, 6 months

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ACIP Meningococcal B Vaccine Recommendations:
Adolescents and Young Adults

Recommended for people 16-23 years of age at increased risk, preferred age 16-18:

- Meningococcal B outbreak
- Asplenia
- Complement deficiency
- Use of complement inhibitors (i.e., eculizumab)
- Microbiologist with potential exposure to Neisseria meningitidis

For others age 16-23, shared decision making recommended

Same vaccine should be used for all doses

Complement Inhibitors and Meningococcal Disease

- Eculizumab and Ravulizumab 1000-2000x increased risk of meningococcal meningitis
- CDC recommendations:
  - Immunize with both quadrivalent and B vaccines at least 2 weeks prior to giving eculizumab if possible
  - Repeat immunization every 5 years while on eculizumab
- Risk remains increased despite vaccination

Pentavalent Meningococcal Vaccine

- MenACWY-TT/MenB-FHbp
- FDA approved 10/2023 for persons age 10-25
- ACIP recommendations:
  - Healthy persons 16-23, when shared decision making favor giving MenB and both vaccines are due
  - For persons age > 10 years at increased risk of disease
    - Subsequent MenB vaccine should be the same (i.e., MenB-FHbp (*Trumenba*)

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Question #8

A 27-year-old pregnant woman presents for her routine obstetrics visit at her 32-week gestation visit. She is G2P1.She has a healthy 2-year-old daughter at home.

Which statement is correct regarding Tdap in pregnancy?

A. She should receive a Tdap today only if she has not received in the past 5 years.
B. She should receive Tdap only if she did not receive during her prior pregnancy
C. She should receive Tdap today

Tdap Recommendations

WHO
- All adolescents aged 11 through 18 years (age 11-12 preferred)
- All adults aged 19 through 64 who have not received a dose
- All adults aged > 65 years (2/2012)
- All pregnant women during each pregnancy

WHAT
- Boostrix preferred for adults > 65 years (but either okay)

WHEN
- Regardless of interval between last Td if has not received Tdap
- During each pregnancy for pregnant women – optimum timing is 3rdtrimester (27-34 weeks)

Question #9

A couple in their 30's plans to adopt a 2-year-old girl from Ethiopia. They have a regular babysitter and another 7-year-old child.

Who should receive the Hepatitis A vaccine?

A. Both parents
B. Mother only
C. Both parents and 7-year-old child
D. Both parents, 7-year-old child, and babysitter

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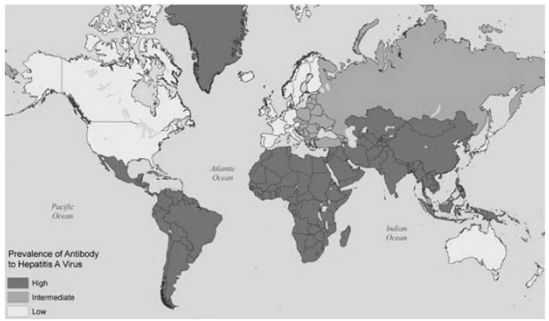
Hepatitis A

- Vaccine recommended for all close personal contacts, including regular babysitters of children adopted from high/intermediate endemic areas
- Timing – ideally *at least 2 weeks prior to arrival* of child but within first 60 days of arrival

Hepatitis A



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Hepatitis A

- Universal vaccination for children since 2006 (between 12-23 months)
- 3 formulations of vaccine available – Havrix, Vaqta, Twinrix (with Hep B vaccine)
  - Havrix and Vaqta are 2 doses 0, and 6-12 months apart
- Duration of protection is unknown but felt to be lifelong
  - No need to check antibody titers after vaccination, except in immunocompromised hosts
  - No clear correlate of immunity

Hepatitis A

- **Any person not fully vaccinated who requests vaccination**
- Travelers
- Men who have sex with men
- Persons who use illicit drugs
- Persons who work with nonhuman primates
- Persons who anticipate close contact with an international adoptee
- Persons with chronic liver disease
- Post-exposure prophylaxis for healthy persons
- **Persons living homeless**

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Travel Medicine: Scope

- ~20% of all Americans travel abroad per year
- 38 million travel to developing countries per year
- Destinations and itineraries increasingly ambitious
- Average 3 days lost to illness per 14-day trip
- Some of these illnesses may be preventable…

Question #10

51-year-old man is planning a 3-week vacation to South Africa, Tanzania, and Kenya in mid-August. Prior international travel to Brazil for vacation 11 years ago. Vaccine history - received all childhood vaccines as well as routine adult vaccines. Yellow fever vaccine 11 years ago. He is very concerned about becoming ill during travel and would like all recommended vaccines.

Which of the following vaccines are recommended?

A. Yellow fever, Hep A, Typhoid, Meningococcal, Japanese encephalitis, Cholera, Polio
B. Hep A, Typhoid, Meningococcal, Cholera, Polio
C. Hep A, Typhoid, Polio
D. Yellow fever, Hep A

Yellow Fever

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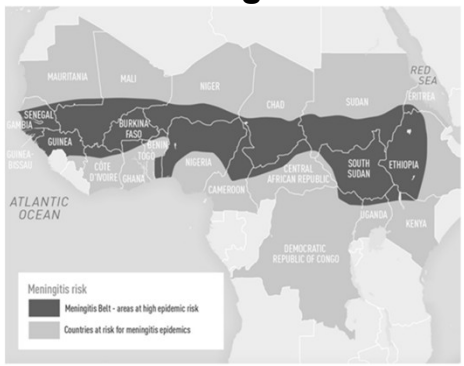
Yellow Fever Vaccine

- Recommended for > 9 months traveling to or living in areas of risk or countries requiring vaccine for entry
- In 2014, WHO concluded that single dose fellow fever vaccine provides lifelong protection, and no booster needed
  - Exceptions if ongoing risk and the following
    - Pregnant when initially vaccinated
    - Underwent HSCT after initial vaccine
    - HIV+

Area of Frequent Epidemics of Meningococcal Meningitis



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Meningococcal Vaccine and Travel

- Quadrivalent meningococcal vaccine recommended for travelers to the meningitis belt during dry season (Dec-June)
  - For ages 2 months and older --> MenACWY recommended
- Meningitis B vaccine not recommended for travel
- Approx 7-10 days after vaccine for the development of protective antibody levels

Meningococcal Vaccine: Travel for Umrah or Hajj

- Travelers to Saudi Arabia for Umrah or Hajj are required to provide documentation of meningococcal vaccination at least 10 days before arrival
  - No more than 3 years before for polysaccharide vaccine
  - No more than 9 years before for conjugate

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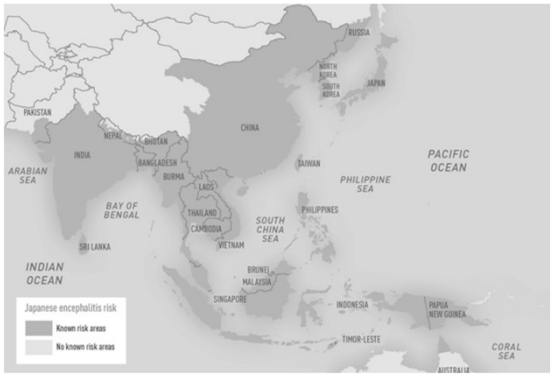
Typhoid Vaccine

- Highest risk for travelers to South Asia (6-30 x more than other destinations)
- Increased risk in West Africa, particularly in rural areas
- 2 vaccines available in US
  - Oral, live attenuated (given at least 1 wk before travel); age 6 and above, q 5 years if ongoing risk or travel
  - IM, polysaccharide (given at least 2 wks before travel); age 2 and above, q 2 years if ongoing risk or travel
  - Both 50-80% effective
- Indicated in travelers
- Delay vaccine >72 hrs after antibacterial medications

Japanese Encephalitis Virus (JEV)



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JEV

- 35,000-50,000 cases/year
- 20-30% mortality
- 30-50% with neurologic sequelae
- Very low risk in travelers *(< 1 case per million travelers)*
- Risks are extended travel > 1-month, rural areas, irrigated areas (rice paddies), or going to an outbreak area
- Vaccine 2 doses, 28 days apart. 2nd dose should be given at least a week prior to travel
- 2 months or older
  - Smaller dose for children under 3
  - ? Booster dose for > 17 years if risk and > 1 year since prior vaccine

Cholera Vaccine

- Approved in 2016
- Single-dose vaccine recommended for adults 18-64years travelling to an area of active transmission(where cases have been reported in the past year)
- Cholera in travelers is extremely rare
- Risk factors: aid workers in outbreak settings
- Vaccine 90% effective in preventing severe diarrhea (declined to 80% after 3 months)

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Hepatitis A

- "The most frequent vaccine-preventable disease in international travelers"
- 2 doses, at least 6 months apart
- Minimum age: 12 months
- Lifetime protection

Polio

- WHO recommends all travelers to polio-affected areas be fully vaccinated against polio
- Visitors for more than 4 weeks should receive an additional dose of vaccine within 4 weeks to12 months of travel

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Question #11

A 30-year-old male is planning on traveling to Angola. He presents to a travel clinic prior to travel and receives appropriate vaccines. One week later, he develops fever, ataxia, confusion, and then seizure.

Which vaccine is most likely responsible for this clinical syndrome?

A. Typhoid vaccine
B. Pneumococcal vaccine
C. Yellow fever vaccine
D. Japanese encephalitis vaccine
E. Malaria vaccine

Yellow Fever Vaccine

- YEL-AND (yellow fever vaccine associated neurologic disease)
  - Can dx by amplification of vaccine-type virus from CSF
- YEL-AVD (yellow fever vaccine associated viscerotropic disease)
  - Fever, N/V, malaise, myalgia, dyspnea
  - Jaundice, renal/hepatic impairment, rhabdo, decreased platelets, respiratory distress, hypotension, DIC
  - Diagnosis - isolate virus from blood

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Vaccines Post-Exposure

Question #12

A 25-year-old spelunker was bitten by a bat 6 days ago. He has never received rabies vaccine in the past.

What do you recommend?

A. Observation as too late to benefit from immunization or immune globulin
B. He should receive HRIG + vaccine today, then in 3, 7, and 14 days (total 4 doses)
C. He should receive HRIG + vaccine today, and day 14 as he is already a week past exposure
D. He should receive HRIG + vaccine today, then in 3, 7, 14, and 28 days (total 5 doses)

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Question #13

A 25-year-old spelunker was bitten by a bat 6 days ago. He received rabies vaccine series 5 years ago.

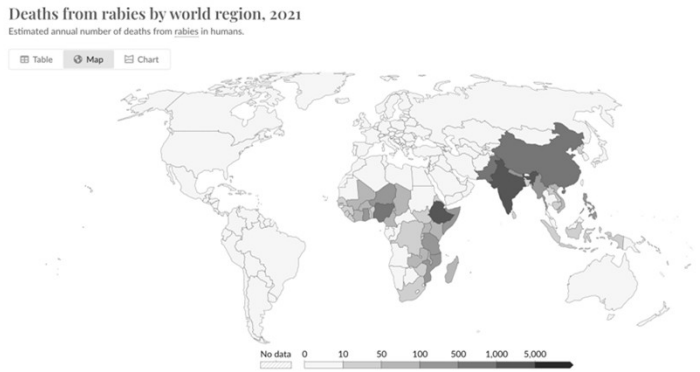
What do you recommend?

A. He does not need HRIG or additional vaccine
B. He does not need HRIG, but should receive vaccine today and in 3 days
C. He should receive HRIG + vaccine today in 3 days
D. He should receive HRIG + vaccine today, then in 3, 7, and 14 days

Rabies

- Nearly uniformly fatal disease, acute, progressive encephalomyelitis
- Incubation period 1-3 months, but can be days to years
- 1-2 cases/year in US since 1960
- 25 cases between 2009-2018 (7 contracted outside US)

Human Deaths Attributed to Rabies, 2021



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Rabies Vaccine

- Pre-exposure prophylaxis – updated February 2021
  - Vaccination on day 0, 7, ~~and 21 OR 28 days~~

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Rabies Vaccine

- Post-exposure
  - Vaccination day 0 (ASAP after exposure), 3, 7, 14
  - If received pre-exposure vaccine, should receive 2 doses PEP vaccine (day 0, 3)
  - If immunocompromised, 5 doses of vaccine on day 0, 3, 7, 14, 28

Rabies Immune Globulin (HRIG)

- Clean wound
- Full dose around and into the wound (if any remaining, give at site distant from vaccine)
- If pre-vaccinated, no RIG

Question #14

A 50-year-old man living homeless is notified by public health that 2 people living in his tent community were diagnosed with hepatitis A in the last week. He does not know if he has been vaccinated but he is not in routine medical care. He denies any symptoms.

Which of the following is most appropriate?

A. He does not need vaccine as he is asymptomatic
B. He should receive Hep A vaccine as soon as possible
C. He should receive combination Hep A and Hep B vaccine as he is likely non-immune to both

Hepatitis A Post-Exposure Prophylaxis

- No PEP needed if healthy and previously vaccinated
- PEP should be given immediately (within 14 days of exposure)
- No data available for combination HepA/HepB vaccine for PEP in HAV outbreak setting (contains only half the Hep A antigen compared to HAV vaccine – so not recommended after exposure)
- If non-immune, should complete 2-dose vaccine series (2nd dose at least 6 months after 1st dose)
- Immune globulin + vaccine (at separate sites) for immunocompromised and those with chronic liver disease
- For infants < 12 months, immune globulin only ASAP (within 2weeks)

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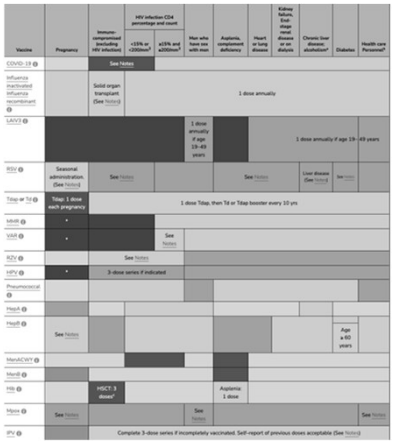
Vaccine Post-Exposure

- *Varicella exposure*
  - If no evidence of immunity and no contraindications (i.e., not severely immunocompromised) --> Give vaccine ideally 3-5 days after exposure
  - For non-immune immunocompromised hosts and pregnant women, passive immunization with VariZIG is recommended
- *Hepatitis B exposure*
  - If unvaccinated or incompletely vaccinated, Hep B vaccine dose + HBIG (can begiven at a different injection site) as soon as possible after exposure
- *Meningococcal exposure*
  - Chemoprophylaxis for close contacts (household members, child-care personnel, persons directly exposed to oral secretions)
  - Vaccination of population in outbreak

Exposure: Anthrax

- **If exposure to aerosolized Bacillus anthracis spores:**
  - 60 days of antimicrobial prophylaxis +
  - 3 doses of anthrax vaccine
- **Contraindications for vaccine:**
  - Pregnant women when risk of anthrax exposure low
- **Precautions for use in:**
  - Individuals with latex allergy
  - H/o anthrax
  - Immunocompromised individuals
  - Moderate to severe illness from anthrax



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Vaccines for Immunocompromised Hosts: Levels of Immunosuppression

- ***High-level Immunosuppression***
  - Combined primary immunodeficiency disorder
  - Receiving cancer chemotherapy
  - Within 2 months after SOT
  - HIV with CD4 count < 200 in adolescents/adults and < 15% in children
  - Daily steroid therapy > 20mg (or > 2mg/kg/day for pts < 10kg) of prednisone or equivalent for > 14days
  - Certain biologic immune modulators or rituximab
  - HSCT (duration of high-level immunosuppression variable)
- ***Low-level immunosuppression***
  - Asymptomatic HIV with CD4 count 200-499 for adolescents/adults and 15-24% in children
  - Lower doses of steroids
  - MTX < 0.4mg/kg/week, azathioprine < 3mg/kg/day, 6-mercaptopurine < 1.5mg/kg/day

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Vaccines for Persons with HIV

If CD4 count > 200	If CD4 count < 200
Inactivated influenza	Inactivated influenza
Tdap	Tdap
Pneumococcal	Pneumococcal
Meningococcal	Meningococcal
HBV	HBV
HPV	HPV
MMR	MMR
Varicella	Varicella

Vaccinations for Persons with HIV

- Meningococcal vaccine
  - 0, 8 weeks; then q5 years thereafter
- Pneumococcal vaccine age 19-64
  - PCV20 or PCV21
  - Recombinant zoster vaccine (2 doses, 0 and 8weeks) recommended for all persons with HIV age18+

Vaccinations for Asplenic Persons

- Live influenza vaccine contraindicated
- Special recommendations
  - Hib (even as adults if not immunized previously or prior to elective splenectomy)
  - MenACWY (q 5 years) and MenB (no recs for booster doses)
  - PCV20 or PCV21
  - Above vaccines should be given at least 2 weeks prior to elective splenectomy, if possible

Question #15

5-year-old nursing student is being seen in student health clinic for routine visit. She brings medical records indicating that she received her first dose of hepatitis B vaccine (Recombivax HB) 18 months ago and the second vaccine 1 month thereafter. She asks today if she requires additional doses. No other medical problems and she is not on any other medications.

Which of the following is most appropriate?

A. No additional doses of HBV vaccination needed
B. Restart HBV vaccine series
C. Check hepatitis B surface Ab titer to assess immunity
D. Give 3rd dose of HBV vaccine series today

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Vaccines for Healthcare Workers

- Hepatitis B
  - Pre-vaccine serologies not indicated unless born in geographic regions with prevalence > 2%, MSM,PWID, immunosuppressed, liver disease NOS
  - All HCP should be vaccinated with at least 3 doses(or 2 doses of HepB-CpG (Heplisav-B))
  - Should have post-vaccination anti-HBs > 10 mIU/mL(drawn 1-2 months after last dose of vaccine)

Post-Vaccine HBV Serologies

- Serologic testing not necessary after routine vaccination of infants, children, or adults
- Anti-HBs recommended for the following:
  - Infants born to HBsAg–positive or unknown mothers (check HBsAb and sAg)
  - Health care personnel and public safety workers
  - Hemodialysis patients
  - Persons with HIV
  - Other immunocompromised persons (e.g., hematopoietic stem-cell transplant recipients or persons receiving chemotherapy)
  - Sex partners of HBsAg-positive persons

Resources

- https://www.cdc.gov/acip/vaccine-recommendations/index.html
- www.immunize.org/acip

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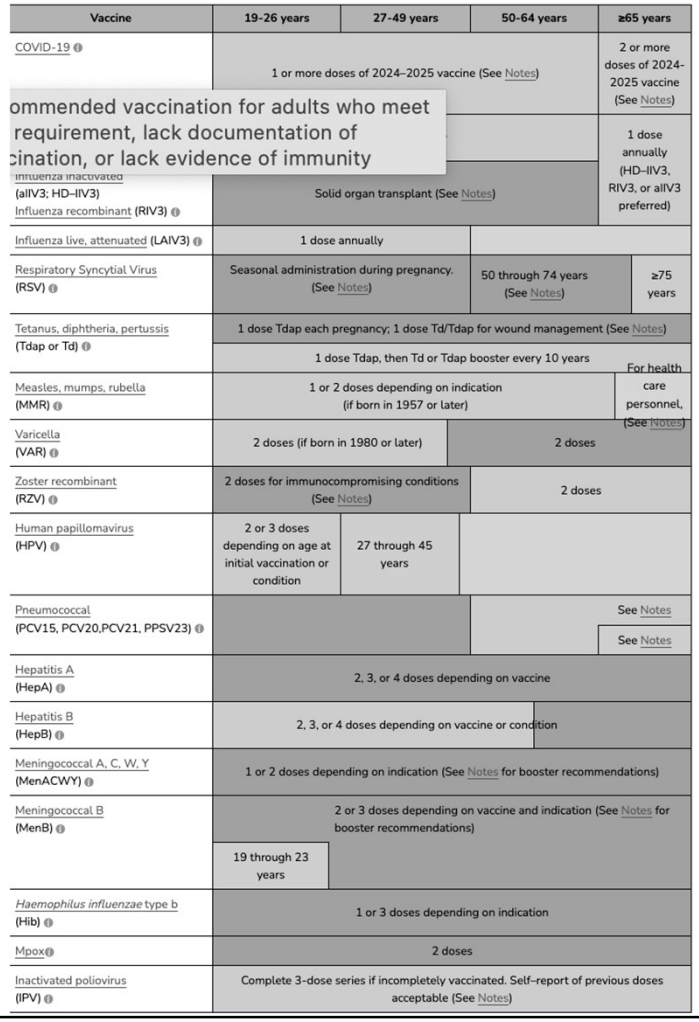
Key Sources



Vaccine	19-26 years	27-49 years	50-64 years	≥65 years
COVID-19	1 or more doses of 2024–2025 vaccine (See Notes)			2 or more doses of 2024–2025 vaccine (See Notes)
Influenza inactivated (aIIV3; HD–IIV3) Influenza recombinant (RIV3)	Solid organ transplant (See Notes)			1 dose annually (HD–IIV3, RIV3, or aIIV3 preferred)
Influenza live, attenuated (LAIV3)	1 dose annually			
Respiratory Syncytial Virus (RSV)	Seasonal administration during pregnancy. (See Notes)		50 through 74 years (See Notes)	≥75 years
Tetanus, diphtheria, pertussis (Tdap or Td)	1 dose Tdap each pregnancy; 1 dose Td/Tdap for wound management (See Notes)			
	1 dose Tdap, then Td or Tdap booster every 10 years			
Measles, mumps, rubella (MMR)	1 or 2 doses depending on indication (if born in 1957 or later)			For health care personnel, (See Notes)
Varicella (VAR)	2 doses (if born in 1980 or later)		2 doses	
Zoster recombinant (RZV)	2 doses for immunocompromising conditions (See Notes)		2 doses	
Human papillomavirus (HPV)	2 or 3 doses depending on age at initial vaccination or condition	27 through 45 years		
Pneumococcal (PCV15, PCV20,PCV21, PPSV23)				See Notes
				See Notes
Hepatitis A (HepA)	2, 3, or 4 doses depending on vaccine			
Hepatitis B (HepB)	2, 3, or 4 doses depending on vaccine or condition			
Meningococcal A, C, W, Y (MenACWY)	1 or 2 doses depending on indication (See Notes for booster recommendations)			
Meningococcal B (MenB)	2 or 3 doses depending on vaccine and indication (See Notes for booster recommendations)			
	19 through 23 years			
Haemophilus influenzae type b (Hib)	1 or 3 doses depending on indication			
Mpox	2 doses			
Inactivated poliovirus (IPV)	Complete 3-dose series if incompletely vaccinated. Self–report of previous doses acceptable (See Notes)			

ommended vaccination for adults who meet
requirement, lack documentation of
cination, or lack evidence of immunity

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Source: https://www.cdc.gov/vaccines/hcp/imz-schedules/adult-age.html

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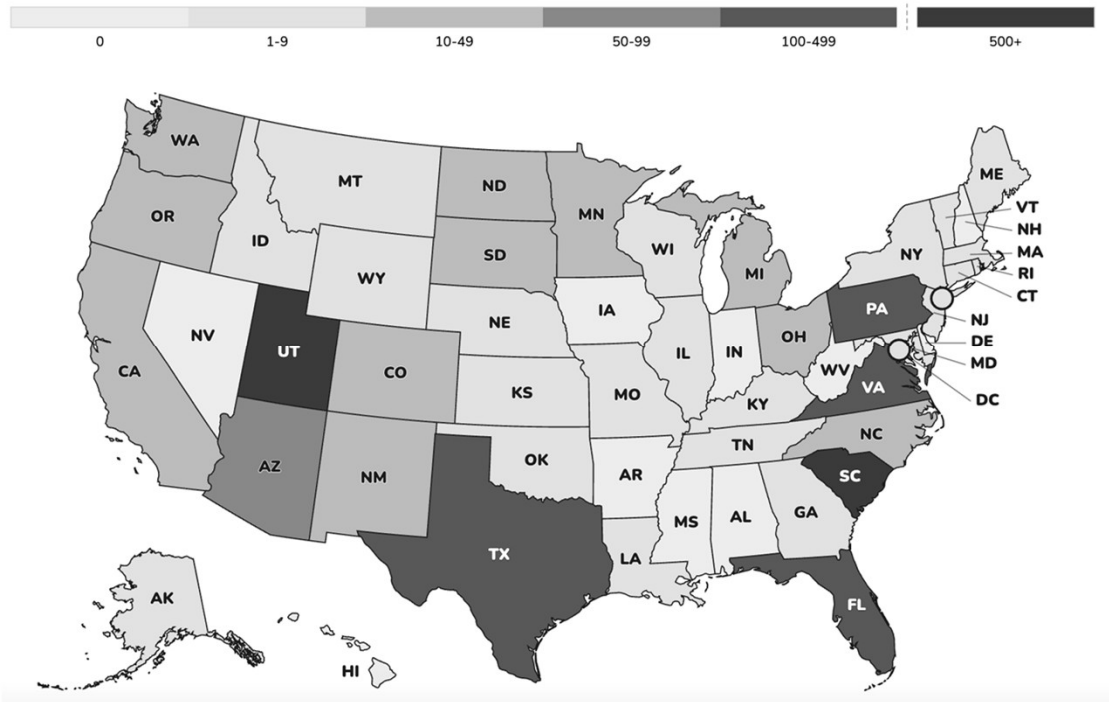
Measles in 2026



Source: https://www.cdc.gov/measles/data-research/index.html#cdc_data_surveillance_section_10-measles-cases-in-2026; accessed 7/13/2026

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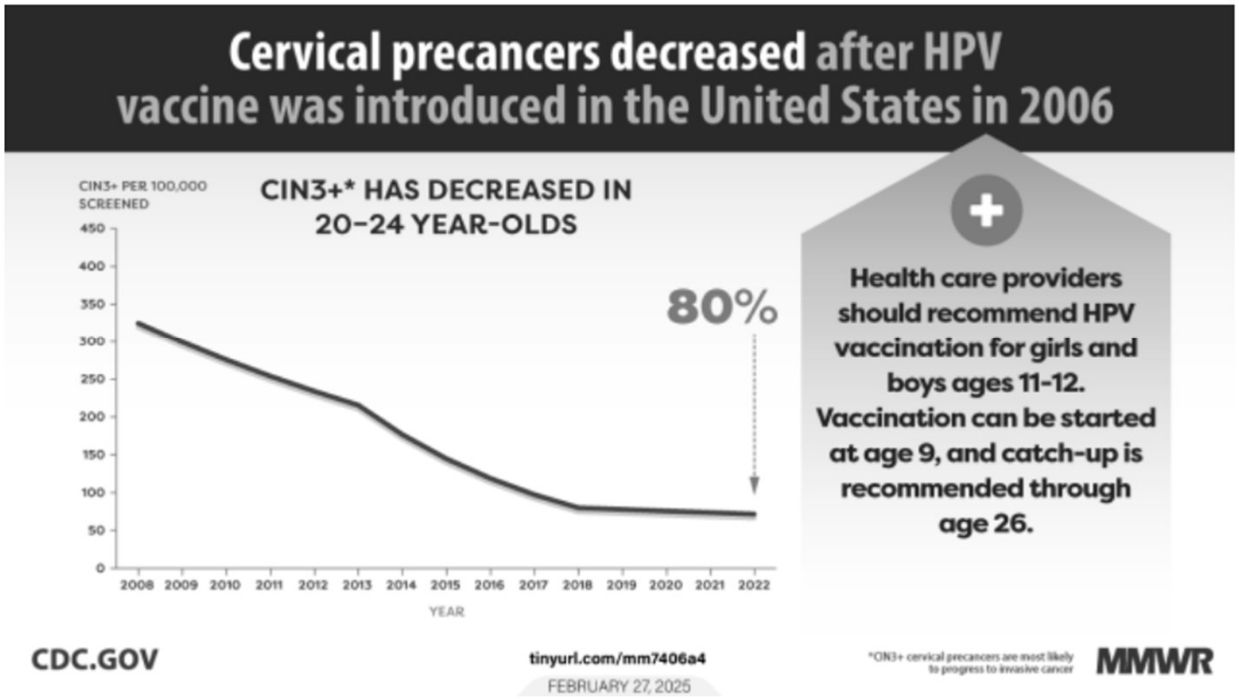
Impact of HPV Vaccination in the US



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Gargano et al. MMWR 2025

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Pneumococcal Vaccine

Adults ≥ 19-49 years old with specified immunocompromising conditions

Complete pneumococcal vaccine schedules

Prior vaccines	Option A
None*	PCV20 OR PCV21
PPSV23 only	≥1 year → PCV20 OR PCV21
PCV13 only	≥1 year → PCV20 OR PCV21
PCV13 and 1 dose of PPSV23	≥5 years → PCV20 OR PCV21
PCV13 and 2 doses of PPSV23	≥5 years → PCV20 OR PCV21

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Pneumococcal Vaccine

Adults ≥ 50 years

Complete pneumococcal vaccine schedules

Prior vaccines	Option A
None*	**PCV20** OR **PCV21**
PPSV23 only at any age	≥1 year → **PCV20** OR **PCV21**
PCV13 only at any age	≥1 year → **PCV20** OR **PCV21**
PCV13 at any age & **PPSV23** at <65 yrs	≥5 years → **PCV20** OR **PCV21**

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PCV20 vs PCV21

- PCV20 favored when proportion of serotype 4 disease is ≥ 30%

Proportion of serotype 4 IPD 2017-2023

Age group (years)	Region	State	2017	2018	2019	2020	2021	2022	2023
50-64	East	CT	0	0	1	0	0	0	0
		GA	0	0	1	0	1	0	1
		MD	0	0	0	0	0	0	0
		NY	0	0	0	4	0	0	0
		TN	0	0	0	0	0	0	3
	West	AK†	0	2	10	48	66	56	41
		CA	16	12	6	15	0	11	18
		CO	13	12	16	23	20	22	14
		MN	0	0	1	1	2	2	12
		NM	0	7	13	18	22	21	15
		OR	0	0	0	0	3	19	43

Age group (years)	Region	State	2017	2018	2019	2020	2021	2022	2023
50-64	East	CT	0	0	1	0	0	0	0
		GA	0	0	1	0	1	0	1
		MD	0	0	0	0	0	0	0
		NY	0	0	0	4	0	0	0
		TN	0	0	0	0	0	0	3
	West	AK†	0	2	10	48	66	56	41
		CA	16	12	6	15	0	11	18
		CO	13	12	16	23	20	22	14
		MN	0	0	1	1	2	2	12
		NM	0	7	13	18	22	21	15
		OR	0	0	0	0	3	19	43

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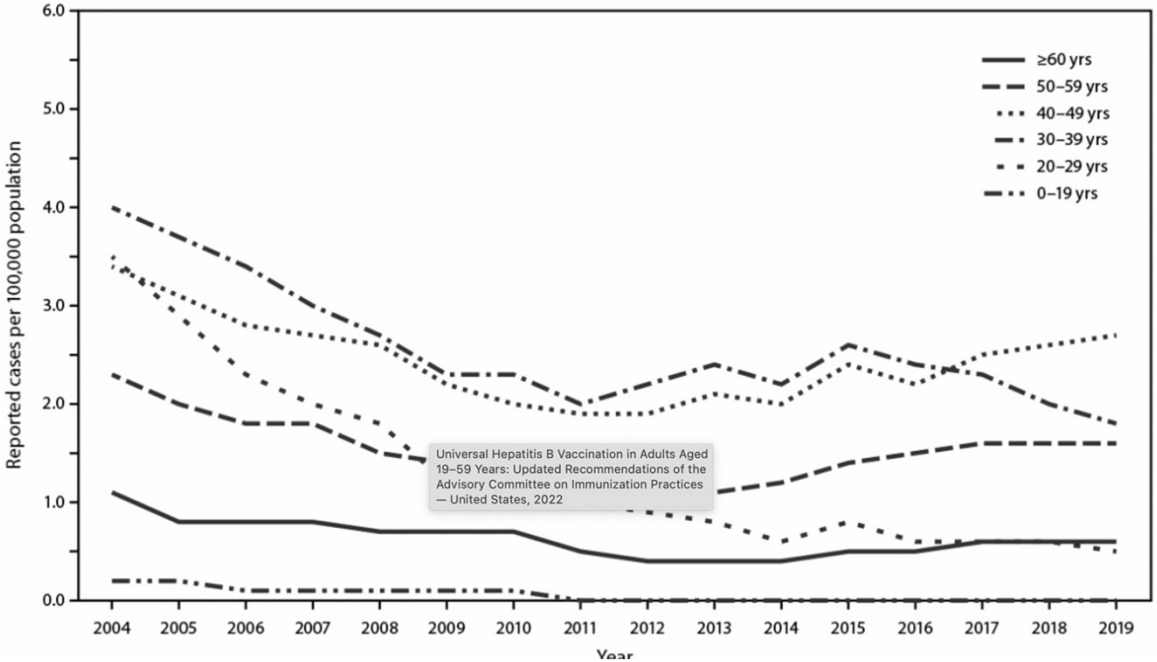
Hepatitis B

Rates of reported acute hepatitis B virus infection, by age group – United States, 2004-2019



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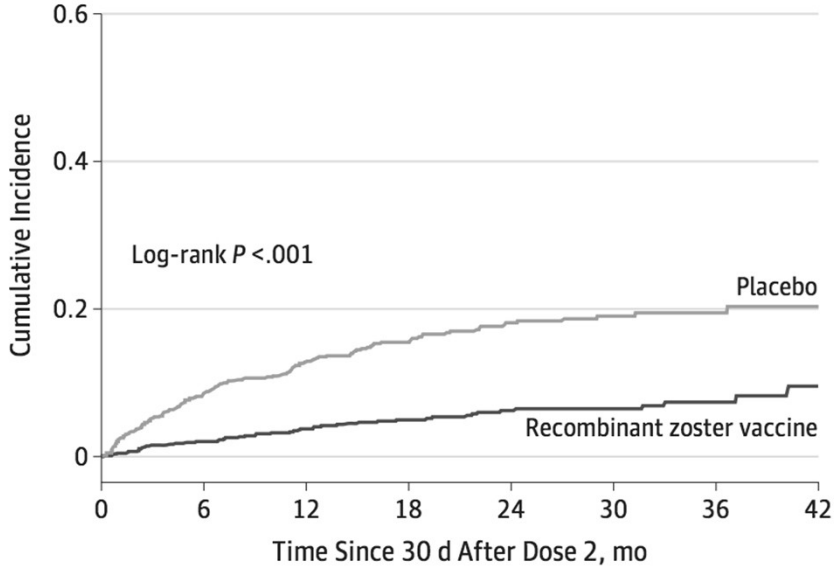
ACIP Recommendations for Zoster Vaccine In Immunocompromised Persons

- RZV recommended for all IC adults 18+
- 2 doses – 2-6 months apart
  - May give 2nd dose early (1-2months) if anticipating more immunosuppression
  - If second dose early, then repeat dose given at least 4weeks later
- For those without h/o VZV,RZV not indicated

Efficacy of RZV in Preventing Incident Herpes Zoster in Patients Who Had Undergone HSCT



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Source: Bastidas et al. JAMA 2019.

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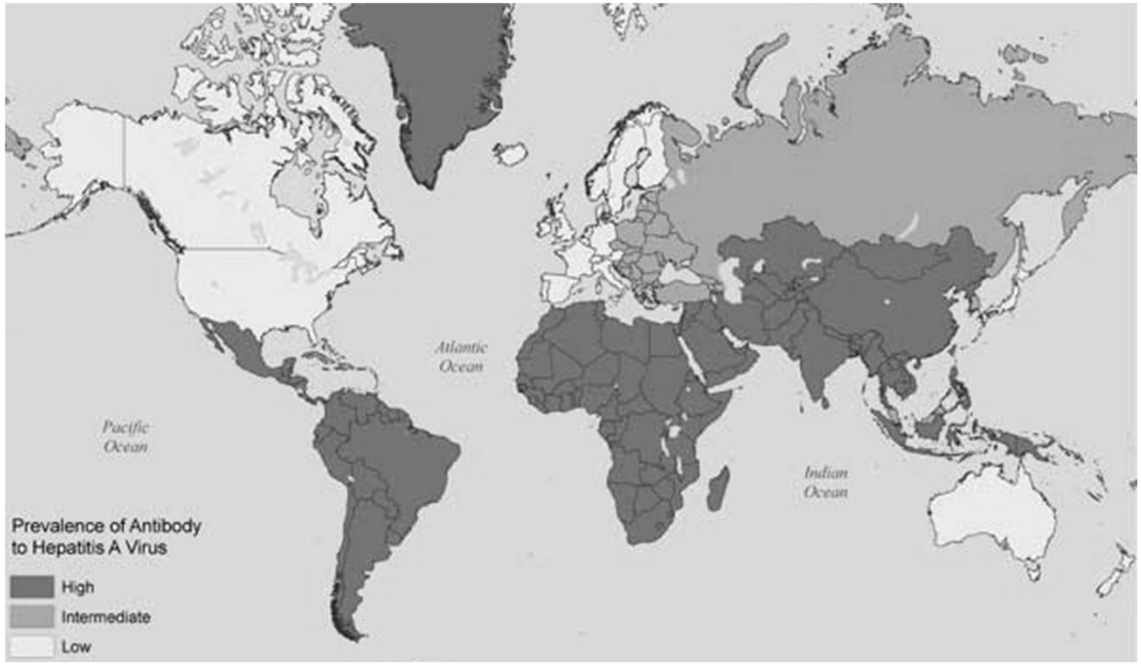
Hepatitis A



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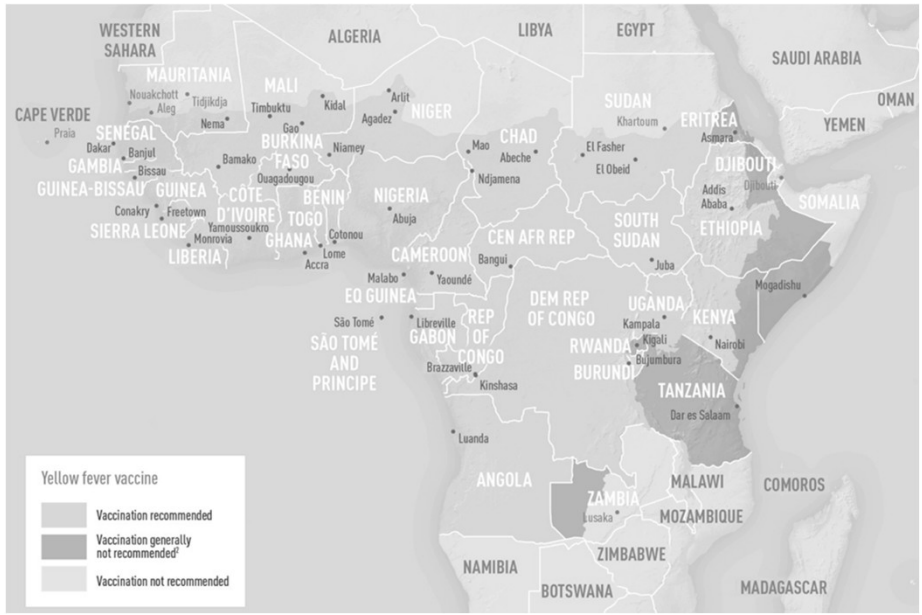
Yellow Fever



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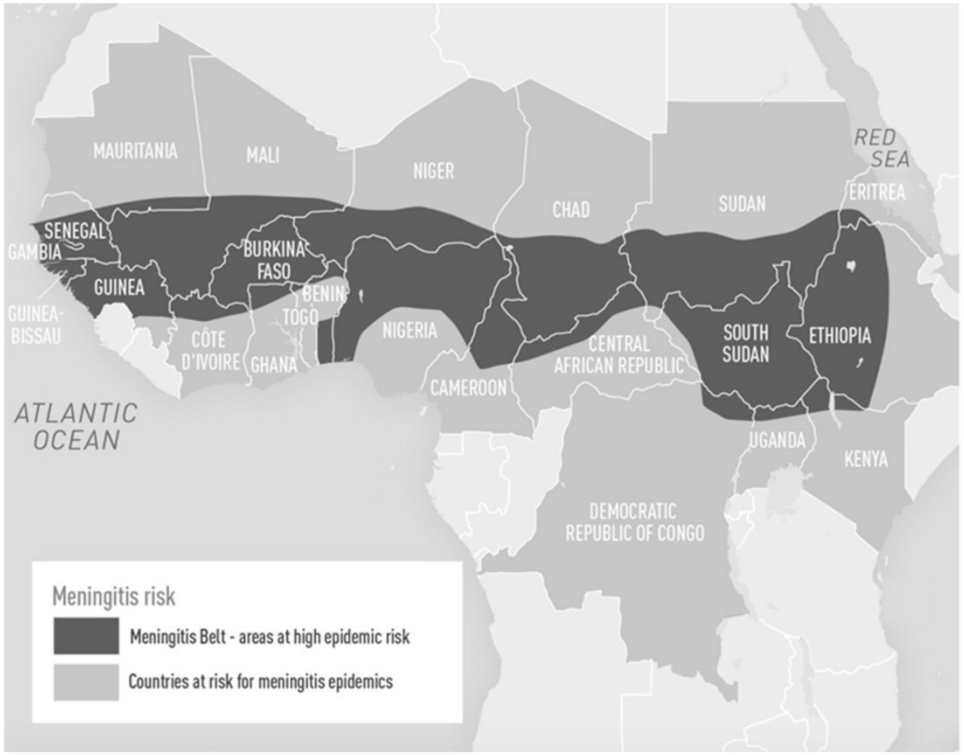
Area of Frequent Epidemics of Meningococcal Meningitis



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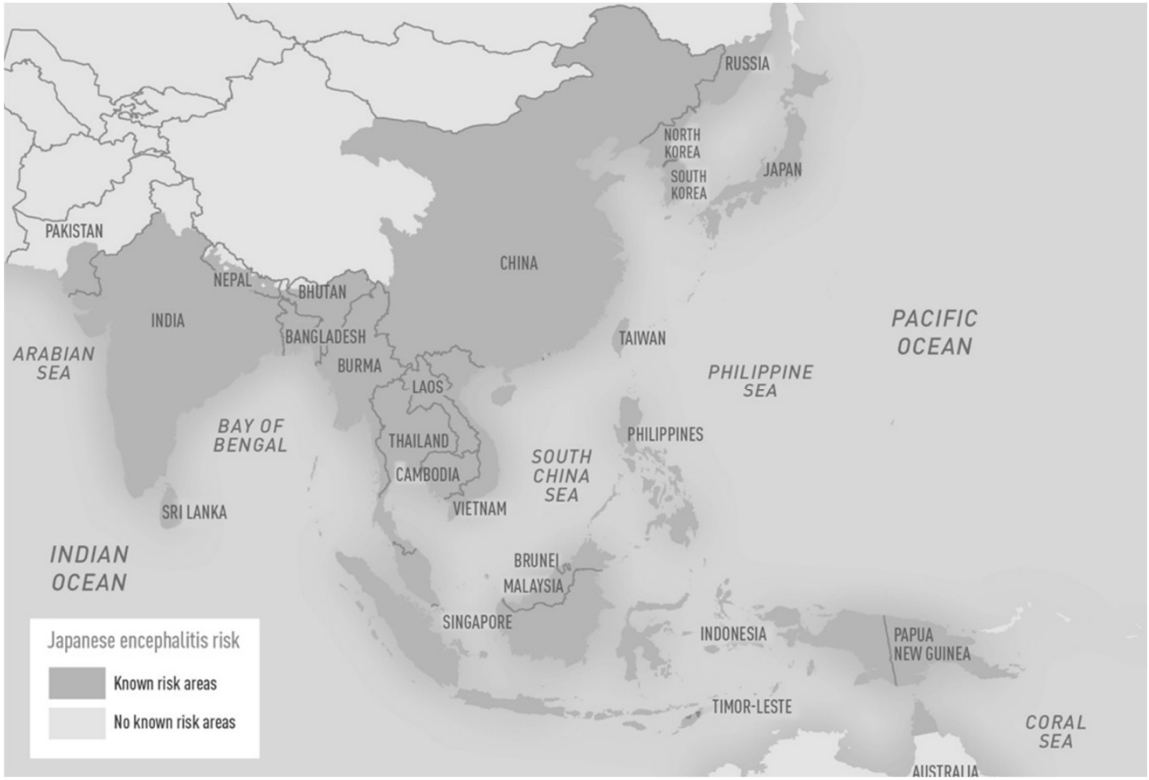
Japanese Encephalitis Virus (JEV)



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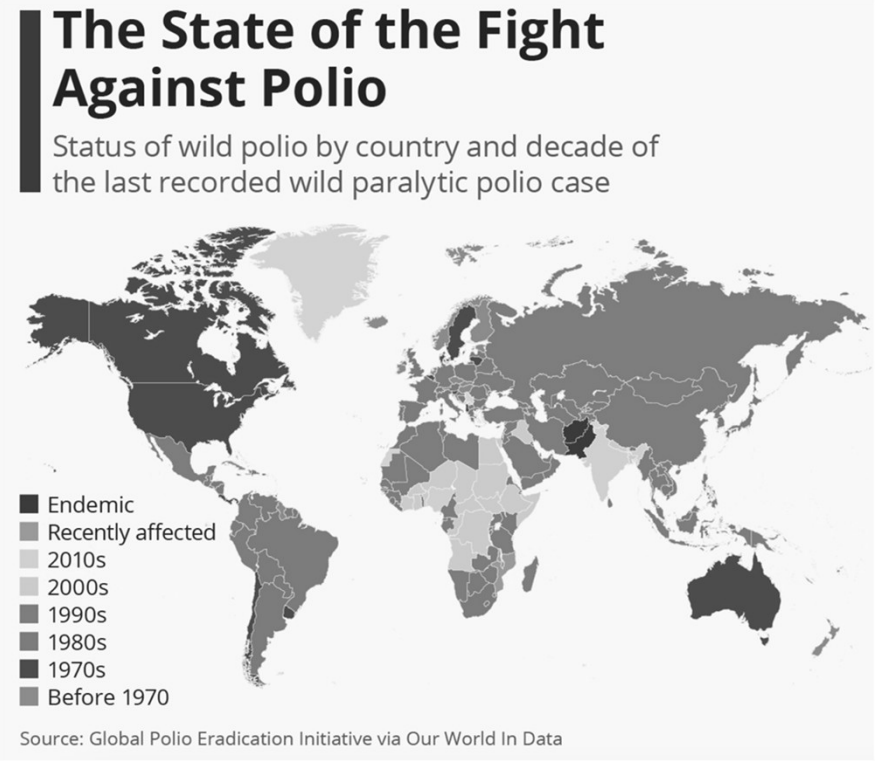
Polio

- WHO recommends all travelers to polio-affected areas be fully vaccinated against polio
- Visitors for more than 4 weeks should receive an additional dose of vaccine within 4 weeks to12 months of travel



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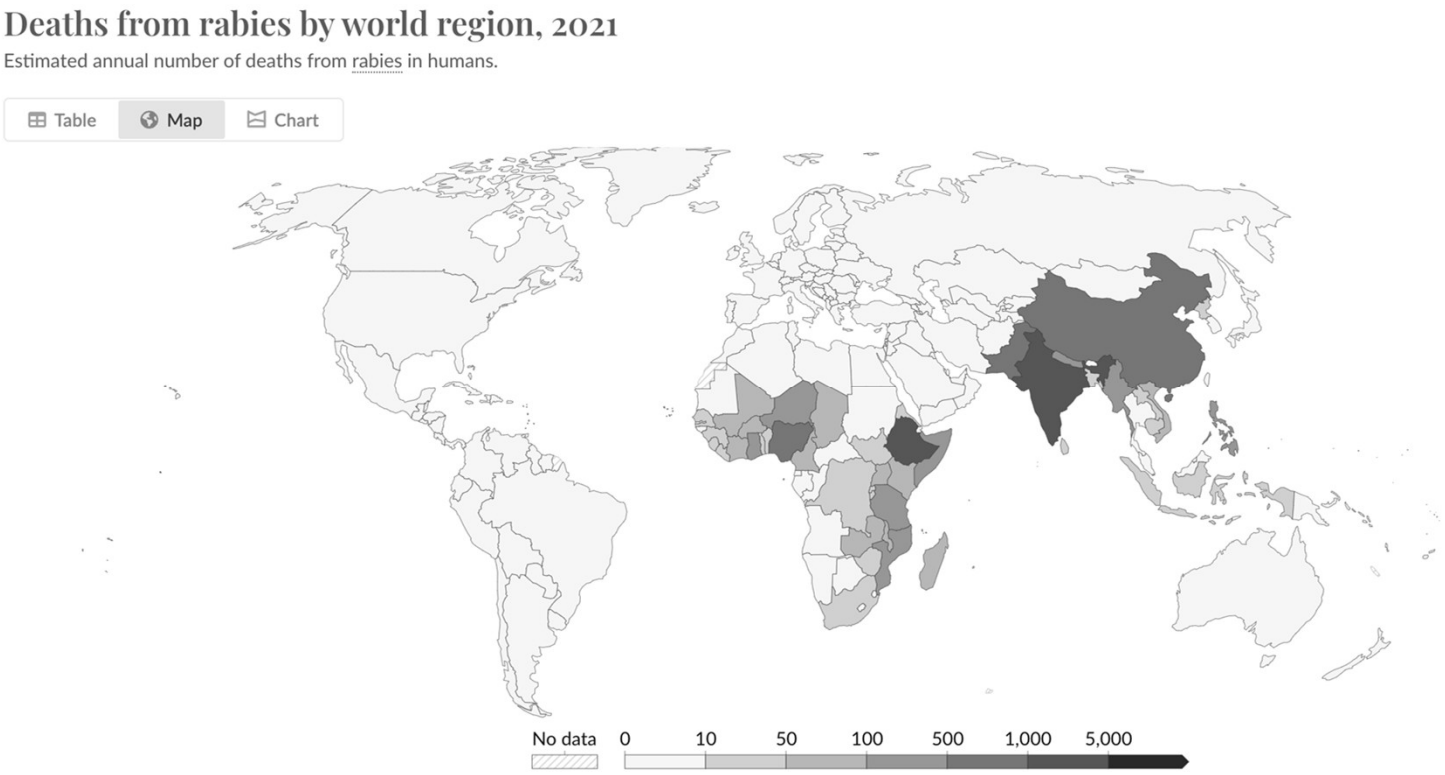
Human Deaths Attributed to Rabies, 2021



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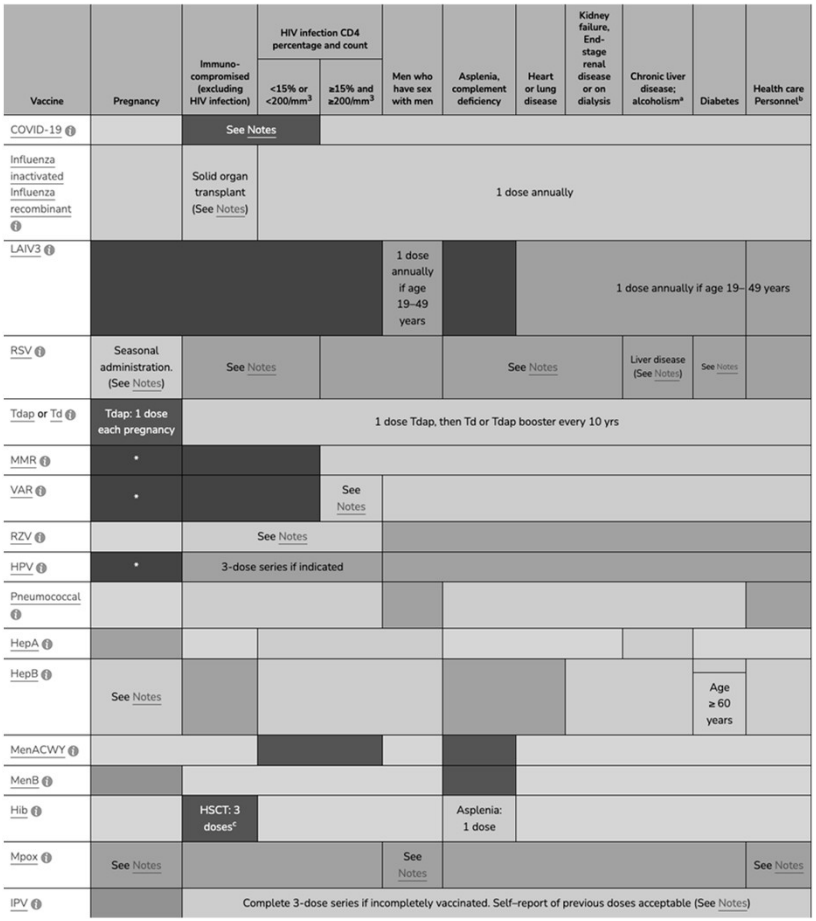

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Monday, August 24, 2026

30

Hospital Epidemiology

Michael Klompas, MD

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Hospital Epidemiology

Michael Klompas, MD, MPH, FIDSA, FSHEA

Professor, Harvard Medical School
Infection Control, Brigham and Women's Hospital, Boston, MA

Disclosures of Financial Relationships with Relevant Commercial Interests

- Grant Funding
  - Centers for Disease Control and Prevention
  - Agency for Healthcare Research and Quality
  - Mass Department of Public Health
- Royalties
  - UpToDate

Question #1

A surgical colleague calls you because 2 of his patients developed *Candida albicans* surgical site infections following spine surgery. You review the hospital's microbiology records and confirm that this is very unusual.

What are potential sources for this cluster?

A. Scrub nurse wearing artificial nails
B. Prolonged use of urinary catheters
C. Contamination of surgical instruments
D. Failure of peri-operative blood glucose control
E. Use of broad-spectrum antibiotics for peri-operative prophylaxis

Nail Add-Ons & Blemishes Can Harbor Pathogens

etsy.com/dk-en/listing/598625946/nurse-nail-art-decals

- **Nail add-ons can act as reservoirs for potentially pathogenic organisms; can persist despite cleaning with an antiseptic**
- **Multiple clusters linked to healthcare workers with artificial nails & infected nails**
  - NICU patients with ESBL *Klebs pneumo* infections
  - Serratia bloodstream infections in dialysis patients linked to RN opening heparin vials with fake nails
  - NICU patients with *Pseudomonas* infections linked to healthcare workers with artificial & infected nails
  - Laminectomy surgical site infections with *Candida albicans* traced to scrub tech with artificial nails
  - Sternal wound infections with *Pseudomonas* traced to OR nurse with onychomycosis
  - Sternal wound infections with *Pseudomonas* traced to cardiac surgeon with onychomycosis

Gupta, ICHE 2004;25:210-215
Gordon, *ICHE* 2007;28:743-744
Foca, *N Engl J Med* 2000;343:695-700
Parry, *Clin Infect Dis* 2001;32:352–7
McNeil, *Clin Infect Dis* 2001;33:317-323
Mermel, ICHE 2003;24:749-52

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MicrobeWorld.org/Tasha Sturm/Cabrillo College

Essential Hand Hygiene Practices

Promote healthy hand skin & fingernails

- Fingernails should be short, healthy, and natural
- Perform hand hygiene per the WHO's Five Moments
  1. Before touching patient
  2. Before clean procedure
  3. After touching patient
  4. After touching body fluids
  5. After touching the patient's environment
- Alcohol-based hand rub typically preferred over soap & water
- Facilitate primary and secondary prevention of dermatitis

Ensure hand hygiene supplies are always readily accessible

- Widespread, convenient alcohol-based hand rub dispensers

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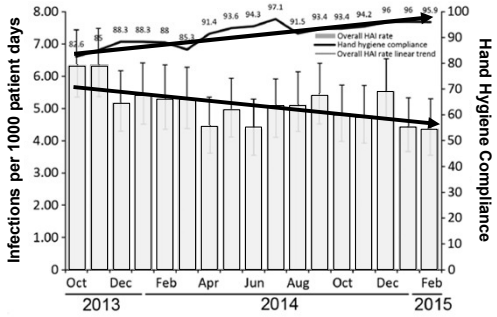
Infection Control & Hospital Epidemiology 2023;44:355-376

Better Hand Hygiene
Fewer Healthcare Associated Infections

University of North Carolina Hospitals, 2013-2015



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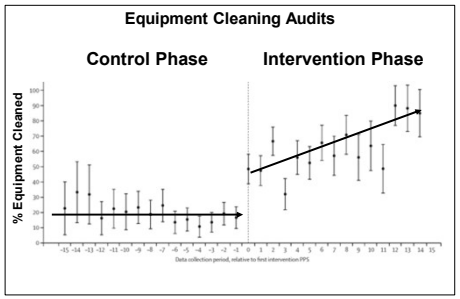
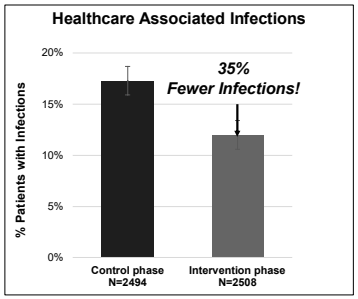
Emerg Infect Dis 2016;9:1628-1630

Cleaning Equipment Prevents Infections

Stepped-wedge cluster randomized trial of enhanced vs routine equipment cleaning, 10 units, 1 hospital, Australia
Enhanced cleaning included 3 extra hours/day of shared medical equipment cleaning + audit & feedback





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Browne, *Lancet Infect Dis* 2024;12:1347-1356

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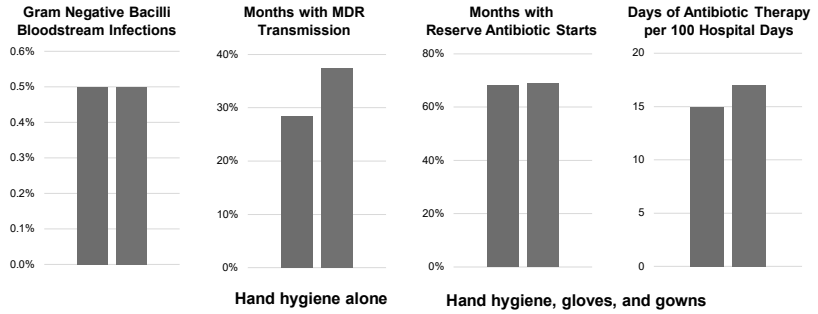
Added Value of Gowns & Gloves Unclear

Cluster randomized cross-over trial of hand hygiene alone vs hand hygiene, gloves, and gowns when caring for infants colonized with gram negative bacilli resistant to 3rd generation cephalosporins, 12 German NICUs, 2020-2023. Cross-over @ 12months.



Faust, *JAMA Network Open* 2026;9(5):e2612759

Question #2

A 43-year-old man is brought to the hospital after being found unconscious with vomit in his mouth. His airway was suctioned, he was intubated for airway protection, and then transferred to the ICU. An LP was performed. Gram stain showed gram negative diplococci.

Which healthcare workers should be offered post-exposure prophylaxis?

A. The scribe who documented the patient's emergency care
B. The respiratory therapist that suctioned the patient's vomitus
C. The medicine intern that did an admission physical in the ICU
D. The radiology technician that did a portable chest x-ray in the ED
E. The nurse that placed his IV in the ED (difficult stick, 3 attempts)

Neisseria Transmission to Healthcare Workers

Comprehensive search for occupational Neisseria infections in healthcare workers in England and Wales 1982-1996

Case 1	Case 2	Case 3
Provider: Doctor Full clinical exam of 9 yo with meningitis, including fundoscopy during which **patient coughed into doctor's face** **0.5-2h** contact time Incubation period: 4d	Provider: EMS worker Transported 16 yo with meningitis to hospital. Care included **airway insertion and delivery of oxygen while patient seizing** in the ambulance **0.5-2h** contact time Incubation period: 7d	Provider: Nurse Nursed a 7mo with sepsis while baby being prepared for transfer to referral hospital; **in close contact while child crying and coughing for at least 5h** **5-6h** contact time Incubation period: 5d

Estimated 0.8 infections per 100,000 healthcare worker contacts with meningococcal patients

SEE ENLARGED SLIDE FOLLOWING ENTIRE PRESENTATION

Gilmore, Lancet 2000;356:1654-1655

Antimicrobial Prophylaxis for *Neisseria meningitidis*

- **Indicated for close contacts <u>of patients with invasive disease</u>***
  - Household members (risk: 4 in 1000)
  - Childcare center contacts
  - Anyone directly exposed to patient's oral secretions
    - Kissing, mouth-to-mouth resuscitation
    - Endotracheal intubation, suctioning oral secretions without respiratory protection
- **Exposure window**
  - From 7 days before symptom onset through 24h after starting treatment
- **Prophylaxis options**
  - Rifampin 600mg PO q12h x 2d
  - Ciprofloxacin 500mg PO x 1
  - Ceftriaxone 250mg IM x 1

*not indicated if Neisseria only isolated from sputum, nasopharynx, conjunctiva, etc.

Cohn, MMWR Recomm Rep 2013;62(RR-2):1

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Question #3

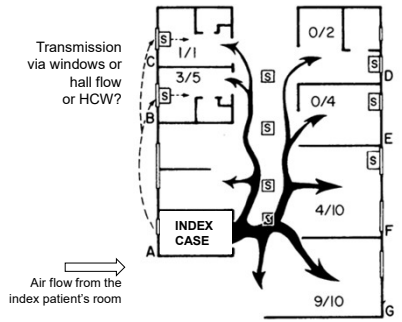
A 69-year-old man is admitted to hospital with fatigue, weight gain, and edema. He is found to have nephrotic syndrome due to multiple myeloma. On hospital day 7, a nurse notes a vesicular rash on his left flank and right chest. The patient is placed on Airborne precautions. PCR of fluid from a vesicle is positive for VZV.

Who of the following requires VariZIG?

A. Unvaccinated seronegative nurse looking after the patient in the next room
B. Unvaccinated seronegative respiratory therapist on rituximab for SLE
C. Patient's pregnant nurse, 2 doses varicella vaccine as child. She is VZV IgG-
D. Hospital roommate, 75 yo poorly controlled diabetes, unknown vax status
E. The dermatologist that unroofed a vesicle for testing. She is VZV IgG+

Varicella Outbreak!

Cluster of 15 varicella cases, attributed to child with varicella pneumonia, Boston Children's Hospital, 1970s



0% attack rate
Distance and fresh air leading to dilution

0% attack rate
Distance and fresh air leading to dilution

40% attack rate
HVAC unit operational

90% attack rate
HVAC unit not working, rendering the room negative pressure relative to the hall

SEE ENLARGED SLIDE FOLLOWING ENTIRE PRESENTATION

Leclair, NEJM 1980;302:450-453

Varicella Transmission

- **Person-to-person spread**
  - Direct contact with active lesions
  - Airborne spread from a person with respiratory involvement
  - Aerosolization from skin lesions or bedsheets (both rare but reported)
- **Incubation period:**
  - 8-21 days (usually 14-16 days)
- **Infectious period:**
  - From 24-48h before rash onset until all skin lesions crusted
- **Highly contagious if not immune:**
  - Varicella household transmission rate among susceptible individuals 85%
  - Herpes zoster household transmission rate ~25%
  - Breakthrough infections and transmissions relatively common but attenuated

Menkhaus, *Lancet* 1990;336:1315 (airborne spread)
Lopez, JID 2008;197:646-653 (skin lesions, linens)

Management of Varicella Exposure

- **Definition of exposure**
  - >15-60mins in same room as person with primary varicella or disseminated zoster involving the respiratory tract, or skin-to-skin contact with exposed varicella lesions
  - No exposure if HCW immune and wearing a mask or respirator
- **Management of Exposures**

Immune Status	Vaccinate?	VariZIG?	Furlough d8-21?	Monitor d8-21?
Fully vaccinated, seropositive, or prior Dx	**No**	**No**	**No**	**Yes**
Partially vaccinated	**Yes**	**No**	**Depends[2]**	**Yes**
Unvaccinated & seronegative	**Yes**	**No**	**Yes**	**Yes**
Unvaccinated & unable to vaccinate[1]	**No**	**Yes[3]**	**Yes[4]**	**Yes**

[1] Vaccine contraindicated if pregnant or immunocompromised
[2] Furlough if vaccine was given >5d after first exposure
[3] Or valacyclovir d7-13 if VariZIG not available
[4] Furlough d8-28 if given VariZIG

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Question #4

A 64-year-old man with coronary disease is admitted with unstable angina and referred for urgent catheterization. A stent is placed in the circumflex. He initially improves but 3 days later develops fever, cough, and recurrent chest pain. His workup is positive for recurrent MI and influenza. The interventional cardiologist discloses that he had mild sniffles during the procedure but no fever and he wore a procedure mask at all times.

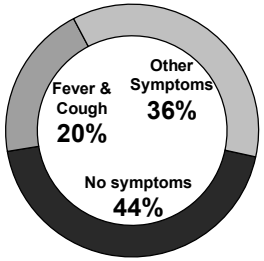
Did the cardiologist infect the patient?

A. No, surgical masks provide excellent protection/control for respiratory viruses
B. No, sniffles alone without fever cannot be influenza
C. No, procedure rooms have excellent ventilation
D. Yes, surgical masks only provide moderate protection/control for respiratory viruses
E. Yes, surgical masks do not provide any protection against respiratory viruses

Influenza Transmission Possible with Few or No Symptoms

1,116 participants from 225 households in South Africa, tested for influenza 2x/week by PCR, 2017-2018

Source Individual Symptom Status



Influenza Transmission rate

- With 0 symptoms: 6%
- With ≥2 symptoms: 17%

27% of secondary flu infections were acquired from asymptomatic index cases

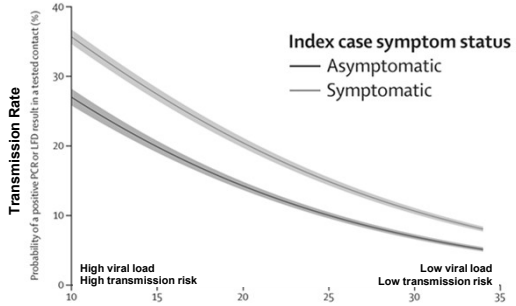
SEE ENLARGED SLIDE FOLLOWING ENTIRE PRESENTATION

Cohen, *Lancet Glob Health* 2021; 9:e863-874

Wong, *Infection Control Hospital Ep*
Birghand, *JAMA Network Open* 2020
Phan, *Infect Control Hospital Epidem*
Kim, *Clin Infect Dis* 2016;63:363-9

Viral Load Predicts Transmission Risk

Secondary attack rates amongst 1,173,643 contacts of 6,263,786 index cases, UK, Jan 2021-Jan 2022



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Eyre, *Lancet ID* 2023; 23:922-932

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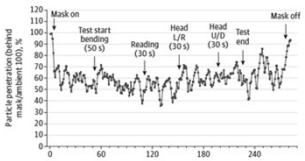
Filtration Efficiency: Surgical Mask vs. N95 Respirator

Surgical Mask with Ear Loops

Particle Penetration Behind Mask

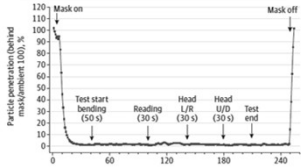


Filtration Efficiency

38.1%

N95 Respirator

Particle Penetration Behind Mask



98.5%

Sickbert-Bennett, *JAMA Internal Med* 2020; 180:1607-1612

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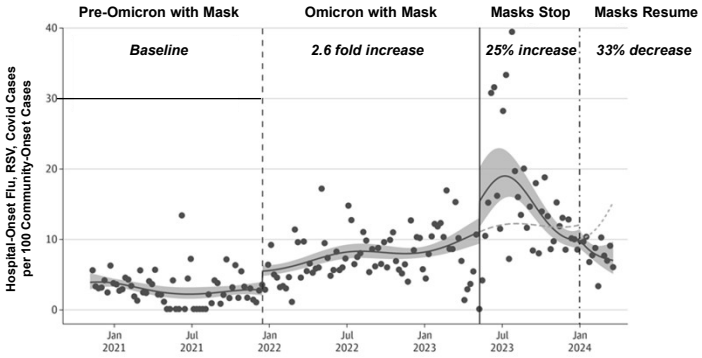
Masking and Hospital-Onset Respiratory Viral Infections

Associations between Masking Policies and Hospital-Onset Influenza, RSV, and Covid in 10 US Hospitals



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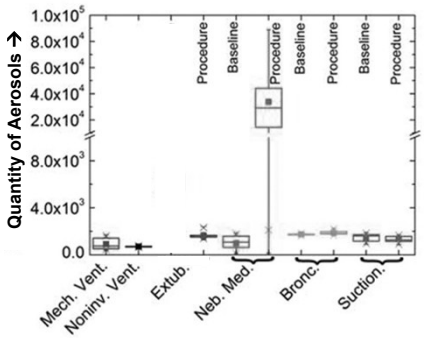
Pak, *JAMA Network Open* 2024;7(11):e2448063

Most "Aerosol Generating Procedures" Do Not Generate Aerosols



Doggett, *Chest* 2020; 158:2467-2473
O'Neil, *Clin Infect Dis* 2017;65:1342-1348
Li, *Open Forum Infect Dis* 2017;4(Suppl 1):S34

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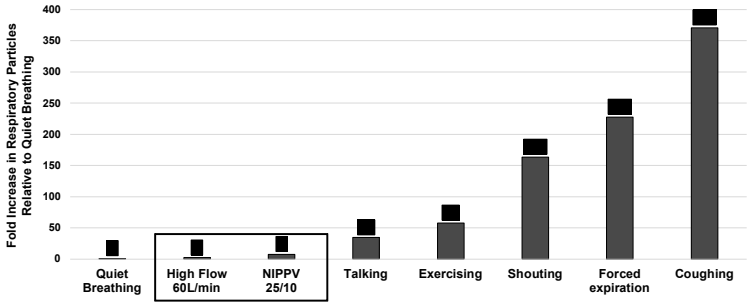
Impact of High Flow O_2 on Respiratory Emissions



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Wilson, *Anaesthesia* 2021;76(11):1465-1474

30 Hospital Epidemiology

Speaker: Michael Klompas, MD, MPH

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Risk & Protection Exists on a Continuum

Factors That Increase Risk	Factors That Decrease Risk
○ High community incidence	○ Low community incidence
○ Higher viral load	○ Lower viral load
○ Symptoms	○ Lack of symptoms
○ Proximity	○ Distance
○ Longer exposure	○ Brevity
○ Poor ventilation	○ Good ventilation
○ Lack of masking	○ Mask on patient
○ Lack of vaccination	○ Mask on provider
	○ N95 > KN95 > facemask
	○ Vaccination

Question #5

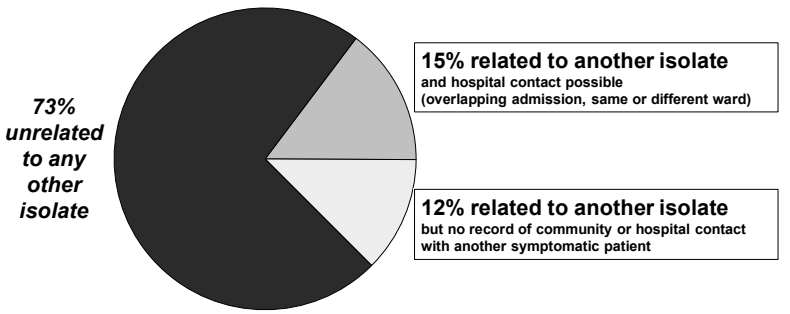
A 63-year-old man with lymphoma is admitted for chemotherapy. His course is complicated by new atrial fibrillation and hospital acquired pneumonia (treated with vancomycin, cefepime, levofloxacin). On hospital day 12 he develops severe diarrhea and is diagnosed with *C. difficile* infection.

Where did the patient most likely acquire this pathogen?

A. From another patient on his ward (carried by healthcare workers' hands)
B. From the previous occupant of his bed
C. From the toilet seat of the shared bathroom in his room
D. From the food provided by the hospital
E. From the community (already colonized on admission)

Where Do Patients Get *C. difficile*?

Whole genome sequencing of 1,250 C. diff isolates from symptomatic inpatients & outpatients, Oxfordshire, UK, 2007-2011



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Eyre, *N Engl J Med* 2013;369:1195-1205

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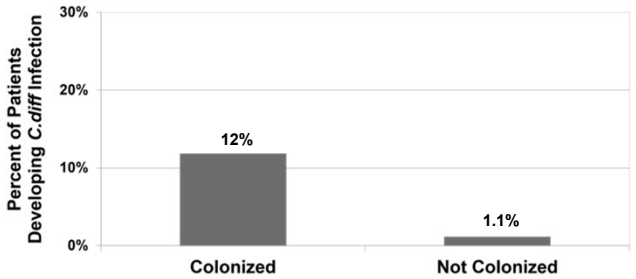
C. diff Colonization in ICU Patients and Progression to Infection

548 ICU patients at Johns Hopkins screened for C. difficile carriage on admission



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Infect Control Hospital Epidemiol 2015;36:1324-1329

So Where Do Inpatients Get *C. diff* From?

1. Present on admission

- Patient colonized prior to arrival, disease activates in the setting of exposure to antibiotics, antacids, immunosuppressants, and frailty

2. Transmission from symptomatic patients

- Spores carried from patient to patient via staff hands & clothing, equipment, the environment

3. Transmission from asymptomatic patients

- Spores carried from patient to patient via staff hands & clothing, equipment, the environment

Risk of *C. diff* Acquisition Higher if Prior Room Occupant had *C. diff*

Medical ICU, University of Michigan Health System, 2005-2006

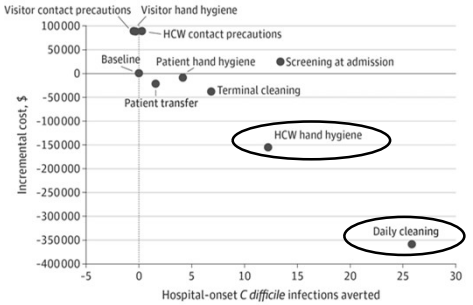
Prior Room Occupant Flagged for *C.diff*	**11.0%**
Prior Room Occupant Not Flagged for *C.diff*	**4.6%**

Adjusted Hazard Ratio **2.4** (95% CI 1.2-4.5)

Infection Control Hospital Epidemiology 2011;32:201-206

Measures to Avert Hospital-Onset *C. difficile* Infections

Modeling study estimating the cost-effectiveness of different measures to prevent hospital-onset C.difficile infections



Barker, *JAMA Network Open 2020;3(8):e2012522*

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Essential Practices to Prevent *C. difficile* in Hospitals

- Encourage appropriate use of antimicrobials through implementation of an antibiotic stewardship program
- Implement diagnostic stewardship to assure appropriate use and interpretation of *C. difficile* testing
  - Guide or limit use of PCR, aid in interpretation
  - Avoid testing patients if no significant diarrhea, recent positive test, or age <1 year
- Use contact precautions, single room preferred
- Adequately clean and disinfect equipment and the environment
  - Use dedicated equipment when possible (e.g., stethoscope, BP cuff, thermometer…)
- Assess the adequacy of room cleaning
  - Consider using sporicidal agents if cleaning adequate but ongoing *C. diff* transmission
- Create lab-based alerts for clinicians and infection control re new cases
- Conduct surveillance for *C. diff* infections and report to stakeholders
- Educate clinicians, enviro services, administrators, & patients about *C. difficile*
- Measure compliance with contact precautions and hand hygiene

SEE ENLARGED SLIDE FOLLOWING ENTIRE PRESENTATION

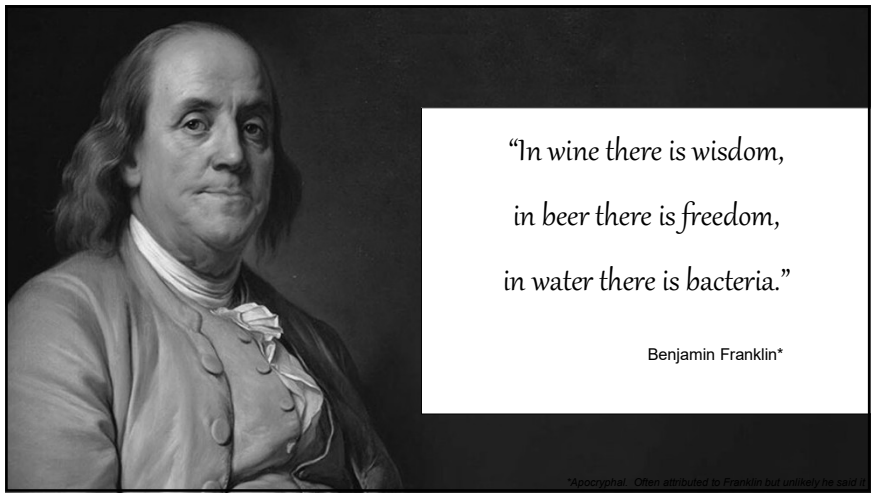
Infection Control & Hospital Epidemiology 2023;44:527-549

Question #6

The MICU attending calls you because she's noticed 4 patients with new *Burkholderia cepacia* complex infections in her unit over the last 6 months. The patients were hospitalized during different periods. All Burkholderia isolates were first detected >7 days after admission.

What potential sources will you investigate?

A. Are providers consistently washing their hands between patients?
B. Are providers wiping down stethoscopes & phones between patients?
C. Did all the patients receive care from a common healthcare worker?
D. Were there any common devices amongst patients (e.g. ventilators, ECMO, bronchoscopes, ultrasound probes, etc.)?
E. Did all the patients visit the same operating room?



Water Avid Pathogens

Pseudomonas spp.
Legionella pneumophilia
Burkholderia cepacia
Sphingomonas spp
Stenotrophomonas maltophilia
Acinetobacter baumannii
Aeromonas spp
Elizabethkingia anophelis
Enterobacter cloacae
Nontuberculous mycobacteria
Yeasts *(Candida spp.)*
Free living amoeba

- Normal inhabitants of water systems
- Promoters of persistence:
  - Biofilm forming
  - Relative resistance to disinfectants
- When clusters occur think:
  - Respiratory care equipment
  - Heating & cooling devices
  - Contaminated IV solutions & meds
  - Decorative water displays
  - Contaminated sink drains, etc.

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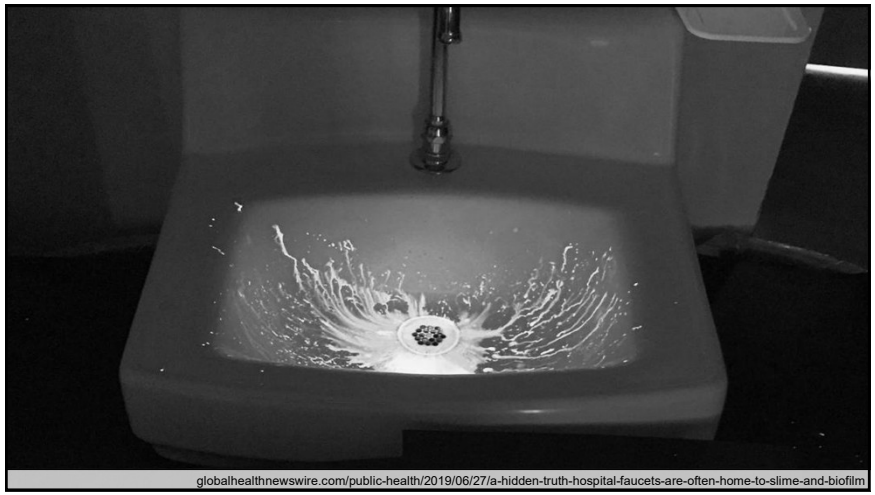
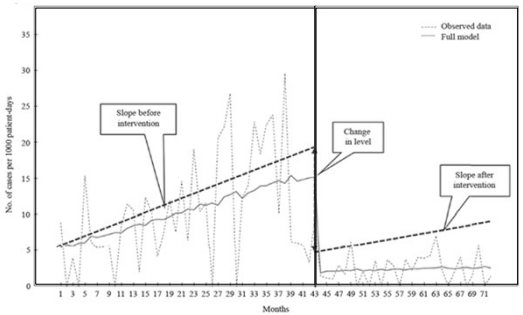


globalhealthnewswire.com/public-health/2019/06/27/a-hidden-truth-hospital-faucets-are-often-home-to-slime-and-biofilm

Drop in MDR Gram Negatives After Sink Removal

Incidence of ICU-acquired MDR gram negatives before vs after removing patients' sinks, Bellvitge University Hospital, Barcelona

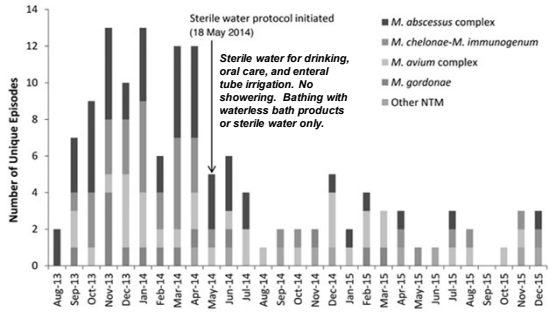


SEE ENLARGED SLIDE FOLLOWING ENTIRE PRESENTATION

Shaw, J Hosp Infection 2018;98:275-281

Eliminating Tap Water Associated with Drop in NTM Infections

Count of patients with new non-tuberculous mycobacteria cultures, 3 ICUs & 1 step-down, Duke University Hospital



SEE ENLARGED SLIDE FOLLOWING ENTIRE PRESENTATION

Baker, *Clin Infect Dis* 2021;73:524-527

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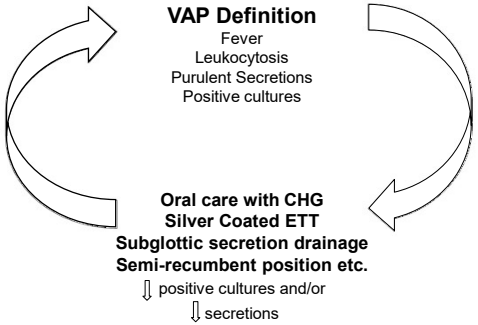
Question #7

The CEO calls you to express her concern that ventilator-associated pneumonia rates in your hospital are double those of a competing hospital.

Which of the following measures are advised to reduce ventilator-associated pneumonia rates and improve patient outcomes?

A. Silver coated endotracheal tubes
B. Oral care with chlorhexidine
C. Daily toothbrushing
D. Placing patients in the lateral Trendelenburg position
E. Probiotics

Circularity Between VAP Prevention Practices and the VAP Definition



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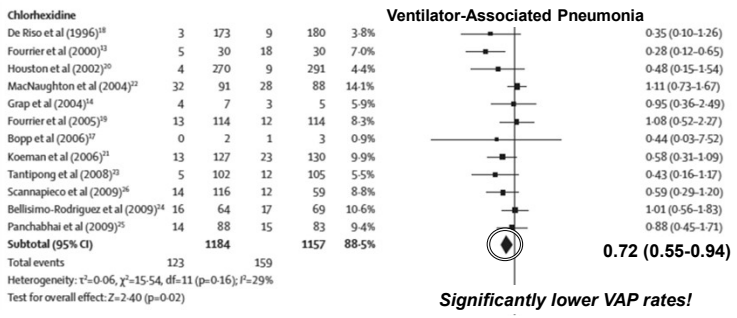
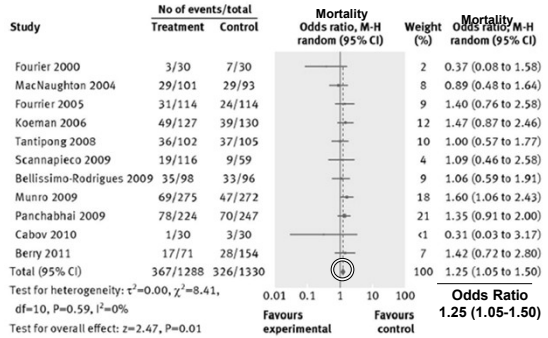
Oral Care with Chlorhexidine: Significantly *Lower* VAP Rates



SEE ENLARGED SLIDE FOLLOWING ENTIRE PRESENTATION

Lancet Infectious Disease 2011;11:845

Oral Care with Chlorhexidine: Significantly *Higher* Mortality Rates



SEE ENLARGED SLIDE FOLLOWING ENTIRE PRESENTATION

BMJ 2014;348:g2197

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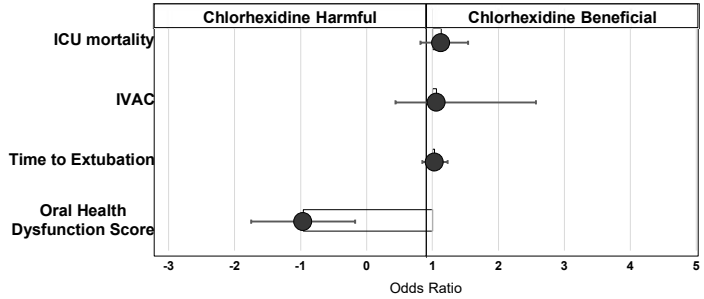
Chlorhexidine De-Adoption Cluster Randomized Trial

Cluster randomized trial of replacing oral CHG with an oral care bundle vs continuing oral care with CHG in 6 Canadian ICUs (N=3260). Oral care bundle included twice daily toothbrushing plus mouth and lip moisturization



SEE ENLARGED SLIDE FOLLOWING ENTIRE PRESENTATION

Dale, Intensive Care Med 2021;47:1295-1302

Toothbrushing: Lower Mortality, Shorter LOS

Meta-analysis of 15 randomized trials of oral care with vs without toothbrushing

	Studies	Patients	Meta-Analysis	
Hospital-acquired pneumonia* *12 of the 14 studies in ventilated patients	14	2557	**Risk Ratio 0.68 (95% CI 0.57-0.82)**	***Lower!***
Ventilator Days	7	1285	**-1.2 days (95% CI -2.4 to -0.1)**	***Lower!***
ICU Length of Stay	6	1284	**-1.8 days (95% CI -2.9 to -0.7)**	***Lower!***
ICU Mortality	6	1331	**Risk Ratio 0.81 (95% CI 0.69-0.95)**	***Lower!***

SEE ENLARGED SLIDE FOLLOWING ENTIRE PRESENTATION

Ehrenzeller, *JAMA Internal Med* 2024;184(2):131-142

Essential Practices to Prevent VAP in Adults

- Avoid intubation and prevent reintubation
  - Use high flow nasal oxygen or non-invasive positive pressure ventilation whenever safe and feasible
- Minimize sedation
  - Avoid benzodiazepines
  - Use a protocol to minimize sedation
  - Implement a ventilator liberation protocol
- Maintain and improve physical conditioning
- Elevate the head of the bed to 30-45 degrees
- Provide oral care *with* toothbrushing but *without* chlorhexidine
- Provide early enteral nutrition
- Change the ventilator circuit only if visibly soiled or malfunctioning

Infection Control & Hospital Epidemiology 2022;43:687-713

Question #8

You are part of a multidisciplinary team working to prevent central line associated bloodstream infections in your hospital. Interventions to date include education, daily patient bathing with chlorhexidine, line insertion checklists, insertion kits, and maximal sterile barrier precautions during insertion.

What additional steps should you consider implementing?

A. Create a standing order for vancomycin for all patients with central lines
B. Replace all central lines every 7 days
C. Preferentially site all lines in the internal jugular vein whenever possible
D. Require “double antiseptic” skin preparation with povidone-iodine-chlorhexidine before all insertions
E. Require “double antiseptic” skin preparation with alcohol-chlorhexidine before all insertions

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Essential Practices to Prevent Line Infections

Before Insertion:

- Disseminate indications for evidence-based central line use to minimize unnecessary use
- Provide education and perform competency assessments
- Daily bathing with chlorhexidine

Infection Control & Hospital Epidemiology 2022;43:553-569

Essential Practices to Prevent Line Infections

At Insertion:

- Use a checklist to assure all steps followed
- Perform hand hygiene
- Subclavian site preferred
- Use a catheter-placement kit with all necessary supplies
- Use ultrasound guidance to place the catheter
- Use maximal sterile barrier precautions
- Use an alcohol-chlorhexidine antiseptic for skin prep

Infection Control & Hospital Epidemiology 2022;43:553-569

Essential Practices to Prevent Line Infections

After Insertion:

- Ensure appropriate nurse:patient ratio and limit use of float nurses in ICUs
- Use chlorhexidine-containing dressings for central lines
- Change transparent dressings and perform site care with a chlorhexidine-based antiseptic q7d (or immediately if soiled)
- Disinfect catheter hubs, connectors, ports before each use
- Remove non-essential catheters promptly
- Replace administration sets q7d or less
- Routinely measure line infection rates and report back to unit staff & hospital leaders

Infection Control & Hospital Epidemiology 2022;43:553-569

Question #9

A 66-year-old gent with poorly controlled diabetes is admitted with fever and a swollen left knee. He underwent knee replacement 3 weeks ago. Arthrocentesis shows gram positive cocci in clusters. Culture is positive for Staph aureus (methicillin-susceptible). The patient is taken to the OR, the prosthesis is removed, and an antibiotic spacer is placed. The patient is devastated by the setback to his recovery and the need for more surgery.

He asks what more could have been done to prevent this infection?

A. Obtain a urine culture before surgery to rule out occult bacteriuria
B. Screen all patients before arthroplasty to identify *Staph aureus* carriers and decolonize them with chlorhexidine washes + nasal mupirocin
C. Prescribe 4 weeks of antibiotic prophylaxis for all arthroplasty patients
D. Only provide arthroplasty to patients with hemoglobin A1C's <7
E. Ensure all knee surgeries are performed with therapeutic hypothermia

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Where Do *Staph aureus* Infections Come From?

80%

of hospital acquired *Staph aureus* infections are attributable to patients' own flora (endogenous)

Staph Bacteremia

Nasal isolates compared to blood isolates in 219 patients with *Staph aureus* bacteremia. 82% matched

von Eiff, NEJM 2001;344:11-16

Surgical Site Infections

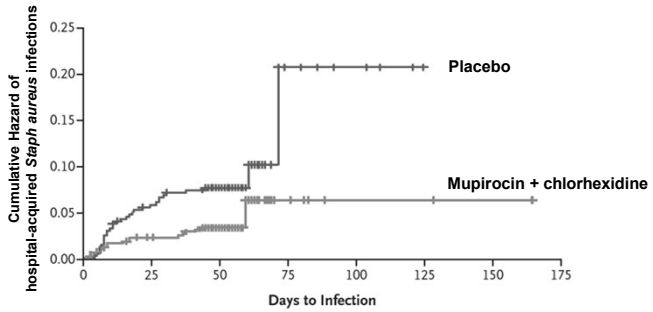
Nasal isolates compared to wound isolates in 39 patients with *Staph aureus* SSIs. 85% matched

Perl, NEJM 2002;346:1871-77

SEE ENLARGED SLIDE FOLLOWING ENTIRE PRESENTATION

Staph aureus Screening & Decolonization

917 hospitalized patients with positive Staph aureus nasal screens randomized to decolonization vs placebo
~90% of enrolled patients were on surgical services. Greatest benefit cardiac > ortho > vascular > GI



SEE ENLARGED SLIDE FOLLOWING ENTIRE PRESENTATION

Bode, NEJM 2010;362:9-17

Targeted vs Universal Decolonization in the ICU

REDUCE MRSA cluster-randomized trial, 74 ICUs, 43 hospitals, 74,256 patients

Screen and Isolate

Nasal MRSA screen

If positive, isolate

Screen and Decolonize

Nasal MRSA screen

If positive, isolate & decolonize with CHG baths x 5 days *+ mupirocin x 5 days*

Universal Decolonization

No screening

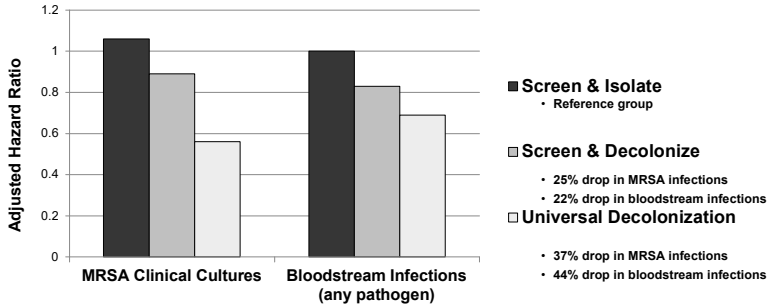
Decolonize **all** patients with CHG baths throughout ICU stay *+ mupirocin x 5 days*

SEE ENLARGED SLIDE FOLLOWING ENTIRE PRESENTATION

Huang et al. NEJM 2013:368:2255-65

Targeted vs. Universal Decolonization in the ICU

REDUCE MRSA cluster-randomized trial, 74 ICUs, 43 hospitals, 74,256 patients



SEE ENLARGED SLIDE FOLLOWING ENTIRE PRESENTATION

Huang et al. *NEJM* 2013:368:2255-65

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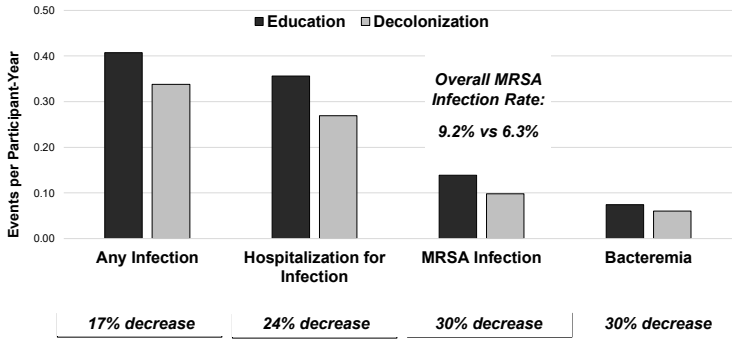
Should We Decolonize Patients <u>After</u> Discharge?

1063 discharged patients colonized with MRSA randomized to education + decolonization vs education alone. Decolonization protocol: CHG mouthwash, CHG body wash, and BID nasal mupirocin x 5d twice a month x 6mo



SEE ENLARGED SLIDE FOLLOWING ENTIRE PRESENTATION

Huang, *NEJM* 2019;380:638-50

Question #10

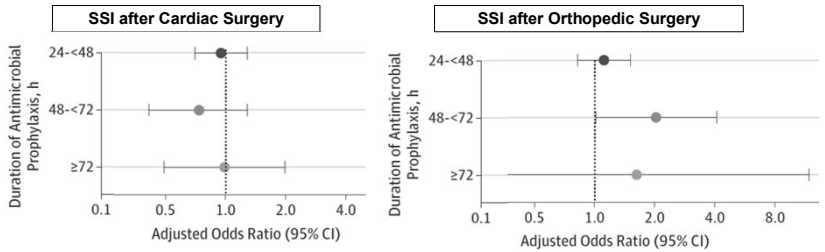
An obese 62-year-old female smoker with COPD is admitted for elective resection of adenocarcinoma of the left upper lobe. She weighs 132kg. She is intubated and undergoes left upper lobe lobectomy. Cefazolin 3g IV is administered 30mins before incision and every 4 hours during surgery. A chest tube is place on the left side. After surgery she is admitted to the ICU for recovery.

How long should cefazolin be continued post-operatively?

A. 0-hours – prophylaxis should be stopped after surgery
B. 12-hours
C. 24-hours
D. Until the chest tube is removed
E. Until the patient is extubated

Extending Antibiotics Beyond Surgery Does Not Prevent Infections…

Retrospective analysis of association between duration of peri-operative antibiotic prophylaxis and adverse events in 79,058 patients who underwent orthopedic, colorectal, and vascular procedures, VA hospitals, 2008-2013

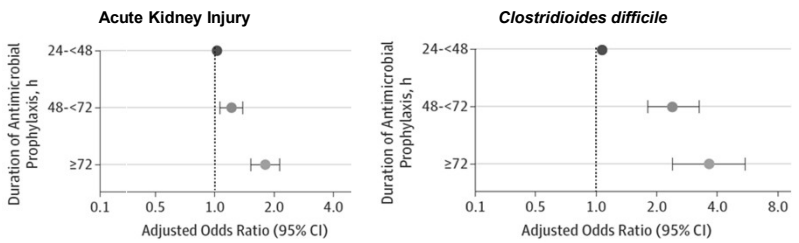


SEE ENLARGED SLIDE FOLLOWING ENTIRE PRESENTATION

Branch-Elliman, *JAMA Surgery* 2019;154:590-598

…But Extending Antibiotics Beyond Surgery May Be Harmful

Retrospective analysis of association between duration of peri-operative antibiotic prophylaxis and adverse events in 79,058 patients who underwent orthopedic, colorectal, and vascular procedures, VA hospitals, 2008-2013



SEE ENLARGED SLIDE FOLLOWING ENTIRE PRESENTATION

Branch-Elliman, *JAMA Surgery* 2019;154:590-598

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Essential Practices to Prevent Surgical Site Infections – Part I

- Administer antimicrobial prophylaxis according to evidence-based practices and standards
- Use parenteral and oral abx prophylaxis before colorectal surgery
- Decolonize patients with an anti-Staphylococcal agent before cardiac and orthopedic procedures (+/- those with prosthetic implants)
- Use an anti-septic vaginal prep for cesareans & hysterectomy
- Do not remove hair at the operative site (unless it interferes with surgery)
- Use skin prep containing a combination of alcohol + an antiseptic
- Maintain normothermia during perioperative period
- Use impervious plastic wound protectors for GI and biliary tract surgery
- Perform intraoperative antiseptic wound lavage
- Control blood-glucose level in the post-operative period

Infection Control & Hospital Epidemiology 2023;44:695-720

Essential Practices to Prevent Surgical Site Infections – Part II

- Perform surveillance for surgical site infections (SSIs)
- Use a checklist and/or bundle to encourage best practices
- Increase the efficiency of surveillance by utilizing automated data
- Provide ongoing SSI rate feedback to surgical and periop personnel
- Measure & provide feedback on compliance with process measures
- Educate surgeons and periop personnel about SSI prevention measures
- Educate patients and their families about SSI prevention as appropriate
- Align SSI prevention practices with evidence-based standards, rules & regulation, and manufacturers' instructions for use
- Observe and review operating room personnel and the environment of care in the operating room and central sterile reprocessing

Infection Control & Hospital Epidemiology 2023;44:695-720

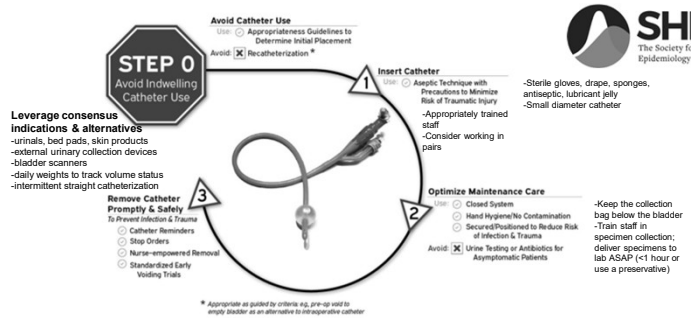
Question #11

A 55-year-old woman is emergently transferred to your hospital after falling and sustaining a spinal cord injury complicated by paraplegia. She is admitted to the intensive care unit following neurosurgery.

Which of the following steps is most likely to reduce her risk of developing a catheter-associated urinary tract infection?

A. Start prophylactic fosfomycin
B. Screen for colonization to inform targeted antibiotic prophylaxis
C. Change the urinary catheter every 7 days
D. Empty the catheter drainage bag before transporting her off the unit
E. Check a urinalysis daily and start pre-emptive antibiotics if she develops pyuria

Essential Practices to Prevent Catheter-Associated UTIs



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Infection Control & Hospital Epidemiology 2023;44:1209-1231

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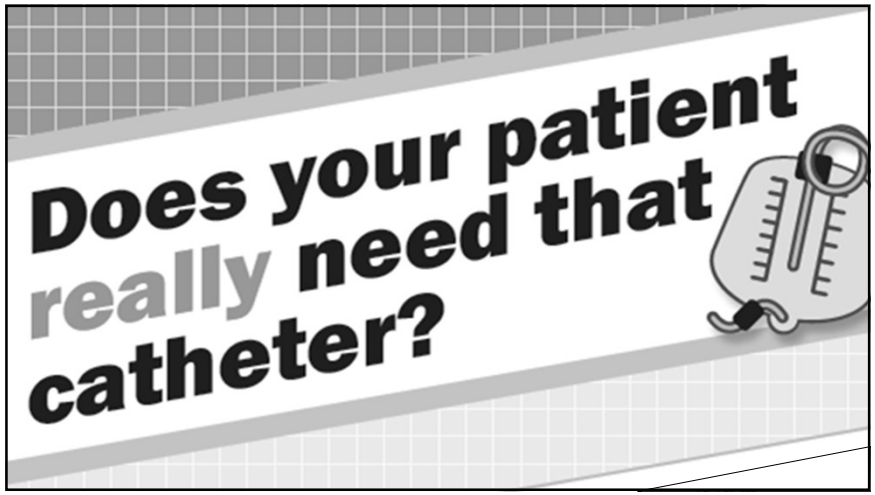

Accepted Indications:

- Perioperative use in selected surgeries
- Acute urinary retention or obstruction
- Accurate measurement of urinary output in critically ill patients
- Strict immobilization for trauma or surgery
- Severe perineal and sacral wounds in incontinent patients
- Hospice/comfort care/palliative care

Question #12

A 52-year-old woman is admitted to hospital with intermittent epigastric pain. ALK, Tbili, and lipase are high. CT shows a thickened and dilated gall bladder with stones in the common bile duct. A foley is placed. The patient goes to ERCP for sphincterotomy and gallstone retrieval. Two days later she develops fever and delirium. Blood cultures are positive for carbapenem-resistant Enterobacterales.

What sources will you consider for this infection?

A. Healthcare workers with poor hand hygiene
B. The hospital's decorative water fountain
C. A contaminated duodenoscope
D. Contaminated intravenous contrast
E. Failure to remove a foley catheter in a timely fashion

Duodenoscopes

- Notoriously difficult to sterilize
- Meta-analysis of 15 studies sampling duodenoscopes after reprocessing (925 scopes):

16% still **culture positive** after high level disinfection performed per manufacturers' instructions

9% still culture positive after **double reprocessing** or gas sterilization

- Many clusters reported

Larsen. *EClinicalMedicine* 2020;25:100451
Forbes, *JAMA Internal Med* 2023;183:191-200

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Outbreak Word Associations

Pathogen	Potential Sources
Legionella	Decorative water fountains, cooling units
Pseudomonas	Respiratory care equipment, drains & sinks
Burkholderia	Water heaters & coolers (e.g., ECMO)
Carbapenem-resistant Enterobacterales	Duodenoscopes
Candida auris	Temperature probes
Mycobacterium abscessus	Ice & water machines, other water sources
Mycobacterium chimaera	Cardiac bypass heater-cooler devices
Aspergillus sp.	Construction, plants & flowers

Summary

- Equipment, hands, and clothing are commonly contaminated by bacteria
- Hand hygiene rates are inversely associated with HAI rates
- All respiratory viruses are spread by aerosols. Risk highest with high viral load, proximity, sustained exposure, poor ventilation. Surgical masks decrease risk by ~50%. N95 respirators decrease risk by ~95%
- Most aerosol generating procedures do not generate aerosols
- Most *C. difficile* is endogenous; activated during medical care in setting of antibiotics, immunosuppressants, frailty. Some hospital transmission too.
- Decolonize *Staph aureus* carriers if lines, surgery, ICU, or after discharge
- Give antibiotic prophylaxis within 60mins before incision; stop after surgery
- Contaminated water, drains, respiratory equipment, and meds can spread water-based pathogens. ICUs working on decreasing water-based care.

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Nail Add-Ons & Blemishes Can Harbor Pathogens

etsy.com/dk-en/listing/598625946/nurse-nail-art-decals

- **Nail add-ons can act as reservoirs for potentially pathogenic organisms; can persist despite cleaning with an antiseptic**
- **Multiple clusters linked to healthcare workers with artificial nails & infected nails**
  - NICU patients with ESBL *Klebs pneumo* infections
  - Serratia bloodstream infections in dialysis patients linked to RN opening heparin vials with fake nails
  - NICU patients with *Pseudomonas* infections linked to healthcare workers with artificial & infected nails
  - Laminectomy surgical site infections with *Candida albicans* traced to scrub tech with artificial nails
  - Sternal wound infections with *Pseudomonas* traced to OR nurse with onychomycosis
  - Sternal wound infections with *Pseudomonas* traced to cardiac surgeon with onychomycosis

Gupta, ICHE 2004;25:210-215
Gordon, *ICHE* 2007;28:743-744
Foca, *N Engl J Med* 2000;343:695-700
Parry, *Clin Infect Dis* 2001;32:352–7
McNeil, *Clin Infect Dis* 2001;33:317-323
Mermel, ICHE 2003;24:749-52

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Essential Hand Hygiene Practices

Promote healthy hand skin & fingernails

- Fingernails should be short, healthy, and natural
- Perform hand hygiene per the WHO's Five Moments
  1. Before touching patient
  2. Before clean procedure
  3. After touching patient
  4. After touching body fluids
  5. After touching the patient's environment
- Alcohol-based hand rub typically preferred over soap & water
- Facilitate primary and secondary prevention of dermatitis

Ensure hand hygiene supplies are always readily accessible

- Widespread, convenient alcohol-based hand rub dispensers

SEE ENLARGED SLIDE FOLLOWING ENTIRE PRESENTATION

Infection Control & Hospital Epidemiology 2023;44:355-376

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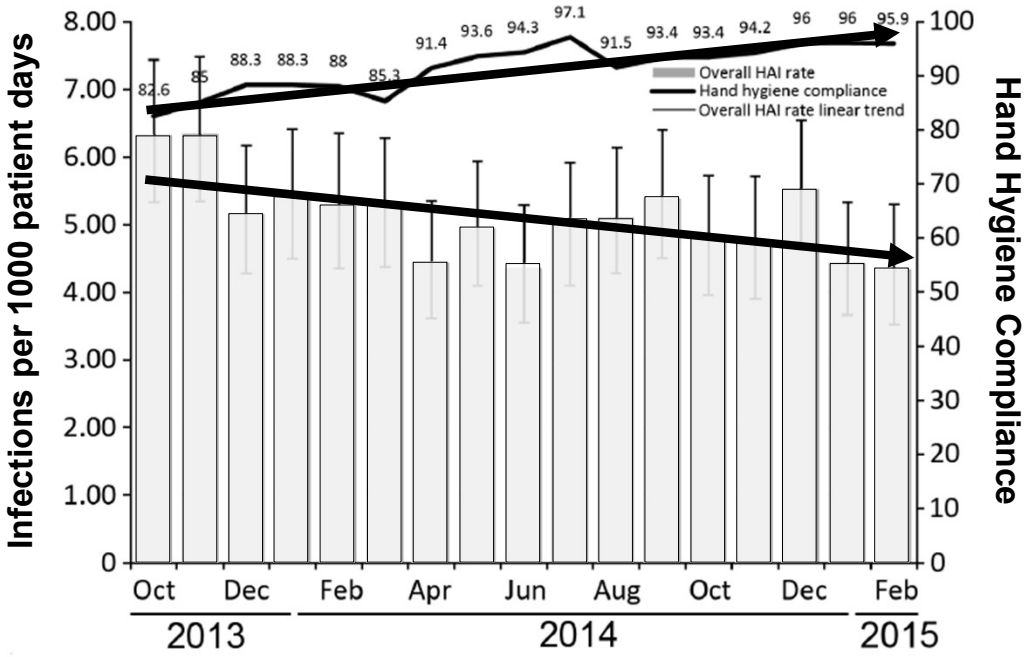
Better Hand Hygiene
Fewer Healthcare Associated Infections

University of North Carolina Hospitals, 2013-2015



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Emerg Infect Dis 2016;9:1628-1630

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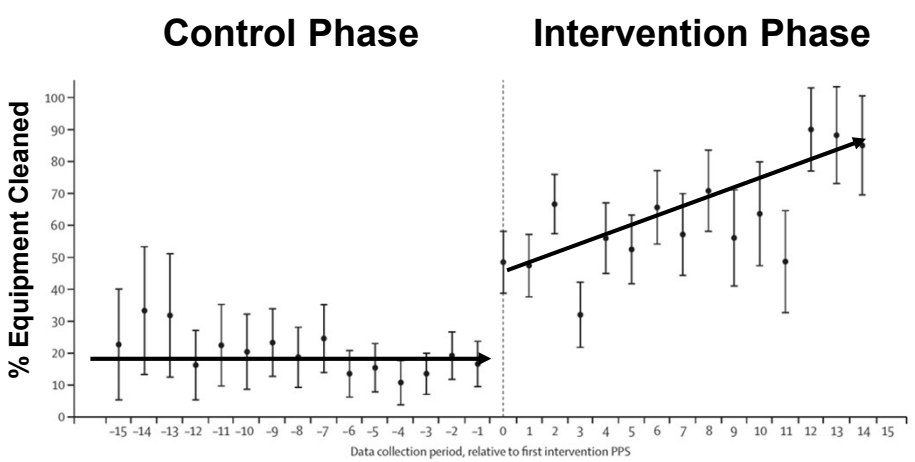
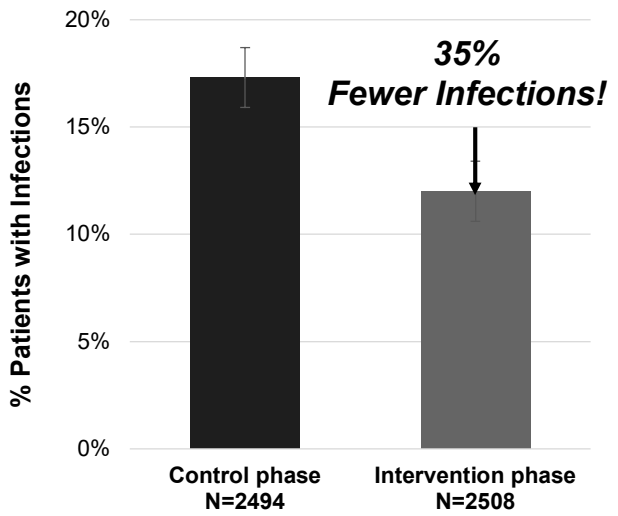
Cleaning Equipment Prevents Infections

Stepped-wedge cluster randomized trial of enhanced vs routine equipment cleaning, 10 units, 1 hospital, Australia
Enhanced cleaning included 3 extra hours/day of shared medical equipment cleaning + audit & feedback

Equipment Cleaning Audits



Healthcare Associated Infections



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Browne, *Lancet Infect Dis* 2024;12:1347-1356

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Neisseria Transmission to Healthcare Workers

Comprehensive search for occupational Neisseria infections in healthcare workers in England and Wales 1982-1996

Case 1

Provider: Doctor

Full clinical exam of 9 yo with meningitis, including fundoscopy during which **patient coughed into doctor's face**

0.5-2h contact time

Incubation period: 4d

Case 2

Provider: EMS worker

Transported 16 yo with meningitis to hospital. Care included **airway insertion and delivery of oxygen while patient seizing** in the ambulance

0.5-2h contact time

Incubation period: 7d

Case 3

Provider: Nurse

Nursed a 7mo with sepsis while baby being prepared for transfer to referral hospital; **in close contact while child crying and coughing for at least 5h**

5-6h contact time

Incubation period: 5d

Estimated 0.8 infections per 100,000 healthcare worker contacts with meningococcal patients

SEE ENLARGED SLIDE FOLLOWING ENTIRE PRESENTATION

Gilmore, Lancet 2000;356:1654-1655

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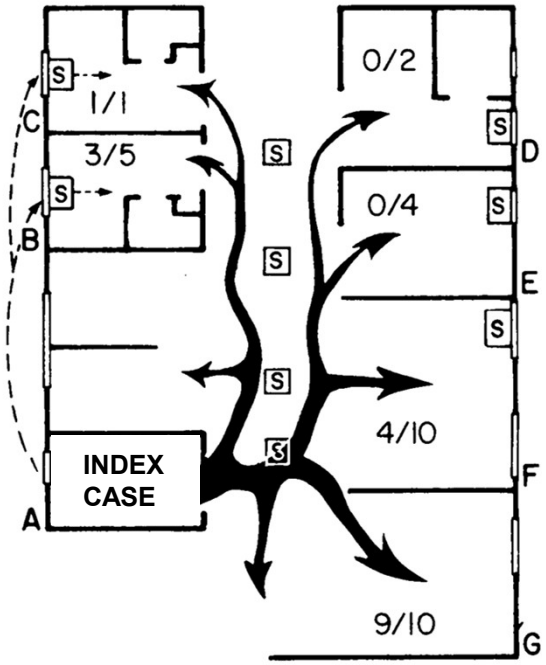
Varicella Outbreak!

Cluster of 15 varicella cases, attributed to child with varicella pneumonia, Boston Children's Hospital, 1970s

Transmission via windows or hall flow or HCW?



Air flow from the index patient's room

0% attack rate
Distance and fresh air leading to dilution

0% attack rate
Distance and fresh air leading to dilution

40% attack rate
HVAC unit operational

90% attack rate
HVAC unit not working, rendering the room negative pressure relative to the hall

SEE ENLARGED SLIDE FOLLOWING ENTIRE PRESENTATION

Leclair, NEJM 1980;302:450-453

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Management of Varicella Exposure

- **Definition of exposure**
  - >15-60mins in same room as person with primary varicella or disseminated zoster involving the respiratory tract, or skin-to-skin contact with exposed varicella lesions
  - No exposure if HCW immune and wearing a mask or respirator
- **Management of Exposures**

Immune Status	Vaccinate?	VariZIG?	Furlough d8-21?	Monitor d8-21?
Fully vaccinated, seropositive, or prior Dx	**No**	**No**	**No**	**Yes**
Partially vaccinated	**Yes**	**No**	**Depends[2]**	**Yes**
Unvaccinated & seronegative	**Yes**	**No**	**Yes**	**Yes**
Unvaccinated & unable to vaccinate[1]	**No**	**Yes[3]**	**Yes[4]**	**Yes**

[1] Vaccine contraindicated if pregnant or immunocompromised
[2] Furlough if vaccine was given >5d after first exposure
[3] Or valacyclovir d7-13 if VariZIG not available
[4] Furlough d8-28 if given VariZIG

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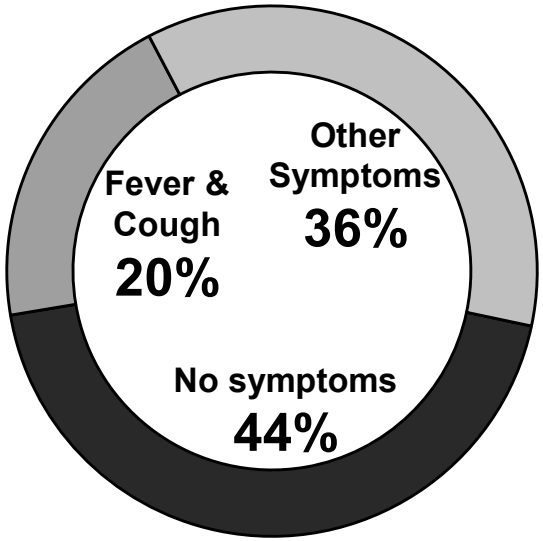
Influenza Transmission Possible with Few or No Symptoms

1,116 participants from 225 households in South Africa, tested for influenza 2x/week by PCR, 2017-2018

Source Individual Symptom Status



Influenza Transmission rate

- With 0 symptoms: 6%
- With ≥2 symptoms: 17%

27% of secondary flu infections were acquired from asymptomatic index cases

SEE ENLARGED SLIDE FOLLOWING ENTIRE PRESENTATION

Cohen, *Lancet Glob Health* 2021; 9:e863-874

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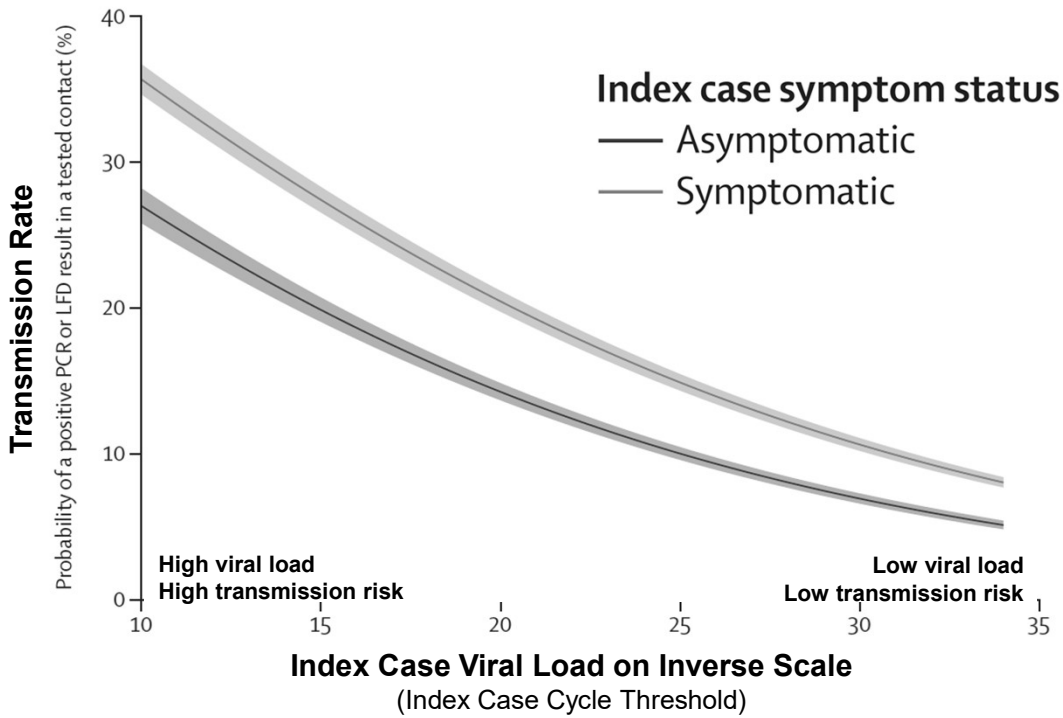
Viral Load Predicts Transmission Risk

Secondary attack rates amongst 1,173,643 contacts of 6,263,786 index cases, UK, Jan 2021-Jan 2022



SEE ENLARGED SLIDE FOLLOWING ENTIRE PRESENTATION

Eyre, *Lancet ID* 2023; 23:922-932

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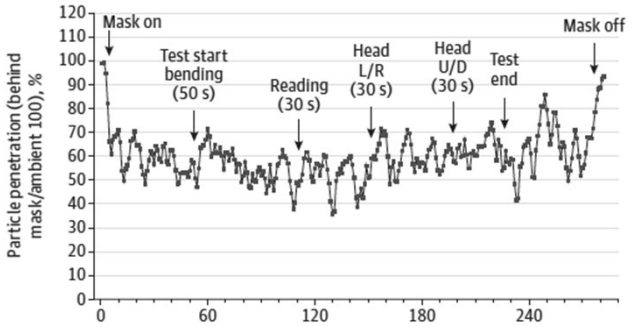
Filtration Efficiency: Surgical Mask vs. N95 Respirator

Surgical Mask with Ear Loops

Particle Penetration Behind Mask

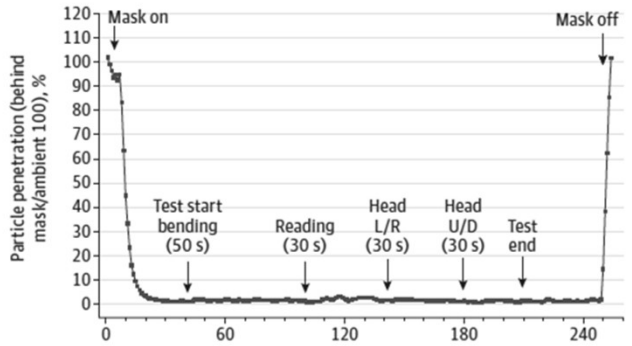


Filtration Efficiency

38.1%

N95 Respirator

Particle Penetration Behind Mask



98.5%

Sickbert-Bennett, *JAMA Internal Med* 2020; 180:1607-1612

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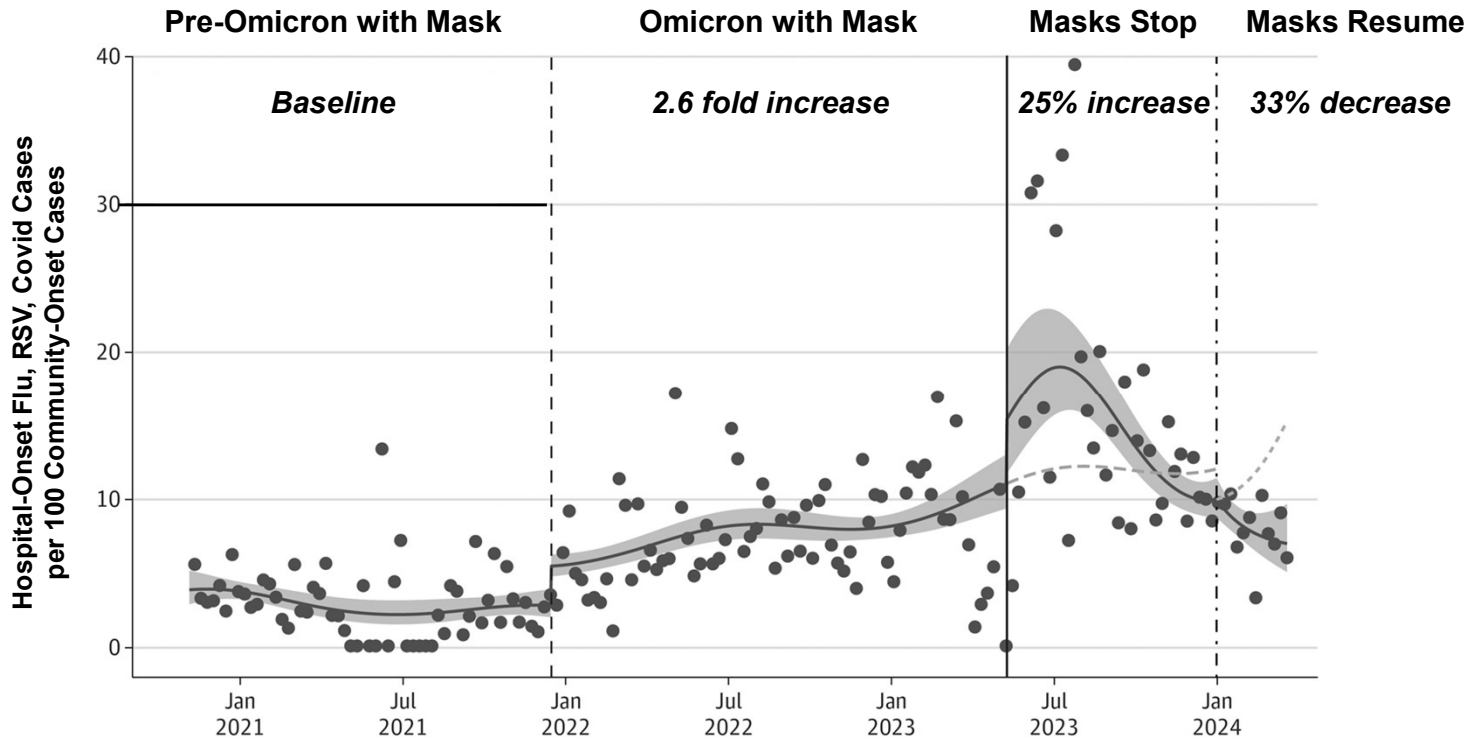
Masking and Hospital-Onset Respiratory Viral Infections

Associations between Masking Policies and Hospital-Onset Influenza, RSV, and Covid in 10 US Hospitals



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Pak, *JAMA Network Open* 2024;7(11):e2448063

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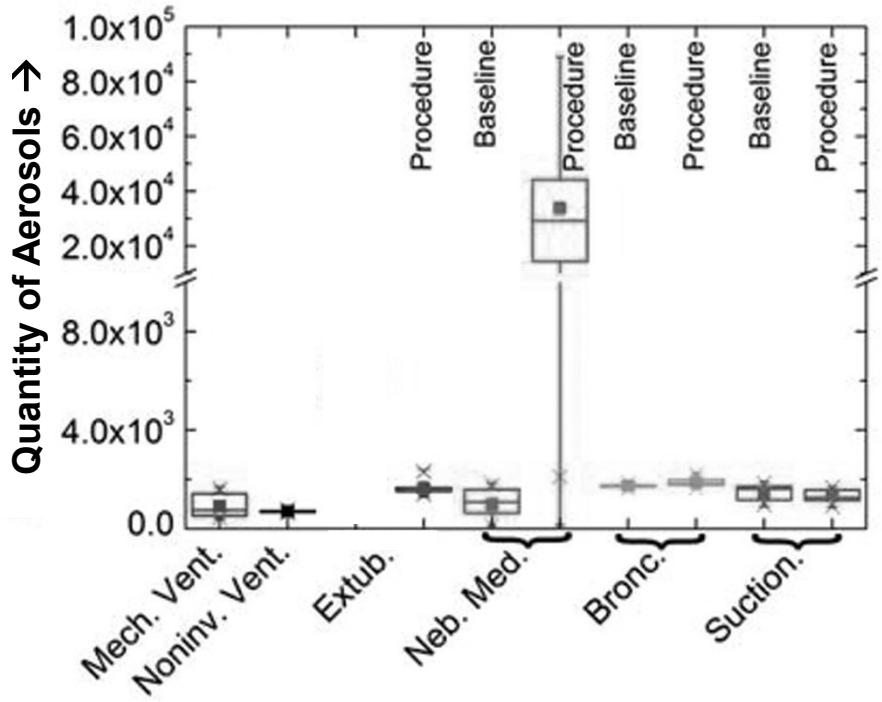
Most "Aerosol Generating Procedures" Do Not Generate Aerosols



Doggett, *Chest* 2020; 158:2467-2473
O'Neil, *Clin Infect Dis* 2017;65:1342-1348
Li, *Open Forum Infect Dis* 2017;4(Suppl 1):S34

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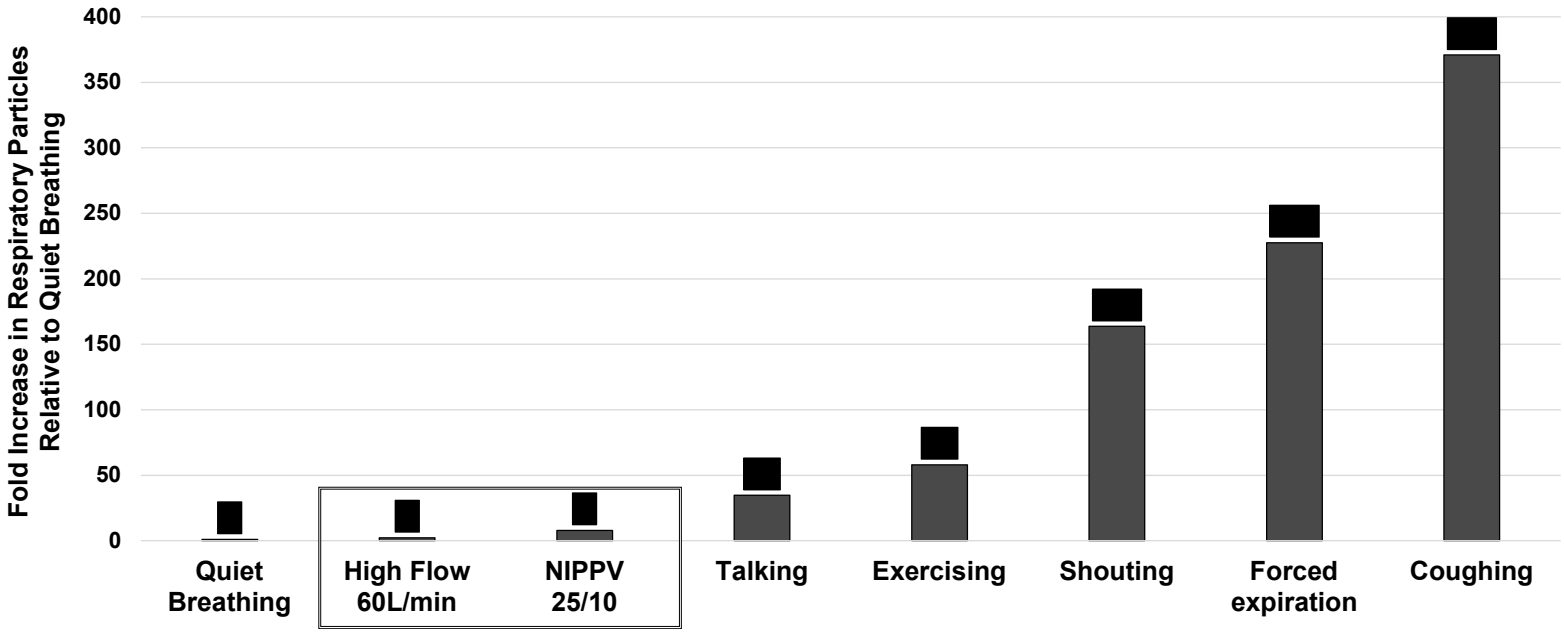
Impact of High Flow O_2 on Respiratory Emissions



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Wilson, *Anaesthesia* 2021;76(11):1465-1474

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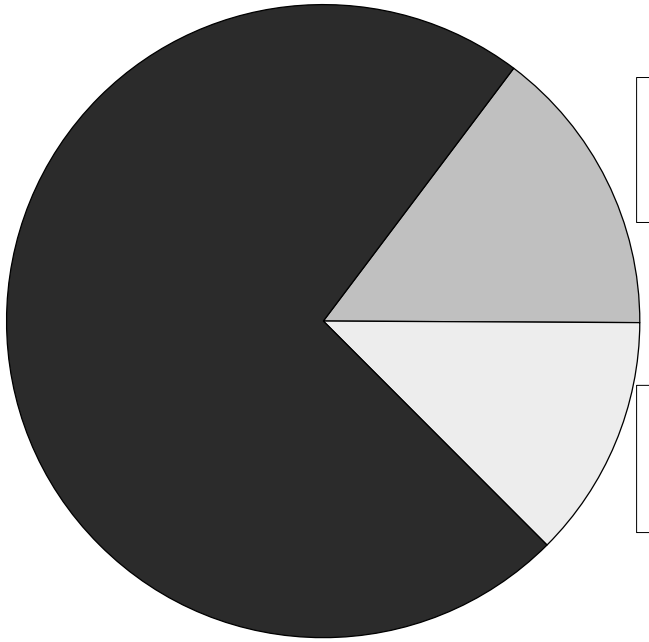
Where Do Patients Get *C. difficile*?

Whole genome sequencing of 1,250 C. diff isolates from symptomatic inpatients & outpatients, Oxfordshire, UK, 2007-2011



73% unrelated to any other isolate

15% related to another isolate
and hospital contact possible
(overlapping admission, same or different ward)

12% related to another isolate
but no record of community or hospital contact with another symptomatic patient

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Eyre, *N Engl J Med* 2013;369:1195-1205

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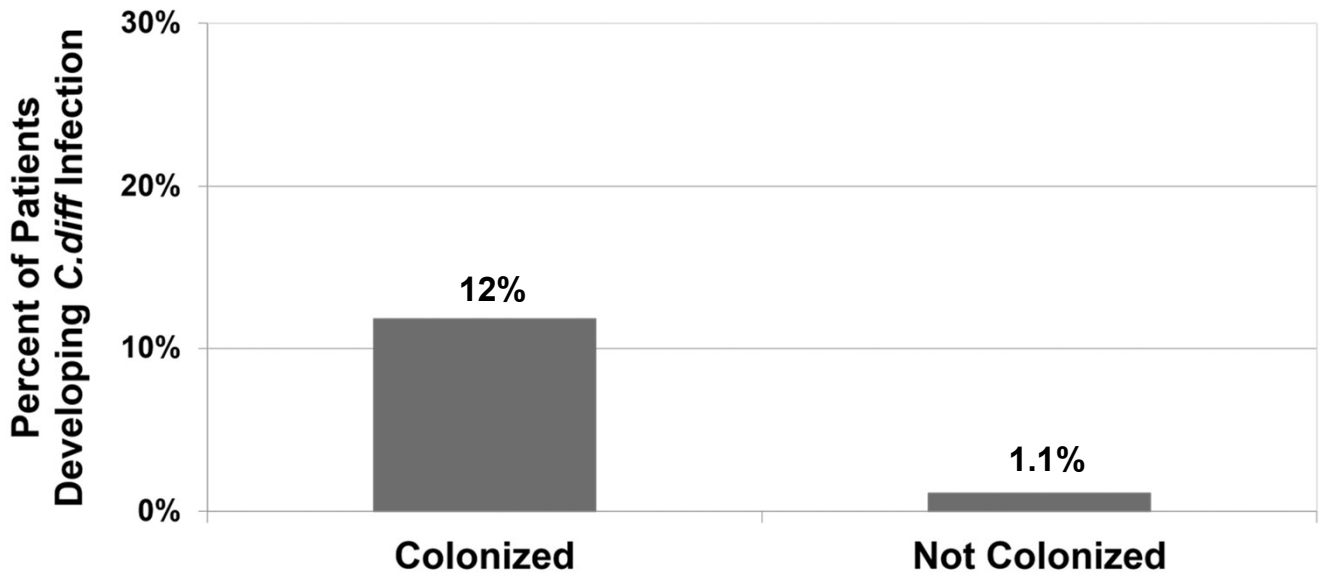
C. diff Colonization in ICU Patients and Progression to Infection

548 ICU patients at Johns Hopkins screened for C. difficile carriage on admission



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Infect Control Hospital Epidemiol 2015;36:1324-1329

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Essential Practices to Prevent *C. difficile* in Hospitals

- Encourage appropriate use of antimicrobials through implementation of an antibiotic stewardship program
- Implement diagnostic stewardship to assure appropriate use and interpretation of *C. difficile* testing
  - Guide or limit use of PCR, aid in interpretation
  - Avoid testing patients if no significant diarrhea, recent positive test, or age <1 year
- Use contact precautions, single room preferred
- Adequately clean and disinfect equipment and the environment
  - Use dedicated equipment when possible (e.g., stethoscope, BP cuff, thermometer…)
- Assess the adequacy of room cleaning
  - Consider using sporicidal agents if cleaning adequate but ongoing *C. diff* transmission
- Create lab-based alerts for clinicians and infection control re new cases
- Conduct surveillance for *C. diff* infections and report to stakeholders
- Educate clinicians, enviro services, administrators, & patients about *C. difficile*
- Measure compliance with contact precautions and hand hygiene

SEE ENLARGED SLIDE FOLLOWING ENTIRE PRESENTATION

Infection Control & Hospital Epidemiology 2023;44:527-549

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Water Avid Pathogens

- Normal inhabitants of water systems
- Promoters of persistence:
  - Biofilm forming
  - Relative resistance to disinfectants
- When clusters occur think:
  - Respiratory care equipment
  - Heating & cooling devices
  - Contaminated IV solutions & meds
  - Decorative water displays
  - Contaminated sink drains, etc.

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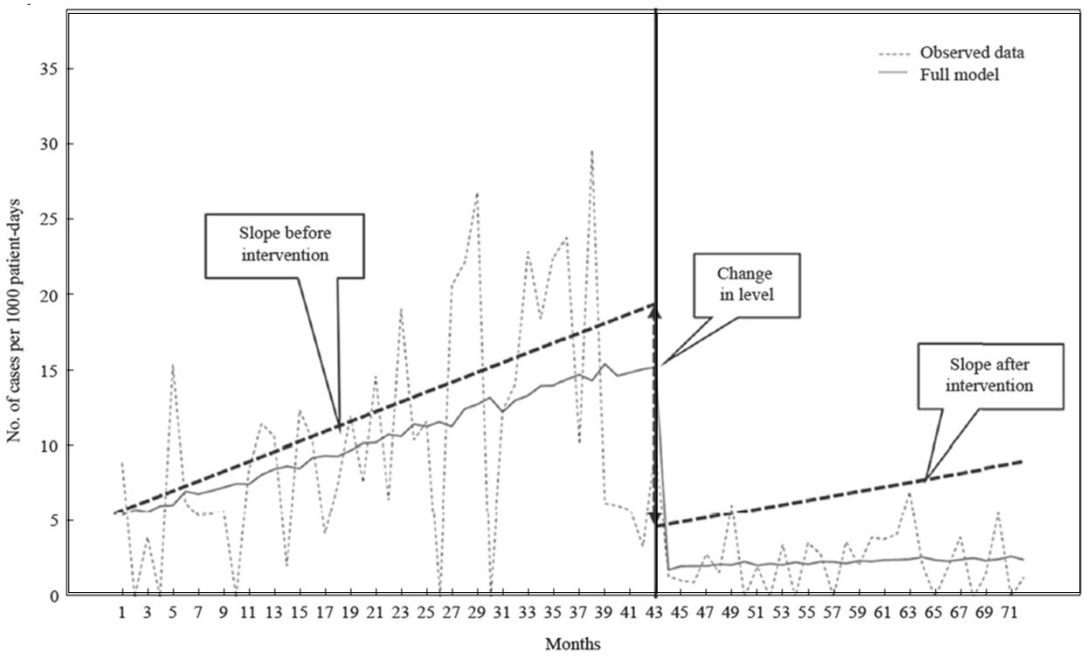
Drop in MDR Gram Negatives After Sink Removal

Incidence of ICU-acquired MDR gram negatives before vs after removing patients' sinks, Bellvitge University Hospital, Barcelona



SEE ENLARGED SLIDE FOLLOWING ENTIRE PRESENTATION

Shaw, J Hosp Infection 2018;98:275-281

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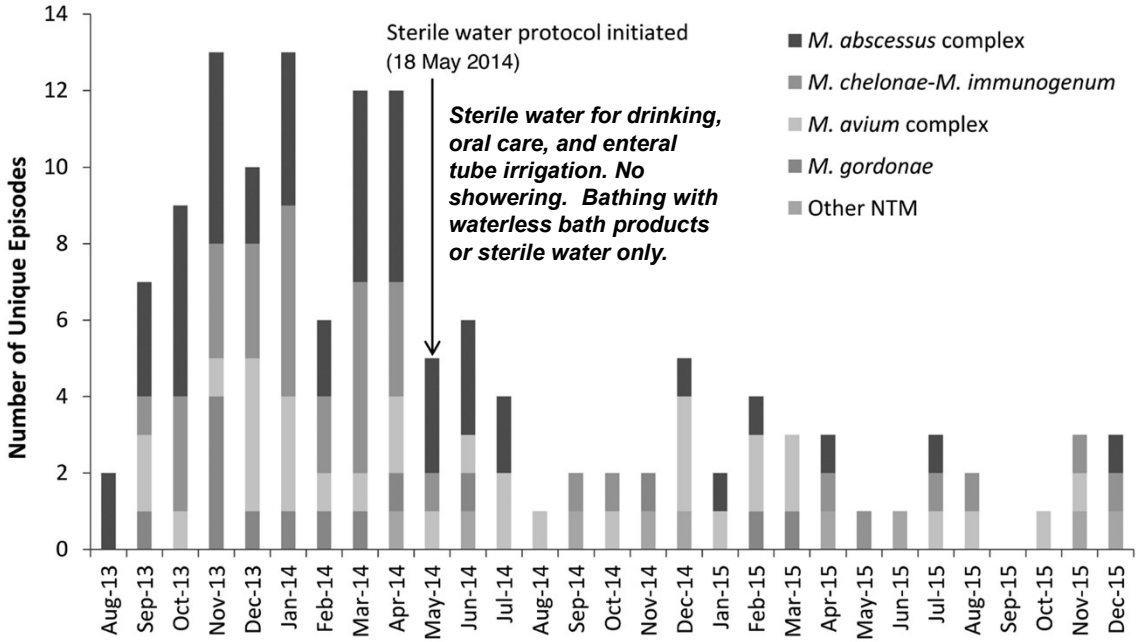
Eliminating Tap Water Associated with Drop in NTM Infections

Count of patients with new non-tuberculous mycobacteria cultures, 3 ICUs & 1 step-down, Duke University Hospital



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Baker, *Clin Infect Dis* 2021;73:524-527

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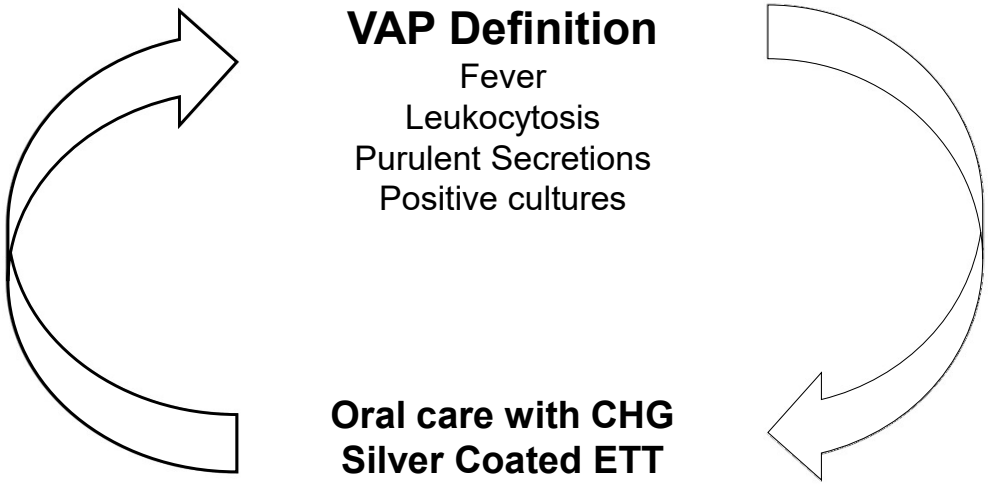
Circularity Between VAP Prevention Practices and the VAP Definition



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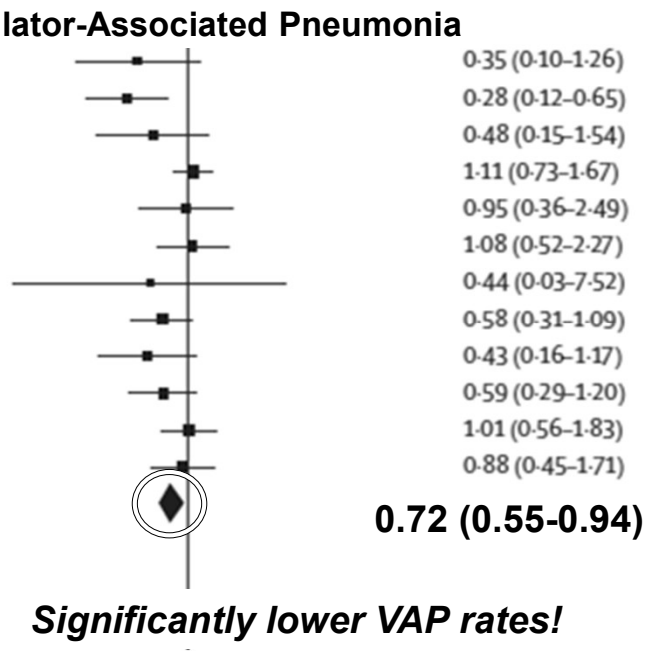
Oral Care with Chlorhexidine: Significantly *Lower* VAP Rates

Chlorhexidine					
De Riso et al (1996)[18]	3	173	9	180	3·8%
Fourrier et al (2000)[13]	5	30	18	30	7·0%
Houston et al (2002)[20]	4	270	9	291	4·4%
MacNaughton et al (2004)[22]	32	91	28	88	14·1%
Grap et al (2004)[14]	4	7	3	5	5·9%
Fourrier et al (2005)[19]	13	114	12	114	8·3%
Bopp et al (2006)[17]	0	2	1	3	0·9%
Koeman et al (2006)[21]	13	127	23	130	9·9%
Tantipong et al (2008)[23]	5	102	12	105	5·5%
Scannapieco et al (2009)[26]	14	116	12	59	8·8%
Bellisimo-Rodriguez et al (2009)[24]	16	64	17	69	10·6%
Panchabhai et al (2009)[25]	14	88	15	83	9·4%
Subtotal (95% CI)		**1184**		**1157**	**88·5%**
Total events	123		159		
Heterogeneity: τ^2=0·06, χ^2=15·54, df=11 (p=0·16); I^2=29%					
Test for overall effect: Z=2·40 (p=0·02)					



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Lancet Infectious Disease 2011;11:845

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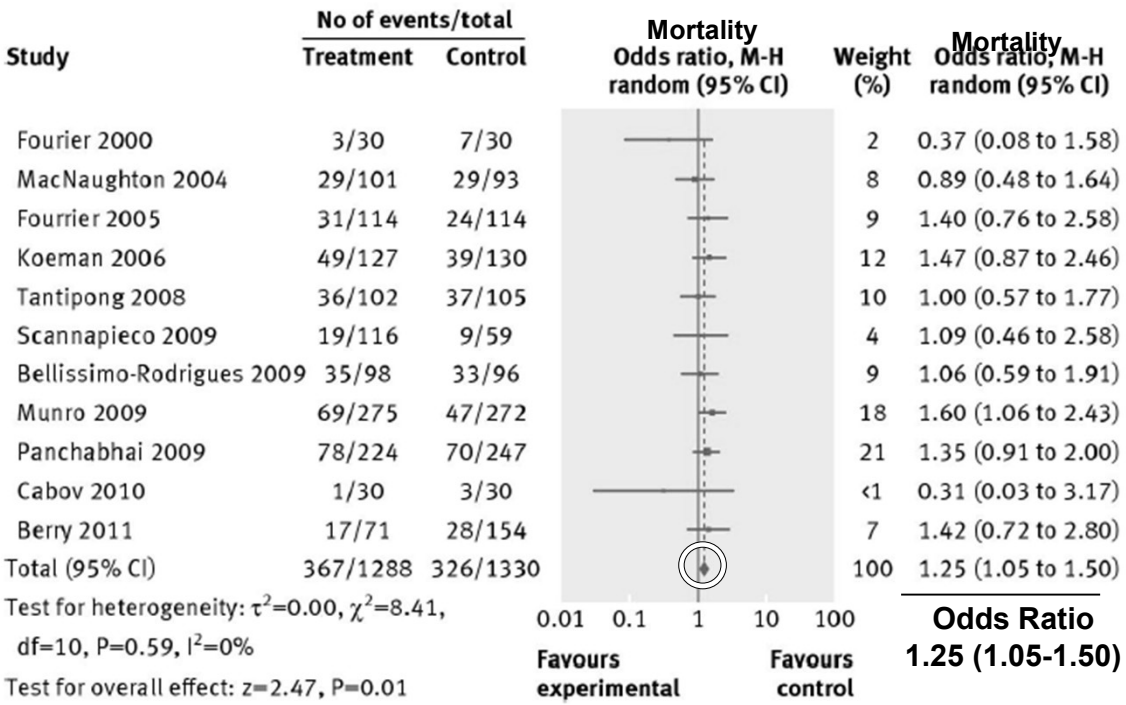
Oral Care with Chlorhexidine: Significantly *Higher* Mortality Rates



Study	No of events/total Treatment	Control	Mortality Odds ratio, M-H random (95% CI)	Weight (%)	Mortality Odds ratio, M-H random (95% CI)
Fourier 2000	3/30	7/30		2	0.37 (0.08 to 1.58)
MacNaughton 2004	29/101	29/93		8	0.89 (0.48 to 1.64)
Fourrier 2005	31/114	24/114		9	1.40 (0.76 to 2.58)
Koeman 2006	49/127	39/130		12	1.47 (0.87 to 2.46)
Tantipong 2008	36/102	37/105		10	1.00 (0.57 to 1.77)
Scannapieco 2009	19/116	9/59		4	1.09 (0.46 to 2.58)
Bellissimo-Rodrigues 2009	35/98	33/96		9	1.06 (0.59 to 1.91)
Munro 2009	69/275	47/272		18	1.60 (1.06 to 2.43)
Panchabhai 2009	78/224	70/247		21	1.35 (0.91 to 2.00)
Cabov 2010	1/30	3/30		<1	0.31 (0.03 to 3.17)
Berry 2011	17/71	28/154		7	1.42 (0.72 to 2.80)
Total (95% CI)	367/1288	326/1330		100	1.25 (1.05 to 1.50)

Test for heterogeneity: $\tau^2=0.00$, $\chi^2=8.41$, df=10, P=0.59, $I^2=0\%$

Test for overall effect: z=2.47, P=0.01

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BMJ 2014;348:g2197

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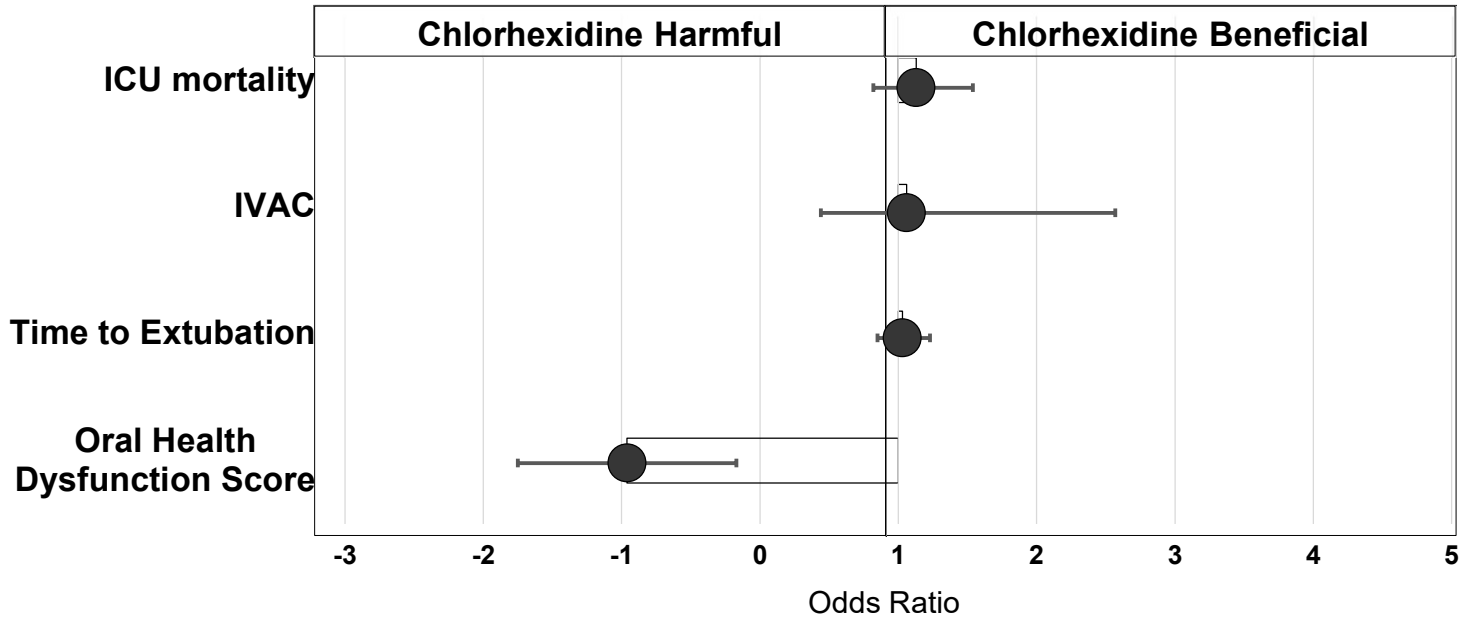
Chlorhexidine De-Adoption Cluster Randomized Trial

Cluster randomized trial of replacing oral CHG with an oral care bundle vs continuing oral care with CHG in 6 Canadian ICUs (N=3260). Oral care bundle included twice daily toothbrushing plus mouth and lip moisturization



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Dale, Intensive Care Med 2021;47:1295-1302

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Toothbrushing: Lower Mortality, Shorter LOS

Meta-analysis of 15 randomized trials of oral care with vs without toothbrushing

	Studies	Patients	Meta-Analysis	
Hospital-acquired pneumonia* *12 of the 14 studies in ventilated patients	14	2557	**Risk Ratio 0.68 (95% CI 0.57-0.82)**	***Lower!***
Ventilator Days	7	1285	**-1.2 days (95% CI -2.4 to -0.1)**	***Lower!***
ICU Length of Stay	6	1284	**-1.8 days (95% CI -2.9 to -0.7)**	***Lower!***
ICU Mortality	6	1331	**Risk Ratio 0.81 (95% CI 0.69-0.95)**	***Lower!***

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Ehrenzeller, *JAMA Internal Med* 2024;184(2):131-142

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Where Do *Staph aureus* Infections Come From?

80%

of hospital acquired *Staph aureus* infections are attributable to patients' own flora (endogenous)

Staph Bacteremia

Nasal isolates compared to blood isolates in 219 patients with *Staph aureus* bacteremia. 82% matched

von Eiff, NEJM 2001;344:11-16

Surgical Site Infections

Nasal isolates compared to wound isolates in 39 patients with *Staph aureus* SSIs. 85% matched

Perl, NEJM 2002;346:1871-77

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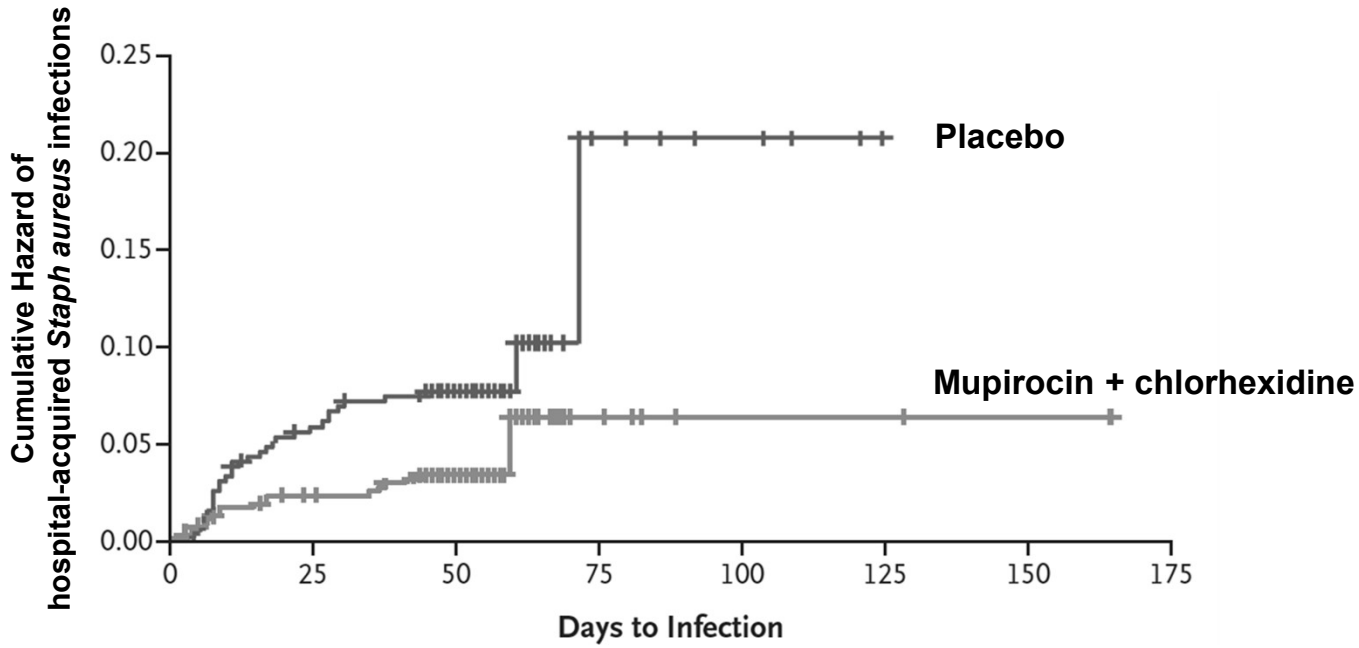
Staph aureus Screening & Decolonization

917 hospitalized patients with positive Staph aureus nasal screens randomized to decolonization vs placebo
~90% of enrolled patients were on surgical services. Greatest benefit cardiac > ortho > vascular > GI



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Bode, NEJM 2010;362:9-17

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Targeted vs Universal Decolonization in the ICU

REDUCE MRSA cluster-randomized trial, 74 ICUs, 43 hospitals, 74,256 patients

Screen and Isolate	**Screen and Decolonize**	**Universal Decolonization**
Nasal MRSA screen If positive, isolate	Nasal MRSA screen If positive, isolate & decolonize with CHG baths x 5 days *+ mupirocin x 5 days*	No screening Decolonize **all** patients with CHG baths throughout ICU stay *+ mupirocin x 5 days*

SEE ENLARGED SLIDE FOLLOWING ENTIRE PRESENTATION

Huang et al. NEJM 2013:368:2255-65

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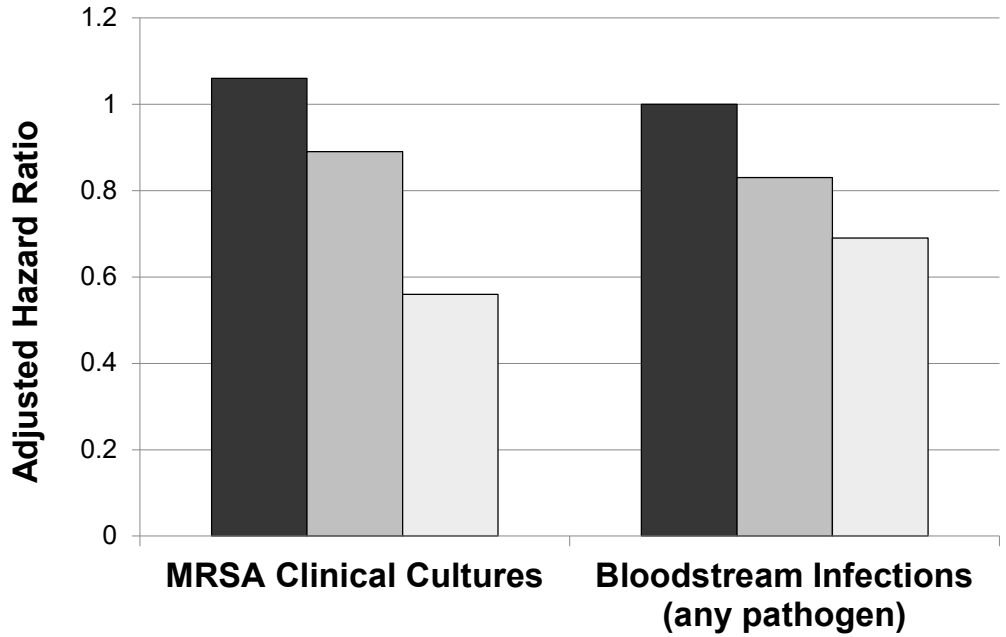
Targeted vs. Universal Decolonization in the ICU

REDUCE MRSA cluster-randomized trial, 74 ICUs, 43 hospitals, 74,256 patients



Screen & Isolate
- Reference group

Screen & Decolonize
- 25% drop in MRSA infections
- 22% drop in bloodstream infections

Universal Decolonization
- 37% drop in MRSA infections
- 44% drop in bloodstream infections

SEE ENLARGED SLIDE FOLLOWING ENTIRE PRESENTATION

Huang et al. *NEJM* 2013:368:2255-65

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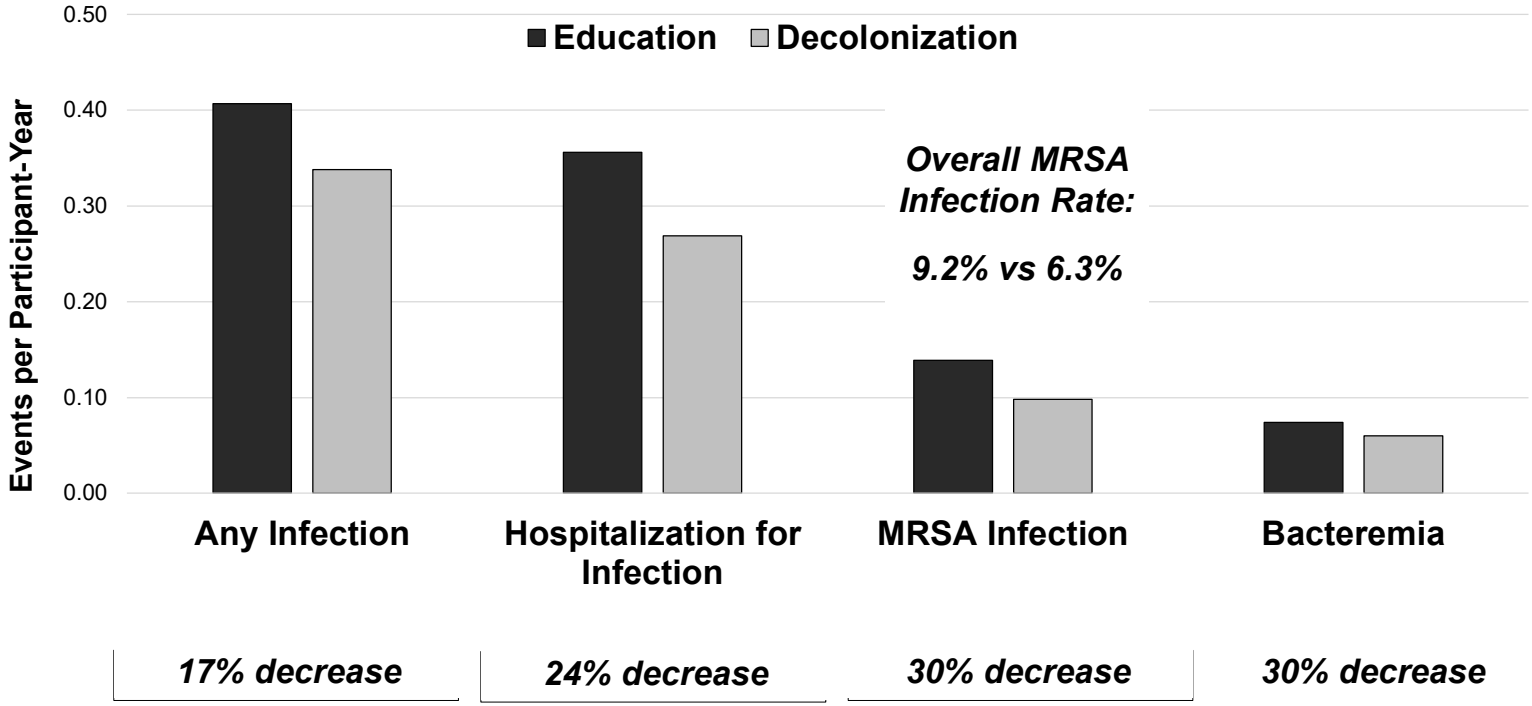
Should We Decolonize Patients <u>After</u> Discharge?

1063 discharged patients colonized with MRSA randomized to education + decolonization vs education alone.
Decolonization protocol: CHG mouthwash, CHG body wash, and BID nasal mupirocin x 5d twice a month x 6mo



SEE ENLARGED SLIDE FOLLOWING ENTIRE PRESENTATION

Huang, *NEJM* 2019;380:638-50

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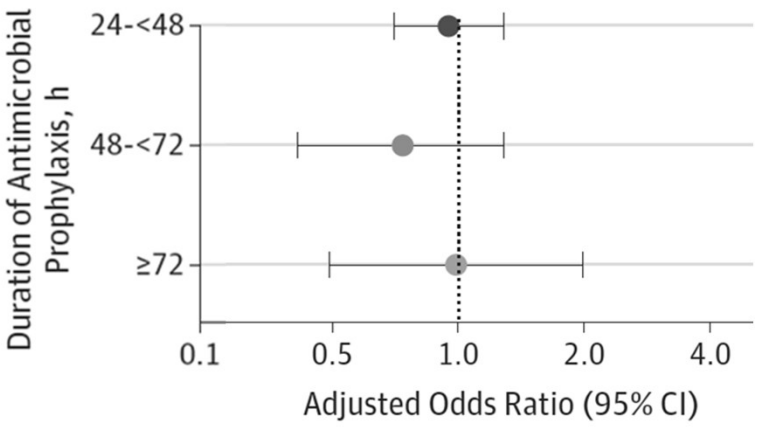
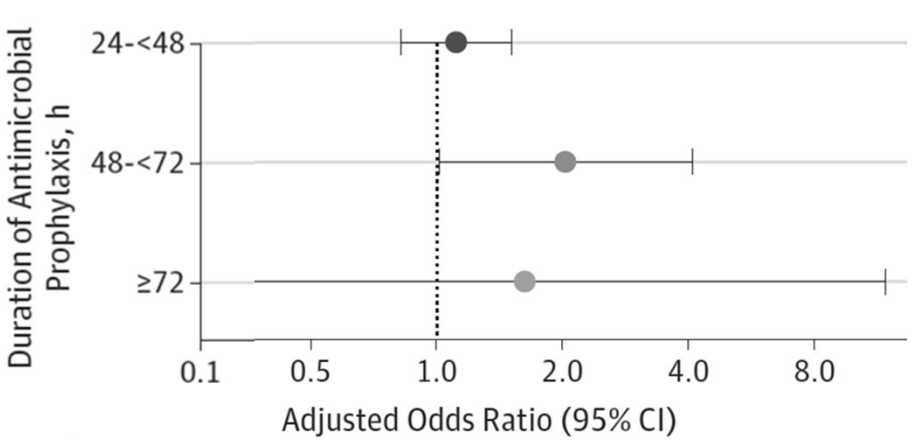
Extending Antibiotics Beyond Surgery Does Not Prevent Infections…

Retrospective analysis of association between duration of peri-operative antibiotic prophylaxis and adverse events in 79,058 patients who underwent orthopedic, colorectal, and vascular procedures, VA hospitals, 2008-2013

SSI after Cardiac Surgery



SSI after Orthopedic Surgery



SEE ENLARGED SLIDE FOLLOWING ENTIRE PRESENTATION

Branch-Elliman, *JAMA Surgery* 2019;154:590-598

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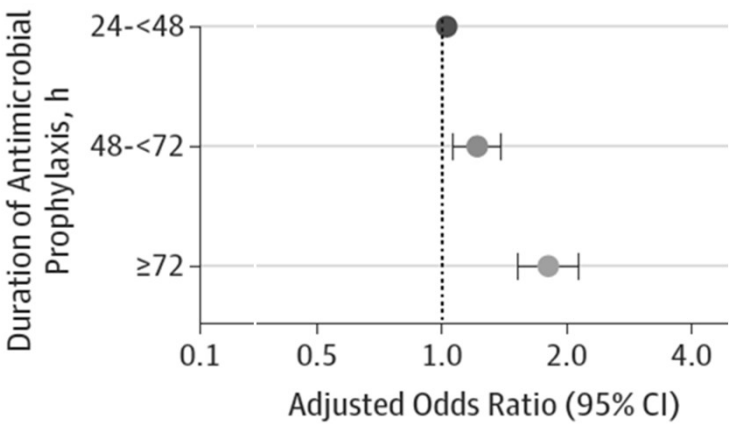
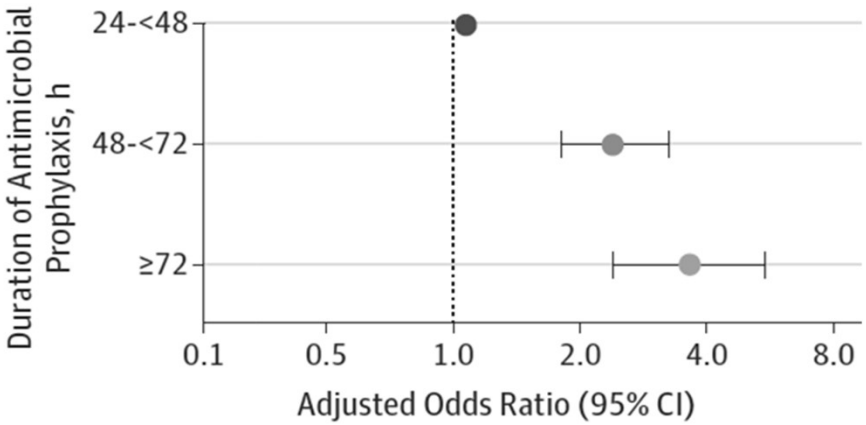
…But Extending Antibiotics Beyond Surgery May Be Harmful

Retrospective analysis of association between duration of peri-operative antibiotic prophylaxis and adverse events in 79,058 patients who underwent orthopedic, colorectal, and vascular procedures, VA hospitals, 2008-2013

Acute Kidney Injury



Clostridioides difficile



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Branch-Elliman, *JAMA Surgery* 2019;154:590-598

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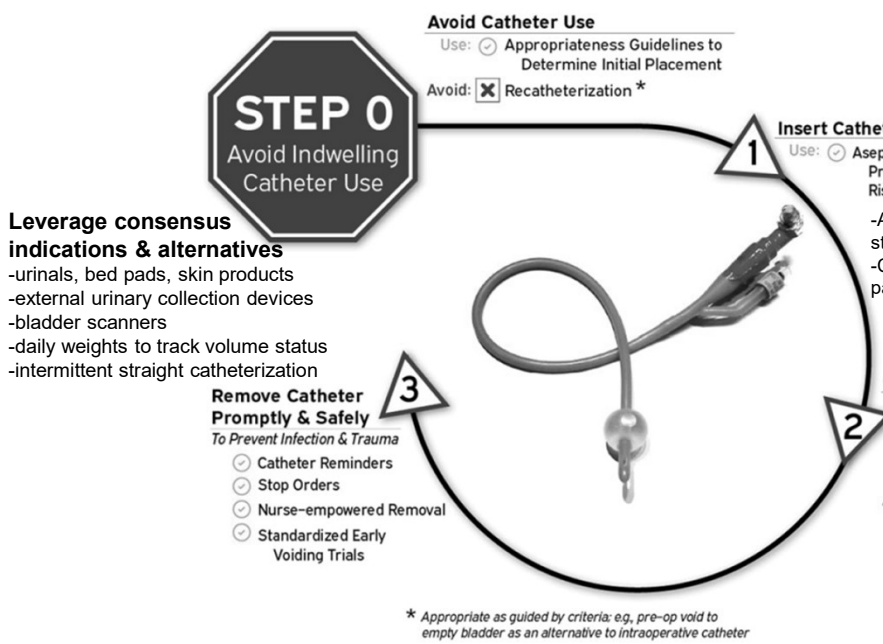
Essential Practices to Prevent Catheter-Associated UTIs



Leverage consensus indications & alternatives
-urinals, bed pads, skin products
-external urinary collection devices
-bladder scanners
-daily weights to track volume status
-intermittent straight catheterization

-Appropriately trained staff
-Consider working in pairs

-Sterile gloves, drape, sponges, antiseptic, lubricant jelly
-Small diameter catheter

-Keep the collection bag below the bladder
-Train staff in specimen collection; deliver specimens to lab ASAP (<1 hour or use a preservative)

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Infection Control & Hospital Epidemiology 2023;44:1209-1231

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Monday, August 24, 2026

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Tuberculosis in Immunocompetent and Immunosuppressed Hosts

Susan Dorman, MD

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Tuberculosis in Immunocompetent & Immunosuppressed Hosts

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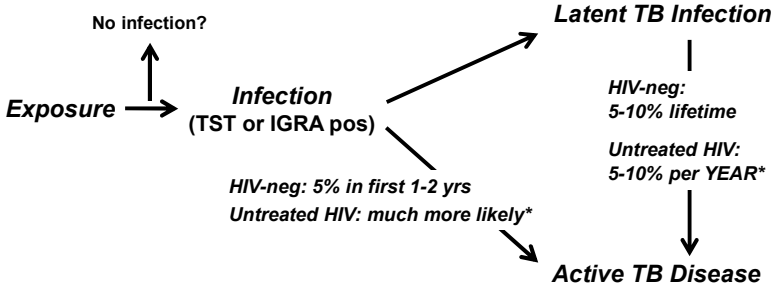
Disclosures of Financial Relationships with Relevant Commercial Interests

- I receive salary support from grants from NIH and CDC for my work on several clinical trials of novel TB regimens and novel TB diagnostics.

Natural History of *M. tuberculosis* Infection



**risk increases as immunosuppression increases*

Risk Factors for TB Disease

Epi Risk Factors for TB INFECTION

- Exposure to person w/ active TB
- From TB endemic area
- Homelessness
- Incarceration
- Works healthcare, corrections
- Injection drug use

Medical Risk Factors for PROGRESSION to TB DISEASE

- Recent TB infection
- HIV infection
- TNF-alpha inhibitors
- Immunosuppression
- Diabetes
- Silicosis
- End stage renal dz
- CXR fibrotic lesions c/w prior TB
- Intestinal bypass, gastrectomy, chronic malabsorption
- CA head or neck, Hodgkins, leukemia

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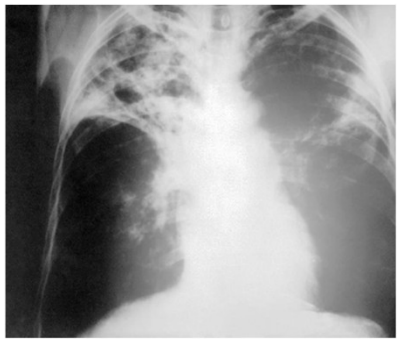
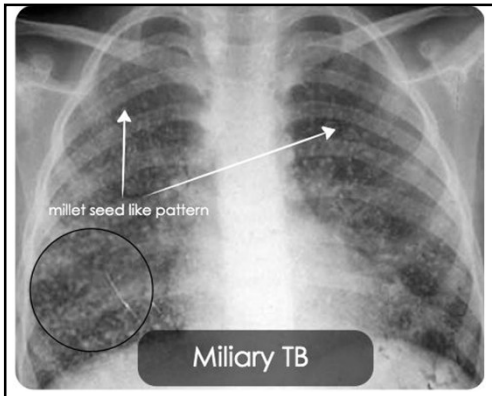
Active TB Disease
Clinical Presentations

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





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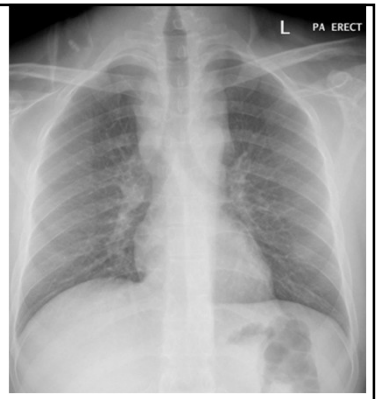

Tuberculous Mediastinal Lymphadenopathy

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

Active TB Disease
Extrapulmonary

Disease Site	Comments
CNS	• Meningitis (esp **basilar** and associated with CN palsies, hydrocephalus, obliterative vasculitis with strokes); focal tuberculomas
Lymphadenitis	
Bone & Joint	• Vertebral (thoracic, lumbar; anterior wedging; +/- psoas abscess • Consider TB in ddx of chronic osteomyelitis, arthritis
Pleural	• Exudative lymphocytic effusion; low bacillary burden; obtain pleural biopsy
Pericardial	• Exudative lymphocytic effusion; low bacillary burden; obtain biopsy
Abdominal / pelvic	• GU: sterile pyuria; obtain multiple urine cultures; can cause **infertility** • GI: can **mimic inflammatory bowel disease**
Disseminated	• Advanced HIV, iatrogenic immunosuppression, d/o of IFNγ/IL12/TNFα axis • Can present as **sepsis** • Mycobacterial blood cultures, get respiratory specimens, other tissue specimens

Obtain specimen(s) from affected site(s)

Active TB Disease
Diagnosis

Smear Microscopy

LOD: 10,000 cfu/ml
Sensitivity: LOW

Nucleic Acid Amplification Tests

100 cfu/ml
Sensitivity: MEDIUM (currently)

Culture

1-10 cfu/ml
Sensitivity: HIGH

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

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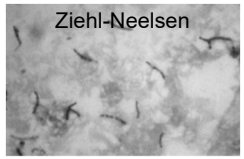
Active TB Disease Diagnosis

Smear microscopy for AFB

- ***NEG SMEARS DO NOT EXCLUDE A DX OF ACTIVE TB***
- Low sensitivity
- Overall 50-60% sensitive for pulmonary TB
- Less sensitive in advanced HIV (30-50%)
- In pulmonary TB: yield of smear microscopy increases if multiple specimens obtained
- Not specific for MTB (mycobacteria look alike)
- Good PPV in TB endemic settings



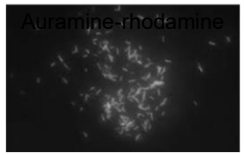


Image credits:
1. CDC/Dr. George P. Kubica
2. https://laboratoryinfo.com/auramine-rhodamine-staining-for-afb-principle-procedure-reporting-and-limitations/

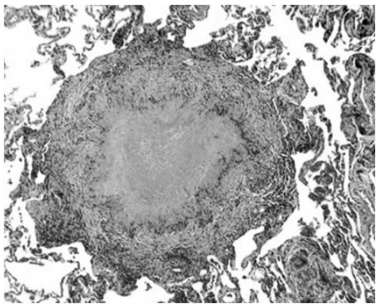
Active TB Disease Diagnosis

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

Active TB Disease Diagnosis

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

Active TB Disease Diagnosis



Typical Caseating Granuloma

Immunodeficient Patients:
(e.g., advanced HIV; use of TNF-α inhibitors)

- Caseation may not be apparent
- Granulomas may lack structure

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

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Question #1

- 38-year-old healthy physician; periodic travel to South Africa for work.
- 6 years ago: pos TST; poor adherence with isoniazid preventive therapy
- Now 5 weeks of fever, chills, night sweats, 10-lb wt loss, productive cough.
- CXR: small RUL cavitary lesion with surrounding infiltrate. HIV negative, LFTs normal. Sputum smears x 3: negative for AFB
- Sputum Xpert MTB/RIF: "MTB detected" & "Rifampin resistance not detected"

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

Extend continuation phase therapy for

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

Corticosteroids: indicated for TB meningitis

- Pericardial TB: probably reduce the risk of constrictive pericarditis
  - Most experts use for patients at high risk for inflammatory complications, e.g.,
    - Large effusion, high levels of inflammatory cells in fluid, early constriction

Question #2

- The 38-year-old physician is started on rifampin, isoniazid, PZA, ethambutol (plus pyridoxine) for presumed pulmonary TB
- 3 weeks later the culture grows *M. tuberculosis*, susceptible to those drugs
- 4 weeks into TB treatment develops nausea, anorexia, abdominal pain
- ALT 380, AST 270. He reports no alcohol consumption or acetaminophen

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

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

TB Drug Adverse Effects

Drug	Key Adverse Effects
INH	• Hepatotoxicity • Peripheral neuropathy (use pyridoxine = vitamin B6)
Rifampin	• Hepatotoxicity (cholestasis usually prominent) • Drug-drug interactions • Red discoloration of urine, sweat, etc.
PZA	• Hepatotoxicity • Arthralgias
Ethambutol	• Retrobulbar neuritis (color vision, acuity)

Hepatotoxicity: INH = PZA > Rifampin

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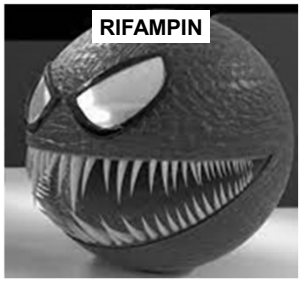
Rifampin Chews Up Some Other Drugs*

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



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

Question #3

53-year-old female recently arrived in US from Ukraine. Reports 3 months of cough. CXR with RUL cavity. Sputum Xpert result "MTB detected" and "Rifampin resistance detected". Additional molecular testing shows mutation in *katG* associated with high-level INH resistance. No mutations in *gyrA* or *gyrB* (i.e., no molecular evidence of FQ resistance).

What is the best treatment approach?

A. Start RIPE plus moxifloxacin, plus amikacin given daily
B. Start RIPE plus moxifloxacin, plus amikacin given 3x/week
C. Start moxifloxacin, amikacin, cycloserine, linezolid, ethionamide
D. Start bedaquiline, pretomanid, linezolid, moxifloxacin

Drug-resistant TB

- Risk factors for:
  - Contact with drug-resistant TB case
  - Prior h/o TB treatment, esp if non-adherent
- **MDR=resistance to isoniazid plus rifampin**
- **XDR=MDR plus resistance to fluoroquinolones plus at least one of bedaquiline or linezolid**
- Treat with multiple agents against which the isolate is susceptible
- Do not add single drug to a failing regimen
- WHO/FDA: BPaL(M) = Bedaquiline + Pretomanid + linezolid (+/- moxifloxacin)

- **Bedaquiline (Sirturo™): novel drug, novel target (MTB ATP synthase); QT prolongation; half-life 4 months**
- **Pretomanid: inhibits mycolic acid synthesis; elevated LFTs**

Question #4

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

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

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

What is the best course of action regarding timing of TB therapy and HIV therapy?

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

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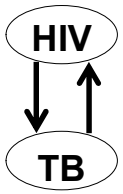
Active TB Disease
Special Considerations for PLWH

HIV:
Increases risk of progression from latent to active TB

CD4 influences TB severity & clinical manifestations



TB:
Can increase HIV viral load

Associated with more rapid progression of HIV

Advanced immunosuppression associated with:
- Increased risk for extrapulmonary (including CNS) & disseminated TB
- Absence of lung cavitation resulting in low bacillary load **in airways**

Active TB Disease: Special Considerations for PLWH

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, monitor HIV VL
    - Good virologic, immunologic, clinical outcomes with rifampin + standard dose EFV regimens
    - PI-based regimens: Do not use rifampin
    - Cabotegravir and cabotegravir/rilpivirine: do not use rifampin

Active TB Disease: Special Considerations for PLWH

Drug-drug Interactions

- **RIFABUTIN (RBT)**
  - Weaker enzyme inducer than rifampin
  - A CYP450 substrate (rifabutin metabolism affected by NNRTIs and PIs)
  - OK with DTG, RAL at standard doses
  - OK with cabotegravir but not with rilpivirine
  - PI-based ART: decrease rifabutin to 150 mg daily, or 300 mg every other day

Active TB Disease
Special Considerations for PLWH

When to start ART

- **CD4 < 50: ASAP 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); start ART when TBM is under control and patient has had at least 2 weeks of TB tx

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Question #5

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

Which is most appropriate?

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

Active TB Disease
Special Considerations for PLWH

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 treatment and ART
- Protean manifestations (fever, new lesions, extension of prior lesions)

Active TB Disease
Special Considerations for PLWH

Immune reconstitution inflammatory syndromes (IRIS)

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

Active TB Disease
Transplant Recipients

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

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Active TB Disease
TNFα Inhibitors

- ***TNF-α inhibitors markedly increase risk of active TB if infected***
  - Atypical presentations (non-cavitary pulm dz, extrapulm, disseminated)
  - Increased TB morbidity, mortality
  - Full monoclonal IgG1 mabs most potent (infliximab, adalimumab, golimumab)
- ***Test for latent TB infection (TST or IGRA) before starting anti-TNF tx***
  - If LTBI, then initiate LTBI tx prior to starting anti-TNF agent
  - Limited data on optimal duration of delay between initiating LTBI treatment and initiating anti-TNF treatment (some say 2-8 weeks)

Why Was The POTATO Unhappy?

Because It Had **Tuber**culosis

Latent TB Infection
Diagnosis

Interferon gamma release assays (IGRAs)

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

Latent TB Infection
Diagnosis

Tuberculin skin test

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

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Classification of TST Induration Diameters

≥ 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
Diagnosis

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

Signs & Symptoms + **CXR**

Latent TB Infection
Treatment

Preferred

- Isoniazid plus rifapentine once weekly x 12 doses (3HP) — **OK with DTG 50 mg qd**
- Rifampin daily for 4 months (4R)
- Isoniazid plus rifampin daily for 3 months (3HR)

Alternative

- Isoniazid daily for 6 months (or 9 months)

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

Bacille Calmette-Guerin (BCG) Vaccine

- 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)

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Bacille Calmette-Guerin (BCG) Preparation

Immunotherapy for Bladder Cancer

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

Thank You & Good Luck!

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